

**Food allergy management
in daily life:
accidental allergic reactions, cofactors
and adherence to dietary advice**

Astrid Versluis

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PhD thesis, Utrecht University, the Netherlands

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ISBN 978-94-6458-715-9

Lay-out Publiss | www.publiss.nl

Print Ridderprint | www.ridderprint.nl

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Food allergy management in daily life: accidental allergic reactions, cofactors and adherence to dietary advice

**Management van voedselallergie in het dagelijks leven:
onverwachte allergische reacties, cofactoren en opvolging van
het dieetadvies
(met een samenvatting in het Nederlands)**

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

dinsdag 10 januari 2023 des middags te 4.15 uur

door

Astrid Versluis

geboren op 23 april 1986
te Gorinchem

Promotoren:

Prof. dr. A.C. Knulst

Prof. dr. G.F. Houben

Copromotoren:

Dr. H. van Os-Medendorp

Dr. T.T.M. Le

Beoordelingscommissie:

Prof. dr. C.K. van der Ent

Prof. dr. S.G.M.A. Pasmans

Prof. dr. L. Schoonhoven (voorzitter)

Prof. dr. T. Jaarsma

Prof. dr. J. Garssen

Contents

Chapter 1	General introduction	7
Chapter 2	Frequency, severity and causes of unexpected allergic reactions to food: a systematic literature review	19
Chapter 3	Accidental food allergic reactions are associated with higher costs and more sick leave but not with quality of life	51
Chapter 4	Cofactors in allergic reactions to food: physical exercise and alcohol are the most important	69
Chapter 5	Potential cofactors in accidental food allergic reactions are frequently present but may not influence severity and occurrence	89
Chapter 6	Low dietary adherence after a positive food challenge in food allergic adults	109
Chapter 7	Reintroduction failure after negative food challenges in adults is common and mainly due to atypical symptoms	129
Chapter 8	General discussion	147
Chapter 9	English summary	169
	Nederlandse samenvatting	175
Chapter 10	List of abbreviations	184
	Contributing authors	185
	Dankwoord (acknowledgements)	187
	List of publications	190
	About the author	193





CHAPTER 1

GENERAL INTRODUCTION

What is food allergy?

Food allergy is an IgE-mediated immune response to food proteins that can cause symptoms involving the skin, gastro-intestinal and respiratory tracts and cardiovascular system (1). In some patients, symptoms can be life threatening (2). The prevalence of food allergy in adults ranges from 0.3-6% between countries (3). Causative foods differ to some degree between countries (3). In Europe, plant food allergy (e.g. for tree nuts and fruit) is most common (3). The diagnostic work-up of food allergy includes a detailed medical history, assessment of sensitization (based on skin prick test and/or serology) and a food challenge (1,4). The double-blind placebo-controlled food challenge is the gold standard to confirm or rule out an allergic reaction to food, to assess severity of symptoms and to investigate threshold for subjective and objective symptoms (4). Currently, there is still no cure available for patients with food allergy and accidental allergic reactions occur in the daily life of patients. The key interventions are elimination of the culprit food from the diet and treatment of accidental allergic reactions with emergency medication (e.g. antihistamines and adrenaline) (1). In most daily practices a multidisciplinary team is involved in the care of food allergic patients, including allergy specialists, dieticians and nurses. Having a food allergy is a significant burden for patients and impairs health-related quality of life (HRQL) (5). In this thesis, we focus on the frequency, severity, causes and impact of accidental allergic reactions (**Chapter 2 and 3**) the impact of cofactors on the severity of these reactions (**Chapter 4 and 5**) and dietary adherence after food challenges (**Chapter 6 and 7**).

How big is the problem of accidental food allergic reactions ?

In daily practice, it is well-known that accidental allergic reactions occur in the daily life of food allergic patients, even in those patients who strictly follow their elimination diet. However, the frequency of accidental allergic reactions to food is unknown. Such reactions can be mild, however, severe, life threatening reactions can also occur (1,6). It is unknown how often reactions are mild or severe. To gain more insight into the frequency and severity of accidental reactions, we carried out a systematic literature review in **Chapter 2**.

What are the causes of accidental allergic reactions?

Various causes can contribute to the occurrence of accidental allergic reactions to food. This paragraph describes several possible causes in more detail.

Adherence to dietary advice

Accurately following the dietary advice is indispensable to prevent accidental allergic reactions. Remarkably, it has been shown that food allergic children and adolescents often

fail to adhere to the prescribed elimination diet (7-9). This puts patients at risk of accidental allergic reactions. Most adolescents with a food allergy generally try to avoid the culprit food (85%) (8). However, less than half enquire about ingredients in restaurants (42%) or at friends' houses (35%) (8). Reasons associated with risk-taking behavior in adolescents who admitted to eating at least a tiny amount of the food, include that similar foods previously did not cause a reaction (57%), a strong wish to eat the food: "it looked good and I wanted to eat it" (49%), neglecting a precautionary allergen labelling warning (33%), did not want to ask about ingredients (23%) and "hanging out" with friends (23%) (10). On the other hand, after ruling out the diagnosis of food allergy or allergy to a specific food in a food allergic patient, the advice is to introduce that food into the diet. It is known that children often do not adhere to the dietary advice: up to 44% fail to reintroduce the food in their daily diet (11-15). Several reasons are reported, including (atypical) symptoms during reintroduction, fear of an allergic reaction and being unconvinced by the challenge test result (11,13). These unnecessary dietary restrictions are worrying, since they are associated with nutritional deficiencies, increased costs and impairment of quality of life (19,38,39).

There are no studies about the frequency and factors influencing dietary adherence after excluding or confirming the diagnosis of food allergy with a food challenge in adults. However, information about this topic is essential for the evaluation and improvement of follow-up care post diagnosis. Therefore, we investigated dietary adherence after a positive food challenge in adults in **Chapter 6**, and the frequency, reasons and risk factors of reintroduction failure after a negative food challenge in adults in **Chapter 7**.

Food labelling and eating outside the home

Patients with food allergy have to eliminate the culprit food from their diet to prevent allergic reactions (16). An elimination diet must be tailored to each individual's specific allergy and nutritional needs (16). Ideally, patients receive counselling from a dietician who is specialized in food allergy (1). The EAACI guidelines (1) recommend education as a key pillar for an effective long-term elimination diet, including 1) raising awareness among patients and their relatives about risk situations, 2) instructions about reading food labels and 3) how to avoid the culprit food both in and outside the home (e.g. restaurants).

Labelling of food allergens on prepackaged food products is often confusing. In many countries, including the Netherlands, major food allergens must be listed in the ingredient list (17). However, labeling of unintended allergen presence, e.g. due to cross contamination of allergens during food processing, is not covered or harmonized in food allergen labelling laws throughout the world, which leads to inconsistent, incorrect and non-transparent precautionary allergen labeling (18). Further, multiple formulations of precautionary

statements are used, including “may contain [allergen]” and “manufactured on shared equipment with [allergen]”. This adds to the confusion and suggests that different wording indicates different levels of risk. It is known that patients increasingly ignore precautionary allergen labeling (19). However, some prepackaged food products with precautionary allergen labelling do contain detectable levels of food allergens, leading to a potential risk of allergic reactions for food allergic consumers (19). And, perhaps even more worrying is the fact that many prepacked food products may contain concentrations of undeclared allergens that may elicit allergic reactions (20-22).

When food allergic patients eat outside their home, it crucial that they communicate about their dietary needs. Patients should not assume that other people (friends or restaurants staff etc.), have knowledge about food allergies and the importance of strict elimination of the culprit food. It has been shown, unsurprisingly, that restaurant staff have knowledge gaps about food allergy (23). This can lead to food being served that is not safe for food allergic consumers, for example due to unintended cross-contamination.

In daily practice it is well-known that accidental allergic reactions occur, even in those patients who strictly follow their elimination diet. Although several issues with food labelling and eating outside the home are known, their role in the occurrence of accidental allergic reactions is unclear. The systematic literature review in **Chapter 2** and prospective study in **Chapter 6** provide more insight into this subject.

Cofactors

There are reports that involvement of cofactors might lead to more severe allergic reactions in some patients (24,25). EAACI guidelines (1) describe cofactors as factors that increase the severity of some food allergic reactions and are sometimes even a prerequisite for elicitation of symptoms of food allergy. Examples of cofactors are use of alcohol, physical exercise, infections and use of some types of medication (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs)). Several underlying mechanisms of cofactors are suggested, including increased gastrointestinal permeability and absorption of proteins after physical exercise or intake of NSAIDs (24,25) and in case of acute infections, fever causing elevated blood circulation and subsequent influx of food allergen (25). Not every cofactor seems relevant for every food allergic patients (25). The EAACI guidelines (1) recommend the assessment of cofactors in any patient with food allergy. The available evidence on the influence and impact of cofactors on allergic reactions to food is however scarce and mostly conducted in patients with a severe food allergy (26-29). To gain more insight into the influence of cofactors on the severity of accidental allergic reactions we conducted a retrospective study in **Chapter 4**, followed by a prospective study in **Chapter 5**.

What are the consequences of accidental allergic reactions for the patient and society?

The following subparagraphs describe the consequences of food allergy on patients' quality of life and also the economic burden of food allergy.

Quality of life

Living with food allergy can be challenging. Patients need to be constantly vigilant in their effort to prevent accidental reactions. As a consequence, they often experience restrictions in social activities. For example, eating out is a source of uncertainty and anxiety, because the food allergy has to be mentioned to the person who provides the food and there is often a risk of cross-contamination leading to an accidental reaction. Another challenge in daily life, is checking food and food labels, recognizing and avoiding possible allergen contamination and dealing with possible accidental reactions (1,8,30). The impact of food allergy from a patient's perspectives can be measured using several questionnaires, including The food allergy quality of life questionnaire (31), The food allergy anxiety scale (32) and The food allergy coping orientation to problems experienced inventory (33). Health-related quality of life (HRQL) may be defined as "The patients' perspective on several domains of life, including physical, mental and social health" (34). It is shown that living with food allergy poses a significant psychosocial burden, causes anxiety and impairs HRQL (35,36). Food allergic adolescents and adults reported significantly more limitations in social activities, more pain, less vitality and poorer overall health than individuals from the general population (5). In addition, the impact of food allergy on the generic HRQL is intermediate in magnitude between diabetes mellitus and rheumatoid arthritis, irritable bowel syndrome and rheumatoid arthritis (5). Multiple factors contribute to the impaired HRQL of food allergic patients, including: the severity of the food allergy, dietary restrictions, type of food allergy, having multiple food allergies, reported epinephrine device usage and sociodemographic factors (38-40). Although the impact of having food allergy has been studied before, there is no evidence about the extent to which accidental allergic reactions contribute to the impairment of HRQL. More information about the impact of accidental reactions on HRQL, will provide a greater insight into the specific problems faced by patients and contribute to tailoring care to the patients' specific needs. Therefore, in **Chapter 3** we investigate the impact of accidental allergic reactions on HRQL.

Economic burden

Food allergy is also a financial burden for the individual patient and society (41-44). Patients with a possible food allergy use more health care services than those without (43). A study

in Europe showed a difference of mean annual costs over one year of 927 international dollars (I\$) comparing individuals with food allergy (mean annual costs: I\$ 2016) and those without food allergy (mean annual costs: I\$ 1089) (43). The economic burden of food allergy is mainly due to health care costs and lost opportunity costs, e.g. due to lost labor (41,42). Furthermore, the costs for health care services is estimated to be double for patients with severe food allergy compared to patients with mild food allergy (43). A study in the United States showed that allergic reactions to food led to an estimated burden of at least \$ 340 million for a given year (42). There is a lack of information about the economic burden of accidental allergic reactions to food in patients with a diagnosed food allergy. Understanding the economic costs of a disease is important for the development of effective and efficient health care policies and guidelines (45). Therefore, more insight into the impact of these accidental reactions on costs is important (8). We evaluated the influence of accidental allergic reactions to food on costs and sick leave in **Chapter 3**.

Do patients adequately treat their accidental allergic reactions?

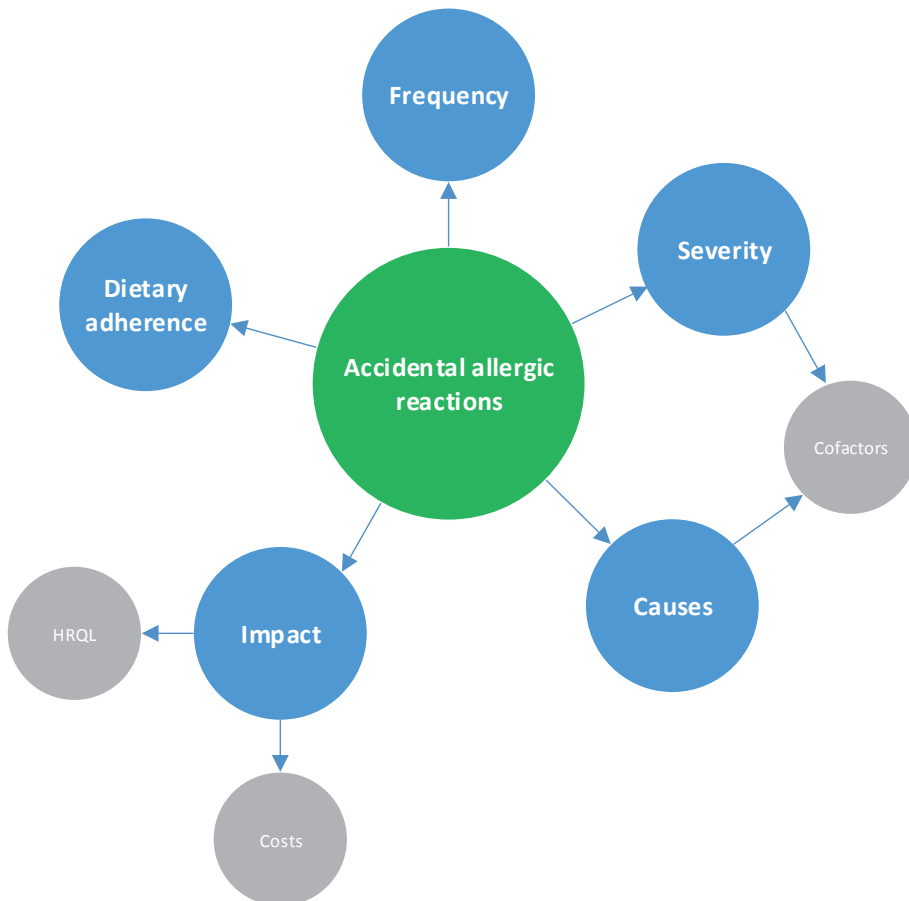
Patients are regularly prescribed emergency medication to treat accidental allergic reactions. In cases of mild/moderate reactions, patients can treat themselves with antihistamines and corticosteroids. In cases of a severe reactions (including respiratory and cardiovascular symptoms) patients should also use their adrenaline auto-injector and (if prescribed) short acting beta agonists, and must be reviewed in an emergency department (1). The EAACI guidelines (1) recommend an adequate instruction about when and how to treat allergic reactions. However, adrenaline auto-injectors are under-used (46,47). Also daily practice shows that patients do not always adequately manage their allergic reactions. More insight into how patients treat their reactions and whether this is adequate, would help to improve advice and guidance in daily practice. Therefore, we summarized the current literature with regard to patients' management of accidental allergic reactions in **Chapter 2**.

What are together the aims of this thesis?

The aims of this thesis are to give insight into: 1) the frequency, severity and impact of accidental allergic reactions, 2) factors related to the occurrence of these reactions, and 3) adherence to dietary advice after a food challenge-supported diagnosis, in adolescents and adults. Figure 1 shows the various aspects with regard to accidental allergic reactions that have been examined in this thesis. The current literature with regard to frequency, severity and causes of accidental allergic reactions to food is summarized in **Chapter 2**. Additionally, the impact of these accidental reactions on costs and quality of life is studied in a prospective

cohort study **Chapter 3**. Furthermore, the association between cofactors and the severity of accidental allergic reactions to food is assessed both in a retrospective study and prospective study in **Chapters 4 and 5** respectively. Evaluation of dietary adherence by adults after a positive food challenge is evaluated in a prospective daily practice study in **Chapter 6**. In addition, the frequency of reintroduction of food after a negative food challenge in adults is described in a prospective daily practice study in **Chapter 7**. The implications of our findings for daily practice and considerations for future research are explored in **Chapter 8**.

Figure 1. Outline of the subjects of this thesis



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CHAPTER 2

FREQUENCY, SEVERITY AND CAUSES OF UNEXPECTED ALLERGIC REACTIONS TO FOOD: A systematic literature review

Astrid Versluis, André C. Knulst, Astrid G. Kruizinga, Anouska Michelsen,
Geert F. Houben, Joe L. Baumert, Harmieke van Os-Medendorp

Clinical Exp Allergy. 2015; 45(2): 347-67

Abstract

Food allergic patients have to deal with an avoidance diet. Confusing labelling terms or precautionary labels can result in misinterpretation and risk-taking behaviour. Even those patients that strictly adhere to their diet experience (sometimes severe) unexpected allergic reactions to food. The frequency, severity and causes of such reactions are unknown. The objective of this review was to describe the frequency, severity and causes of unexpected allergic reactions to food in food allergic patients aged > 12 years, in order to develop improved strategies to deal with their allergy. A systematic review was carried out by two researchers, in six electronic databases (CINAHL, Cochrane, EMBASE, Medline, Psychinfo and Scopus). The search was performed with keywords relating to the frequency, severity and causes of unexpected allergic reactions to food. This resulted in 24 studies which met the inclusion criteria; 18 observational and six qualitative studies. This review shows that knowledge about the frequency of unexpected reactions is limited. Peanut, nuts, egg, fruit/vegetables and milk are the main causal foods. Severe reactions and even fatalities occur. Most reactions take place at home, but a significant number also take place when eating at friends' houses or in restaurants. Labelling issues, but also attitude and risky behaviour of patients can attribute to unexpected reactions. We conclude that prospective studies are needed to get more insight in the frequency, severity, quantity of unintended allergen ingested and causes of unexpected allergic reactions to food, to be able to optimize strategies to support patients in dealing with their food allergy. Although the exact frequency is not known, unexpected reactions to food occur in a significant number of patients and can be severe. For clinical practice, this means that patient education and dietary instructions are necessary.

Introduction

The prevalence of food allergy is estimated to affect more than 2% and possibly up to 10% of the population (1). At present no curative treatment is available. This implies that patients can only avoid symptoms by strictly adhering to their avoidance diet. Patients are not always adequately advised how to deal with their diet, and confusing labelling terms and rampant use of multiple forms of precautionary labels (i.e. May Contain X, Produced in a facility that processes X, etc.) has resulted in risk-taking behaviour by some allergic patients (2). In daily practice, it is well-known that even those patients that strictly adhere to their diet experience unexpected allergic reactions to food during their life. Symptoms can be mild and limited to the oral cavity, but also generalized and severe allergic reactions can occur, sometimes involving multiple organ systems such as the skin and mucosal tissues and the gastrointestinal, respiratory and cardiovascular tract (3). The frequency of unexpected allergic reactions to food is unknown. The overall prevalence rate of anaphylaxis is estimated to be 10 per 100.000 inhabitants per year and is primarily caused by food, drugs and insect venoms (4).

Appropriate labelling of food allergens is essential to help people manage their allergy and prevent food allergic reactions (5). Although labelling of well-known allergens or primary food allergens is adequately regulated in many countries throughout the world, cross contamination during food processing can cause the unintended presence of food allergens in a variety of packaged foods. Regulation of cross contact of allergens is not specifically addressed under the mandates of food allergen labelling laws throughout the world (6,7). The labelling laws specifically address the accurate labelling of major food allergens in terms that can easily be understood by consumers (i.e. casein would be labelled as 'milk' on the packaged food product label) when the allergenic source is used as a direct ingredient or processing aid in the food product (5). Labelling laws are different in different countries (8). In the European Union wheat/cereals, eggs, milk, peanut, fish, crustaceans, soy, tree nuts, sesame, shellfish/molluscs, mustard, celery and lupine are considered major allergens. In the United States these are wheat/cereals, eggs, milk, peanut, fish, crustaceans, soy, tree nuts (8). Regulatory authorities require proper management of food allergens to minimize the chance of allergen cross contamination in the processing facility by utilizing good manufacturing practices, including the development of a robust allergen control program. Some manufacturers voluntarily use precautionary labelling to alert consumers to products that might be subject to such adventitious contamination (5). However, the increased use of this type of labelling, along with the inconsistent and non-transparent way by which various companies decide to use these labels, has resulted in devaluation of its intended message to relay potential risk to allergic consumers. As a result, up to 40% of allergic individuals ignore

these recommendations and taking risks by consuming these products (2,9). These products have been shown to contain sporadic and varying levels of undeclared food allergens at levels that could result in adverse allergic reactions. It is highly recommended that allergic consumers avoid products bearing precautionary labels. However, it is unknown how often an unexpected allergic reaction occurs due to ignoring food labels or due to other causes. It is important to advise patients on how to recognize the first signs of an allergic reaction so that they can treat themselves and seek qualified medical attention (10,11).

The aim of this review is to summarize the current evidence about frequency, severity and causes of unexpected allergic reactions to food in food allergic patients.

Methods

Design

A systematic literature review was carried out, following the recommendations of the preferred reporting item for systematic reviews and meta-analyse statement (12).

Eligibility criteria

Studies which contributed to the aim and were published between January 2001 and April 2013 were included. Inclusion criteria were: articles from peer reviewed journals that were written in English, German or Dutch, and participants of 12 years or older who had an indication/diagnosis of food allergy. In case of mixed populations of children and adults, the study was included when >50% of the participants were at least 12 years of age. Children < 12 years of age were excluded, because in younger children parents or other caregivers take mainly responsibility for their food choice and a safe environment (13,14). Around 12 years of age, children start to develop independence and take their own responsibility for managing their food allergy (15,16). Case studies were excluded.

Information sources and search methods

The search was performed by two researchers independently, in April 2013. The studies were identified by searches of six electronic databases (CINAHL, Cochrane, EMBASE, Medline, Psychinfo and Scopus), and by using the snowball method, by screening the reference lists of the included articles and through authors' knowledge about relevant studies.

The following keywords were used based on disease characteristics (e.g. type of food allergy) and possible determinants (for example attitude, labelling, place of reaction and allergens): (food allergy) AND (reactions OR anaphylaxis OR anaphylactic OR accidental OR reactions OR exposure OR ingestion OR eating OR labelling OR labeling OR (food labelling) OR

(food labelling) OR restaurant OR (consumer attitudes) OR (food products) OR information OR (quality of life) OR kiss OR (soy OR soybean OR soya) OR milk OR egg OR crustacean OR shellfish OR fish OR lupin OR mustard OR celery OR molluscs OR peanut OR (sesame OR (sesame seeds)) OR (nuts OR almond OR hazelnut OR walnut OR (cashew nut) OR (pecan nut) OR ((brazil nut) OR (para nut)) OR (pistachio nut) OR ((macadamia nut) OR (queensland nut)) OR (kemiri nut))). The limit title/abstract was used.

The articles were first screened for relevance to the stated study aims by reading the title and abstract. Of the articles that appeared to fit the criteria for the study after the primary review, the full text was then critically reviewed for relevance and quality. The entire process was performed independently by two researchers who then came to consensus on the articles that fit the criteria for inclusion in the study.

Quality appraisal

The methodological quality of the included studies was evaluated to get insight in the methods and to assess the risk of bias of the studies. Because of the various designs, two different quality appraisal tools were used. The quality of observational studies (e.g. cohort, case-control or cross-sectional studies) was evaluated with the criteria of the 'strengthening the reporting of observational studies in epidemiology' (STROBE) statement (17). The evaluation of qualitative studies (e.g. grounded theory practice or phenomenology and data collection by e.g. interviewing, participant observation and focus groups) was performed with the 'consolidated criteria for reporting qualitative research' (COREQ) checklist (18).

Data abstraction and synthesis

The included articles were analysed by two researchers. The characteristics of the studies were recorded on a data extraction form, comprising of the following items: author and year; design, participants and setting; and results relating to the research question of interest: frequency, severity, causes and locations of unexpected reactions, labeling issues and attitude or behavior related to unexpected reactions. The severity of unexpected reactions was classified according to an adapted version of the Mueller classification. Reactions with local symptoms (Mueller 0) were classified as mild, with skin and mucosal (Mueller 1) or gastro-intestinal symptoms (Mueller 2) as moderate and with respiratory (Mueller 3) or cardiovascular symptoms (Mueller 4) as severe (19,20).

In studies with mixed populations (adults and children), we only reported results of patients of at least 12 years of age. Since different designs and outcomes were used in the study, it was not possible to pool the data in a meta-analysis. Therefore, the findings were reported by using a narrative summary technique.

Results

Included studies

The initial search generated 176 articles. After screening for duplication and relevance, twenty-four articles were identified that fit our defined criteria and were included in this analysis. Major reasons for exclusion include 1) studies where more than 50% of the results were dedicated to caregivers and children < 12 years of age and 2) with no clear difference between the first reaction and unexpected, recurrent reactions after establishing an indication/diagnosis of food allergy. The process of inclusion is presented in Figure 1. Eighteen studies had an observational design, whereof three were prospective (21-23), ten were retrospective (15,24-32), two were cross-sectional (33,34) and three were based on a registry (35-37). Six studies had a qualitative design (38-43). In thirteen studies (21-23,27,28,30-32,34-37,42) the time frame of data collection was reported, it varied from 1993 to 2009.

Eight studies showed results pertaining to the frequency of unexpected allergic reactions to food (22,24,25,27,28,34-36). Nine studies provided details relating to the severity of adverse reactions (21,22,24-26,29,31,33,37). Allergens that caused an unexpected reaction were described in thirteen studies (21-26,29-31,33,35-37). Eight studies discussed how the eating location is an important factor that can contribute to allergic reactions (21,24,26,29,30,35,36,39). Five studies reported about labelling issues that may have contributed to the unexpected reactions (29,32,38,39,43). Finally, Nine studies reported about attitude or behaviour as a factor that plays a role in causing allergic reactions (15,26,29,38-43). These results are presented in Tables 1 and 2.

Figure 1. Flowchart presenting the process of inclusion and exclusion of articles

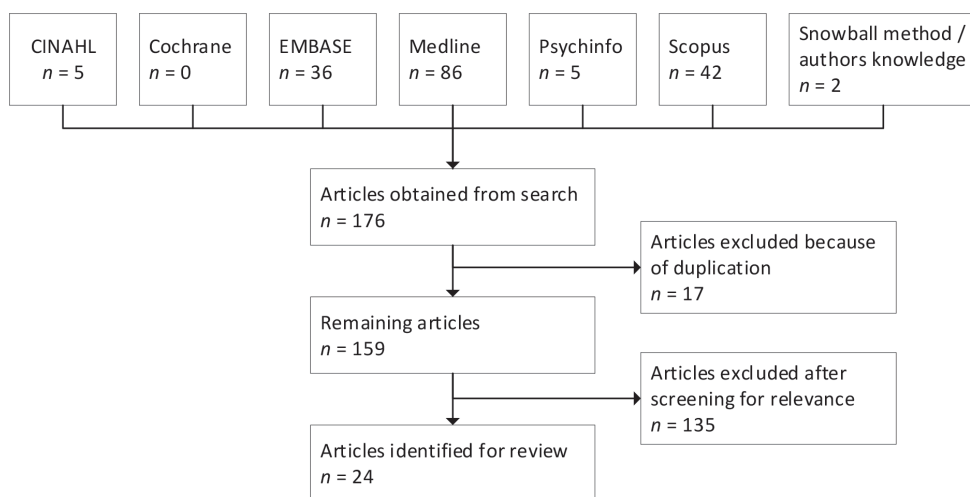


Table 1. Overview of studies pertaining to prevalence, severity and causes of unexpected food allergic reactions

Author, year	Design, participants and setting	Frequency of unexpected reactions	Severity and treatment of unexpected reactions ^a	Causes and locations of unexpected reactions
Añibarro et al., 2007 (24)	Retrospective study, review of food allergic reactions over a 5 year period Time frame: not specified - N = 436 patients with 530 food reactions; 52% were known to have FA prior to the reaction to the hidden allergen - Age: >17 years of age (mean age 33.4, SD 15.4) - Type of FA: not specified - Mean age at onset symptoms FA: 46 ± 13.8 years - 32% asthmatic - Diagnosed with FA by clinical history, SPT's and/ or presence of IgE and oral challenge test when needed Setting: Allergy Unit; Spain	- 530 reactions were analysed - 1.98 reactions per patient (range 1-10)	- 32% of these were anaphylactic reactions (Mueller 4) - 0% fatal reactions Treatment of reaction: not specified	Causes: 22.4% were due to hidden allergens, of them: 9%: nuts 61%: fish / shell fish / anisakis simplex 15%: legumes / fruit 4%: egg 10%: others: Location: Fish / shell fish: in restaurants or other place outside the home
Bock et al., 2001 (36) & 2007 (35)	Quantitative study based on a registry Time frame article 2001: 1994 to 1999 Time frame article 2007: 2001 to 2006 Article 2001 - N = 32 fatalities over a 5-year period (26 fatalities included in our analysis) - Age: >12 years of age - Diagnosed with prior history of FA reaction - 81% asthmatic Article 2007 - N = 31 fatalities, over a 5-year period (23 fatalities included in our analysis) - Age: >12 years of age - Diagnosed with prior history of FA reaction - 87% asthmatic Type of FA and mean age at onset symptoms is in both studies not specified Setting: registry USA	Article 2001 - 26 fatalities over a 5-year period Article 2007 - 23 fatalities, over a 5-year period		Article 2001: Cause of unexpected reaction (N = 26): 73%: peanut 27%: nuts Location of reaction: 31%: restaurant or club 23%: school 27%: home 12%: friend's home 8%: other Article 2007: Cause of unexpected reaction (N = 23): 52%: peanut 35%: nuts 9%: milk / whey 4%: shrimp Location of reaction: 17%: friend's home 26%: restaurant 22%: work or school 26%: home 0,04%: other

Table 1. Continued

Author, year	Design, participants and setting	Frequency of unexpected reactions	Severity and treatment of unexpected reactions ^a	Causes and locations of unexpected reactions
Comstock et al., 2008 (25)	Retrospective study based on a questionnaire and interview Time frame: not specified - N = 471 participants - Age: 41/45 contacted for interviewing, 78% >18 years - Type of FA: With peanut (83%), tree nut (66%) or seed allergy (17%) - Diagnosed: on convincing medical history - N = 45 had a reaction during flight - Age at onset symptoms FA: not specified - 68% asthmatic Setting: selected out of a nut and seed allergy database, USA	- 9% reported reactions during a flight - 10% of these people had >1 reaction during flight	Severity of reactions: 9%: Mueller 0 to 1 11%: Mueller 1/2 22%: Mueller 2 53%: Mueller 3/4 4%: Mueller 4 Treatment of reaction (some individuals used more than one treatment): - 58% used emergency medication - 51% on plane, whereof 19% injectable epinephrine, 10% inhaled epinephrine, 71% antihistamines, 24% albuterol - 29% on the ground (75% also treated reaction on plane), whereof: 50% emergency department, 8% hospitalized, 17% injectable epinephrine, 25% antihistamines, 8% albuterol	Causes: 73%: peanuts 23%: tree nuts 5%: sesame seeds Reported mode of exposure: 58%: through inhalation, 9%: through contact 33%: through ingestion
De Swert et al., 2008 (21)	Prospective study Time frame: May 2004 - April 2006 - N = 64 cases of anaphylaxis which occurred in 48 children - Diagnosed: doctor diagnosed FA - Age: We only report about 5 cases of children aged ≥ 12 years Type of FA and age at onset symptoms: not specified Setting: pediatric department's outpatient allergy clinic of the university hospital Gasthuisberg Leuven and two private pediatric practices, Belgium		Severity N = 3: Mueller 3 N = 2: Mueller 4 Treatment of reaction: antihistamines (N=5), corticosteroids (N=1), beta-2-mimetics (N=2)	Cause: N = 3: peanut N = 2: egg Location: N = 1: home N = 3: outside N = 1: restaurant

Table 1. Continued

Author, year	Design, participants and setting	Frequency of unexpected reactions	Severity and treatment of unexpected reactions ^a	Causes and locations of unexpected reactions
Eriksson et al., 2003 (33)	<p>Questionnaire-based survey (cross-sectional)</p> <p>Time frame: not specified</p> <ul style="list-style-type: none"> - N = 1139 patients - Diagnosed: self-reported food hypersensitivity, referred for allergy testing - Age: 29 years (range 1-84); 80% >16 years - 12 cases, we report about 11 patients >12 years, describing kiss-induced food allergy symptoms - Type of FA (probably only the major allergens were reported): milk (N=2), egg (N=2), nuts (N=9), fruit/vegetables (N=9), crustaceans (N=1), fish (N=2), peanut (N=5), shellfish (N=2), sesame seeds (N=1), others (N=3) - Age of onset symptoms FA: <15 years (N = 9), 21 years (N=1) unknown (N = 1) <p>Setting: 17 allergy clinics in Sweden, Denmark, Estonia, Lithuania, Russia</p>	<p>Severity of reactions in 11 cases with kiss-induced FA:</p> <p>n=4: Mueller 0</p> <p>n=5: Mueller 1</p> <p>n=2: Mueller 2/3</p> <p>Treatment of reaction: not specified</p>	<p>Allergic symptoms by indirect contact:</p> <p>17%: when foods are handled in the kitchen</p> <p>13%: when sitting beside another person, eating a food that the patient could not tolerate</p> <p>12%: on close contact (e.g. kissing)</p> <p>Causes in individual cases (n=11; more causes possible):</p> <p>N = 1: milk/egg</p> <p>N = 1: apples or carrots</p> <p>N = 3: peanuts</p> <p>N = 4: fruit or vegetable</p> <p>N = 5: nuts</p>	
Gallagher et al., 2012 (39)	<p>Qualitative interview study</p> <p>Time frame: not specified</p> <ul style="list-style-type: none"> - N = 26 - Age: 13-19 years and their parents (N=28) - Diagnosed: self-reported anaphylaxis to food in the last 5 years or an earlier reactions and/or testing indicating high risk - Type of FA: peanut (N = 18), nuts (N = 10), milk/dairy (N = 4), egg (N = 2), legumes/fruit (N = 2), sesame (N = 2), fish (N = 1), shellfish (N = 1), lentils (N = 1) - Age at onset symptoms FA: not specified - Setting: UK 		<p>In general, reactions took place in everyday situation: at home, at school, in restaurants, at weddings and parties</p>	

Table 1. Continued

Author, year	Design, participants and setting	Frequency of unexpected reactions	Severity and treatment of unexpected reactions ^a	Causes and locations of unexpected reactions
Greenhawt et al., 2009 (26)	Retrospective online 32-questionsurvey study Time frame: not specified - N = 287 students - Age: >18 years of age - Diagnosed: all have a known FA or likely had an allergic reaction attributable to food - Type of FA: Milk 19%, tree nut 16%, shellfish 16%, peanut 15%, fish 5%, wheat 4%, soy 3%, egg 3%, other food 36% - Age at onset symptoms FA: not specified Setting: the University of Michigan, USA		Severity of reported symptoms (more answers were possible) 34-36%: Mueller 0 30%: Mueller 1 18-22%: Mueller 2 16-30%: Mueller 3 36%: Mueller 4	Causes of reaction: - Milk, fish, tree nut, peanut and shellfish were significantly related to anaphylactic symptoms Locations of symptoms: 21%: restaurant 37%: home 36%: friend's or parent's home 14%: work/school 5%: other
Kalogeromitros et al, 2005 (22)	Prospective study Time frame: March 2001 to April 2003 - N=11 patients with history of allergic reactions to grapes or grape products - Age: 16-44 years - Diagnosed: clinical history and SPT - Type of FA: diagnosed with grape allergy - Age at onset symptoms FA: not specified Setting: allergy department of a hospital of the university of Athens, Greece	Recurrent reactions: N = 1: 1 reaction N = 2: 2 reactions N = 4: 3 reactions N = 2: 4 reactions N = 2: 5 reactions	Severity: N = 1: Mueller 2 N = 23: Mueller 3 Treatment of reaction: 91% used emergency medications, whereof: 28% used their emergency kit (antihistamine, self-injected adrenaline, corticosteroids and inhaled B2-agonist) and 72% were treated at the emergency department	Cause: N = 10: wine N = 2: wine vinegar N = 8: grape plant leaves N = 3: raisin N = 1: grape juice N = 11: grape
Kalogeromitros et al, 2013 (27)	Retrospective questionnaire-based survey Time frame: October to December 2006 - N = 3673 participants - Diagnosed: self-reported FA - Age: between 18 and 74 years - Type of FA: Fruit/vegetables 24%, shellfish/seafood 11%, nuts 9%, fish 5%, milk/dairy 5%, egg 5%, sesame 3%, beans/legume/peas 2%, cereals 2%, more than one food group 1%, other food 34% - Age at onset symptoms FA: 0-10 years 19%, 10-20 years 29%, 20-30 years 31%, 30-40 years 14%, >40 years 9% - Setting: online information portal in Greece	81% consumed a suspected allergic food again after a food allergic reaction. Most of them (74%) within one year. 75% emerged recurrent reactions after re-exposure		

Table 1. Continued

Author, year	Design, participants and setting	Frequency of unexpected reactions	Severity and treatment of unexpected reactions ^a	Causes and locations of unexpected reactions
Kanny et al., 2001 (28)	Epidemiologic survey based on two questionnaires. (retrospective) Time frame: 1997 to 1998 - N= 724 participants - Diagnosed: self-reported or physician diagnosed FA - Age: 0-61 years whereof 12% 7-15 years, 54% >31 years - Type of FA: Fruit/vegetables 28%, milk 8%, crustaceans 8%, shellfish 7%, egg 4%, tree nut 3%, peanut 1%, intolerance to alcohol 6% - Age at onset symptoms FA: not specified Setting: participant were distributed by a national polling organization in France	4.7 ± 5.6 (mean ± SD) reactions 53% had 2 or more reactions (time period unknown) Recurrent reactions: 20%: 1 reaction 15-20%: 2 reactions 10-15%: 3 reactions 10-15%: 4-5 reactions 2-5%: 6-9 reactions 10-15%: 10 reactions 25-30%: unknown	Reported severity of allergic symptoms (more answers were possible): 48%: Mueller 1 59%: Mueller 2 42%: Mueller 3 20%: Mueller 4 Treatment of reaction: not specified	65% had a reaction on a known allergen, but reported to be unaware of eating it in the restaurant restaurant/canteen (28%) or in the eaten packaged food (21%) 29% reacted on a product they did not recognize as a product with allergen. Most common causes of these reactions were: 17%: nuts 10%: milk 8%: soy Cause of anaphylactic death (N = 3): N = 2: peanut N = 1: fish Location of reaction (N = 3): N = 2: work or school N = 1: friends home
Lämmel & Schnadt, 2009 (29)	Retrospective questionnaire-based study Time frame: not specified - N = 450 - Diagnosed: IgE mediated FA - Age: 74% Adults FA, 26% caregivers of children with FA - Type of FA: not specified - Age at onset symptoms FA: not specified Setting: recruitment under members of the Deutsche Allergie und Astma Bund, Zietschrift Allergie and specific newsletters for patients, Germany			
Liew et al., 2009 (30)	Retrospective study based on a national database Time frame: January 1997 to December 2005 - N=112 anaphylaxis fatalities. We only report about 3 patients - Age group: 10-14 years, 15-19 years and 30-34 years - Diagnosed: food anaphylactic death, with a history of previous food allergic reactions - 2/3 were asthmatic - Type of FA and age at onset symptoms FA: not specified Setting: Australia			

Table 1. Continued

Author, year	Design, participants and setting	Frequency of unexpected reactions	Severity and treatment of unexpected reactions ^a	Causes and locations of unexpected reactions
Malmheden, 2004 (37)	<p>Analysis of food samples from the National Food Administration. A registry based study.</p> <p>Time frame: over a period of >10 years, since 1993</p> <ul style="list-style-type: none"> - N = 171 suspected food samples that caused allergic reactions - Age: all ages - Type of FA and age at onset symptoms FA: not specified <p>Setting: Sweden</p>	<p>Reactions caused by casein (milk protein) (N = 16, multiple answers were possible):</p> <ul style="list-style-type: none"> N = 1: Mueller 0 N = 3: Mueller 1 N = 15: Mueller 2 N = 4: Mueller 3 N = 3 (N = 2 were fatal): Mueller 4 <p>Reactions caused by ovalbumin (egg protein) (N = 5, multiple answers were possible):</p> <ul style="list-style-type: none"> N = 1: Mueller 1 N = 5: Mueller 2 N = 1: Mueller 3 N = 1: Mueller 4 <p>Reactions caused by corylin (hazelnut protein) (N = 7, multiple answers were possible):</p> <ul style="list-style-type: none"> N = 1: Mueller 0 N = 5: Mueller 1 N = 2: Mueller 2 N = 3: Mueller 3 N = 2: (N = 1 was fatal): Mueller 4 <p>Reactions caused by soy protein (N = 8, multiple answers were possible):</p> <ul style="list-style-type: none"> N = 1: Mueller 0 N = 1: Mueller 1 N = 2: Mueller 2 N = 3: Mueller 3 N = 5 (N = 3 fatalities): Mueller 4 <p>Treatment of reaction: not specified</p>	<p>Causes of adverse reaction (n=154):</p> <ul style="list-style-type: none"> 28%: milk 18%: peanuts 17%: tree nuts 14%: eggs 11%: soya 4%: pea protein 5%: other seeds <p>Causes of most severe reactions (n=72):</p> <ul style="list-style-type: none"> 32%: peanuts 21%: tree nuts 15%: soya 14%: milk 18%: other 	

Table 1. *Continued*

Author, year	Design, participants and setting	Frequency of unexpected reactions	Severity and treatment of unexpected reactions ^a	Causes and locations of unexpected reactions
Mullins, 2003 (23)	Prospective study, followed by a questionnaire-based survey Time frame: February 1995 to July 2000 - N = 432; of them 61% had FA - Follow-up: N = 304 - Age: 27.4 years (SD: 19.5) - Diagnosed by SPT and some by food challenge - Type of FA and age at onset symptoms FA: not specified Setting: community-based specialist medical practice in Australia			Food as risk factors for recurrence of anaphylaxis (relapse/100 patient years): 58: peanut / nut 60: egg 20: fruit and vegetables 20: fruit / vegetables and exercise 65: wheat 158: wheat and exercise 30: fish 18: crustaceans 90: cow's milt 12: soya 105: meat
Schnadt, 2009 (31)	Retrospective questionnaire based telephone interviews Time frame: March to August 2006 - N = 265 - Age: We report about N = 95 adults with anaphylaxis to food - 79% had a known FA to the trigger, 14% assumed to have an allergy to the trigger, 3% was in the diagnostic phase - Diagnosed: 63% was diagnosed by SPT, IgE and/or food challenge - Type of FA and age at onset symptoms FA: not specified Setting: Germany		All reactions were at least Mueller 2. (Anaphylaxis was defined as systematic allergic reaction with at least 2 organ systems) Treatment of reaction: not specified	Cause (multiple answers were possible): 20%: peanut 17%: fruit 14%: nuts 14%: soy 14%: fish 11%: milk 6%: egg 6%: celery 13%: other

Table 1. Continued

Author, year	Design, participants and setting	Frequency of unexpected reactions	Severity and treatment of unexpected reactions ^a	Causes and locations of unexpected reactions
Sicherer, et al., 2004 (34)	<p>Cross sectional telephone survey</p> <p>Time frame: October to December 2002</p> <ul style="list-style-type: none"> - N = 327 households reported 1 or more individuals - Diagnosed: physician diagnosed FA or self-reported FA - Age: 34% was <18 years old - Type of FA: sea food allergy - 34% was <18 years old - Age of onset of FA was during adulthood for 40% with fish and 60% with shellfish allergy <p>Setting: USA (nationwide)</p>	<p>Recurrent reactions were reported in 58%:</p> <p>Fish: 53%, distribution:</p> <ul style="list-style-type: none"> - 2 to 5 reactions in 33% - >6 in 20.7% <p>Shellfish 57%, distribution:</p> <ul style="list-style-type: none"> - 2-5 reactions in 42% - >6 reactions in 15% 		

Abbreviations: FA, food allergy; UK, United Kingdom; USA, United States of America; SPT, skin prick test

^aSeverity of complaints are based on the adapted Mueller-classification:

0 = local symptoms = mild

1 = skin and mucosal symptoms = moderate

2 = gastro-intestinal symptoms = moderate

3 = respiratory symptoms = severe

4 = cardiovascular symptoms = severe

Table 2. Overview of studies about attitudes that causes unexpected allergic reactions to food and the prevalence of these reactions

Author, year	Design, participants and setting	Labelling issues related to unexpected reactions	Attitude or behaviour related to unexpected reactions
Barnet et al. 2011 (38)	<p>Qualitative interview study</p> <p>Time frame: not specified</p> <ul style="list-style-type: none"> - N = 32 - Age: > 15 years of age - Diagnosed: with FA by SPT and/or specific IgE measurements and/or seen by GP of a hospital specialist - Type of FA: peanut (N=23), tree nut (n=27), fruit/vegetable (N=5) - Age at onset symptoms FA: not specified <p>Setting: recruited from Southampton University Hospital Trust, primary care setting or the University of Surrey, UK</p>	<p>Use of information on food packaging to make food choices:</p> <ul style="list-style-type: none"> - Problems related to readability and interpretability of ingredients lists. - No allergy advice box could be incorrectly considered to be a signal that there was nothing to worry about. - Some avoided products where the product name raised concern, even if the ingredients list/allergy advice box indicated the product to be safe. 	<p>Risk assessment is based on product brand or name, prior experiences with the product; if this strategy does not lead to a confident decision, printed packet information is used.</p>
Gallagher et al., 2012 (39)	<p>Qualitative interview study</p> <p>Time frame: not specified</p> <ul style="list-style-type: none"> - N = 26 - Age: 13-19 years and their parents (N=28) - Diagnosed: with self-reported anaphylaxis to food in the last 5 years or an earlier reactions and/or testing indicating high risk - Type of FA: peanut (N = 18), nuts (N = 10), milk/dairy (N = 4), egg (N = 2), legumes/fruit (N = 2), sesame (N = 2), fish (N = 1), shellfish (N = 1), lentils (N = 1) - Age at onset symptoms FA: not specified <p>Setting: UK</p>	<p>Labelling issues:</p> <ul style="list-style-type: none"> - all participants attempt to avoid allergens by checking ingredients - most participants admitted taking some risks with may-contain labelled foods 	<ul style="list-style-type: none"> - experience with anaphylaxis left adolescents with heightened sense of danger - restricting their lives in terms of eating out and foreign travel - Carrying epinephrine improved risk-taking

Table 2. Continued

Author, year	Design, participants and setting	Labelling issues related to unexpected reactions	Attitude or behaviour related to unexpected reactions
Greenhawt et al. 2009 (26)	<p>Retrospective online questionnaire-based survey</p> <ul style="list-style-type: none"> - N = 287 students - Age: > 18 years of age - Diagnosed: with a known FA or likely had an allergic reaction attributable to a food - Type of FA: milk 19%, tree nut 16%, shellfish 16%, peanut 15%, fish 5%, wheat 4%, soy 3%, egg 3%, other food 36% - Age at onset symptoms FA: not specified <p>Setting: the University of Michigan, USA</p>		<p>Risk-taking behaviour:</p> <ul style="list-style-type: none"> - 12% reported that dining hall food was always labelled to identify allergens. 37% reported main course alternative was available. - 33% of the group with anaphylactic symptoms was concerned about potential exposure. - 40% always avoided ingesting the food items of concern. - 60% did not always avoid the food items of concern. A significantly higher number of students without symptoms of anaphylaxis continued eating a food to which they identified to be allergic to. <p>Reasons for risk taking behaviour (N = 173):</p> <ul style="list-style-type: none"> 22-38%: no severe of inconsistent symptoms 15-21%: not perceiving as risky action 18%: belief of patient that he/she could self-treat any reaction 12%: indifference 10%: last reaction in distant past
Lämmel & Schnadt, 2009 (29)	<p>Retrospective questionnaire-based study</p> <ul style="list-style-type: none"> - N = 450 - Age: 74% adults FA, 26% caregivers of children with FA - Diagnosed: IgE mediated FA - Type of FA: not specified - Age at onset symptoms FA: not specified <p>Setting: recruitment under members of the Deutsche Allergie und Astma Bund, Zietschrift Allergie and specific newsletters for patients, Germany</p>	<p>70%: readability problems: labels difficult to read</p> <p>85%: interpretation problems: not enough information on labels</p> <p>Interpretation problems with 'may contain' label:</p> <ul style="list-style-type: none"> 70% think that a product may contain the allergen 17% think that a product certainly contains the allergen 15% assume that a product doesn't contain the allergen 	<p>Risk taking behaviour:</p> <ul style="list-style-type: none"> - 3% would buy a product without ingredient list - 82% would not buy a product in which the allergen is mentioned in the may contain box

Table 2. Continued

Author, year	Design, participants and setting	Labelling issues related to unexpected reactions	Attitude or behaviour related to unexpected reactions
Leftwich et al. 2011 (40)	Qualitative interview study Time frame: not specified - N = 32 adults - Age: adults - Diagnosed: Doctor-diagnosed - Type of FA: peanut and/or tree nut allergy - Age at onset symptoms FA: not specified Setting: allergy clinic, GP practices and an university campus, UK		Strategies to manage the risk of consuming nuts: avoidance and communication. - avoidance of potentially high risk restaurants and foods; seeking familiarity to reduce uncertainty and risks. - availability of medical care plays a role in the decision making. - communication themes: coping language barriers by learning the language, using translation cards. - balancing between communication and fear of potential social embarrassment from the disclosure of their allergic status.
Mackenzie et al. 2010 (41)	Qualitative interview study, phenomenological approach Time frame: not specified - N = 21 - Age: 13-18 years of age - Diagnosed: by food challenge, SPT or serum-specific IgE - Type of FA: Peanut 57%, nuts 62%, sesame 19%, wheat 14%, fruit/vegetables 24%, fish 5%, shellfish 14%, milk 5%, egg 10%, mustard 5% Age at onset symptoms: early childhood-2 years (N=11), 5-12 years (N=7), 14-15 year (N = 3) Setting: recruited from clinical records of paediatric allergy clinics, UK		Attitudes and beliefs in living with food hypersensitivity: - Some felt other people could not be trusted to take precautions on their behalf. - May contain labelling place undue restriction. Managing of risk: - 43%: very strict in managing their FA and not prepared to take risks, regardless of the situation. - 48%: slightly more tolerant of risk and the level of taking precautions was situation-dependent. - 10%: tolerant of risk and consequently took fewer precautions.
Monks et al. 2010 (42)	Qualitative interview study Time frame: October 2008 and April 2009 - N = 18 - With a doctor-diagnosed FA - Age: 11-18 years of age (median 15) - Almost all had co-existing atopic disease - Type of FA: All had peanut or tree nut allergy: Peanut 78%, tree nuts 83%, seafood 6%, egg 17%, soya 6% - Age at onset symptoms FA: not specified Setting: paediatric outpatient clinic, UK		Attitude related to allergen avoidance: - The majority only checked labels of new foods or when they felt unsure. - >75% ate food labelled with 'may contain' labels, and avoid 'may contain' foods depending on the terms. - >50% try foods that might contain an allergen. A few first try a small amount of the product before eating the entire portion. - The majority would take more risks with what they eat in familiar environments, with people they knew or if they had their self-injectable adrenaline ready.

Table 2. Continued

Author, year	Design, participants and setting	Labelling issues related to unexpected reactions	Attitude or behaviour related to unexpected reactions
Sampson et al. 2006 (15)	<p>Retrospective study based on online questionnaire</p> <p>Time frame: not specified</p> <ul style="list-style-type: none"> - N = 174 patients - Age: 13-21 years - Diagnosed: self-reported FA - Type of FA: peanut 75%; tree nut 56%; shellfish 21%; milk 20%; egg 16%; fish 14% - Age at onset symptoms FA: not specified <p>Setting: Cambridge, Massachusetts, Minneapolis and Minnesota, USA</p>		<p>Reading labels:</p> <ul style="list-style-type: none"> - 64% always - 18% most of the time - 4% half of the time or less <p>Frequency of avoiding food with precautionary labelling: 58% avoid the food, 5% eat these foods because they believe the risk is low, 19% eat it because they had no prior reactions when doing so, 13% tasted it and continued to eat it if they had no symptoms.</p> <p>Risk taking behaviour:</p> <ul style="list-style-type: none"> - 54% ate at least a tiny amount of a food known contain allergen - 17% did this a few times a month or more, 44% a few times a year, 39% once or twice in their lifetime <p>Reasons for risk taking behaviour:</p> <ul style="list-style-type: none"> - 57%: that similar foods had not caused a reaction - 49%: "it looked good and I wanted to eat it" - 3%: presence of "may contain" label - 23%: did not want to ask about ingredients - 23%: "hanging out" with friends - 23%: testing to see if still allergic - 18%: "all of my friends were eating the food"
Vierk et al. 2007 (32)	<p>Population-based retrospective random digit-dial survey study</p> <p>Time frame: April to august 2001</p> <ul style="list-style-type: none"> - N = 750 - Age: > 18 years of age - Diagnosed: 63% self-reported FA, 37% reported having a doctor-diagnosed FA - Type of FA: milk/dairy: 23%, fish: 8%, eggs: 7%, crustaceans 7%, tree nuts: 7%, wheat/gluten: 6%, peanuts: 7%, soy: 1%, fruit/vegetable: 32%, shellfish: 17%, chocolate: 6%, food additive: 6% - Age at onset symptoms FA: 0-2 jaar: 5%, 3-9 jaar: 19%, 10-19 jaar: 22%, 20-29 jaar: 20%, 30-39 jaar: 16%, 40-49 jaar: 10%, >50 jaar: 6% <p>Setting: USA</p>	<p>Labelling issues:</p> <ul style="list-style-type: none"> - 63% of patients with self-reported FA and 77% of patients with doctor-diagnosed FA read labels to avoid foods to which they were allergic. - Around 40% of FA patients reading labels found various label issues which are a very serious problem for managing their disease. <p>These label issues were:</p> <ul style="list-style-type: none"> - 40-44% readability problems - 40% problems with interpretation - 30% problems related to clarity 	

Table 2. Continued

Author, year	Design, participants and setting	Labelling issues related to unexpected reactions	Attitude or behaviour related to unexpected reactions
Voordouw et al. 2009 (43)	<p>Qualitative study based on observations and interviews</p> <p>Time frame: not specified</p> <ul style="list-style-type: none"> - N = 40 - Age: adults (50%) and caregivers of children (50%) - Diagnosed: With self-reported, perceived or diagnosed FA - Type of FA: milk (53%), egg (33%) and/or (pea) nuts (65%) - Age at onset symptoms FA: not specified <p>Setting: supermarket in Greece and the Netherlands</p>	<p>Labelling issues were:</p> <ul style="list-style-type: none"> - Readability problems - Clarity problems - Interpretation problems because of insufficient information and in precautionary labelling or changes in recipes 	<p>Risk taking behaviour:</p> <ul style="list-style-type: none"> - Patients with severe allergic reactions were risk adverse. - Patients with less severe reactions take more risks, i.e. used product with precautionary labelling. - People with severe allergies systematically read labels more carefully. - After an allergic reaction to a product, patients would not buy it again for a long period of time. Only young adolescents were willing to 'take the risk'.

Abbreviations: FA, food allergy; UK, United Kingdom; USA, United States of America; SPT, skin prick test

Quality of the studies and potential risk on bias

The observational studies, assessed with STROBE (17), had an average score of seventeen out of twenty-two items, with a range of thirteen to twenty-one. Most articles clearly described the rationale and objective of the study, the study population, data measurements and outcomes. Less than half of the studies reported about potential sources of bias in the methods section, how the study size was arranged, reasons for non-participation and funding. Seven studies had a self-report questionnaire (15,23,26-29,33). (table 3)

The qualitative studies, assessed with COREQ (18), scored an average of sixteen of the thirty-three items of interest, with a range of eleven to twenty-one. Most articles described the sample, data collection and outcomes. Frequent limitation concerns were lack of information about the personal characteristics of the interviewers and their relationship to the participants. Only three studies gave a minimal description about this domain (39,41,42). None of the studies reported about field notes or carried out repeat interviews to get participant feedback on the finding. Two study reported about non-participation (39,42). Only one study reported about the methodological orientation of the study (41). (table 4)

Overall, the methodological quality of the observational and qualitative studies was moderate.

The moderate methodological quality and differences in designs and outcomes used in the included studies leads to potential risk of bias. Possible selection bias could not be determined when reasons for non-participating and study size were not reported. The use of self-reported questionnaires could have led to information bias or less accurate data.

Participants in the included studies

Characteristics of participants differed in the included studies (Tables 1 and 2). In eight studies the participants were diagnosed by a skin prick test, specific IgE blood test, food challenge and/or evaluated by an allergist or general practitioner (21-24,38,40-42). Nine studies included participants with self-reported food allergy (15,25-27,29,32,33,39,43). In three studies were both participants with doctor-diagnosed food allergy and self-reported food allergy included (28,31,34). In three studies data were collected from a medical database (35-37). Fifteen studies reported about the known food allergies of the participants (15,22,25-28,32-34,38-43). In most of these studies participants with the major allergens peanut (15,25,26,28,32,33,38-43), nuts (15,25-28,32,33,38-43), egg (15,26-28,32,33,39,41-43) and milk allergy (15,26-28,32,33,39,41,43) were included.

Nine studies used a mixed population of adults and caregivers of children with food allergy or children <12 years old (21,23,28-31,33,34,43). However the samples consisted of more than 50% of patients >12 years (23,28,29,34,43), or it was possible to distinguish the

Table 3. STROBE checklist for observational research

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Titel and abstract																	
1. Title & abstract	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Introduction																	
2. Background & rationale	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3. Objective	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Methods																	
4. Study design	1	0	0	1	0	1	1	1	1	1	0	0	0	1	1	1	1
5. Setting	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
6. Participants	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
7. Variables	0	0	0	1	0	1	1	0	1	0	1	0	0	0	0	1	1
8. Data sources & measurements	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1
9. Potential sources of bias	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0	1	0
10. Study size	1	1	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0
11. Quantitative variables	1	0	1	0	0	1	0	1	0	0	1	1	1	1	0	1	1
12. Statistical methods	0	0	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1
Results																	
13a. Report numbers of participants	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
13b. Reasons for non-participation	0	-	0	-	0	0	0	0	0	1	-	0	0	0	0	1	1
14. Descriptive data	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1
15. Outcome data	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
16. Main results	1	0	1	0	0	1	0	1	1	0	0	0	1	1	0	1	1
17. Other analyses	-	-	-	-	1	1	0	0	1	-	-	-	-	-	0	-	-
Discussion																	
18. Key results	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1
19. Limitations	0	0	1	1	0	1	0	1	1	0	1	0	1	1	1	1	1
20. Interpretations	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
21. Generalisability	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1
Other Information																	
22. Funding	0	0	0	1	1	0	0	1	1	0	0	0	1	1	1	1	0
Total score	16	13	16	16	15	18	14	19	20	15	18	14	18	17	15	21	19

Legend: 0 = not described, 1 = described, - = not applicable

1. Añibarro et al. (2007) (24), 2. Bock et al. (2001) (36) & Bock et al. (2007) (35) (articles used the same methodology), 3. Comstock et al. (2008) (25), 4. De Swert et al. (2008) (21), 5. Eriksson et al. (2003) (33), 6. Greenshaw et al. (2009) (26), 7. Kalogeromitros et al. (2005) (22), 8. Kalogeromitros et al. (2013) (27), 9. Kanny et al. (2001) (28), 10. Lämmel & Schnadt (2009) (29), 11. Liew et al. (2009) (30), 12. Malmheden (2004) (37), 13. Mullins (2003) (23), 14. Sampson et al. (2006) (15), 15. Schnadt (2009) (31), 16. Sicherer et al. (2004) (34), 17. Vierk et al. (2007) (32)

Table 4. COREQ checklist for qualitative research

Study	1	2	3	4	5	6
Research team and reflexivity						
1. Interviewer / facilitator	0	1	0	1	1	0
2. Credentials	0	0	0	0	0	0
3. Occupation	0	1	0	0	1	0
4. Gender	0	1	0	0	0	0
5. Experience and training	0	0	0	0	0	0
6. Relationship established	0	0	0	0	0	0
7. Participant knowledge of the interviewer	0	0	0	0	0	0
8. Interviewer characteristics	0	0	0	0	0	0
Study design						
9. Methodological orientation and theory	0	0	0	1	0	0
10. Sampling	1	1	0	0	1	0
11. Method of approach	0	1	1	1	0	0
12. Sample size	1	1	1	1	1	1
13. Non-participation	0	1	0	0	1	0
14. Setting of data-collection	1	1	0	1	1	1
15. Presence of non-participants	0	1	0	0	1	0
16. Description of sample	1	1	1	0	1	1
17. Interview guide	1	1	1	1	1	0
18. Repeat interviews	0	0	0	0	0	0
19. Audio / visual recording	1	1	1	1	1	1
20. Field notes	0	0	0	0	0	0
21. Duration	0	1	1	1	1	0
22. Data saturation	0	1	0	1	1	0
23. Transcripts returned	0	0	0	1	0	0
Analysis and findings						
24. Number of data coders	1	1	1	1	1	1
25. Description of the coding tree	0	0	1	0	1	0
26. Derivation of themes	1	1	1	1	1	1
28. Software	1	1	1	0	1	1
29. Participant checking reporting	0	0	0	0	0	0
30. Quotations presented	1	1	1	1	1	1
31. Data and findings consistent	1	1	1	1	1	1
32. Clarity of major themes	1	1	1	1	1	1
33. Clarity of minor themes	1	1	1	1	1	1
Total score	13	21	14	16	20	11

Legend: 0 = not described, 1 = described

1. Barnett et al. (38), 2. Gallagher et al. (39), 3. Leftwich et al. (40), 4. MacKenzie et al. (41), 5. Monks et al. (42), 6. Voordouw et al. (43)

data of the sample >12 years from the other data (21,30,31,33). Finally, of four studies we only used the data of teenagers (15,39,41,42).

Frequency and severity of unexpected reactions

Little is known about the frequency of unexpected reactions in patients with a known food allergy and all studies describe different parameters, making it difficult to elucidate the frequency among different populations. Añíbarro (24) studied unexpected reactions due to hidden allergens in a sample of 436 patients over a 5-year period and showed a mean of 1.98 (range 1-10) unexpected reactions per patient. Comstock (25) reported about allergic reactions aboard airliners. Among 471 patients with peanut, tree nut or seed allergy, 9% reported reactions during a flight, of which 10% had more than one reaction (25). Kanny (28) and Sicherer (34) reported that 53%-58% had recurrent reactions, whereof 12%-20% had more than six recurrent reactions. Kalogeromitros (22) studied patients with allergy to grape. Among 11 patients, all had recurrent reaction, but none more than 6 reactions. Kalogeromitros (27) reported that 75% had a recurrent reaction, after re-exposure to a suspected allergic food.

Four studies (30,35-37) reported about fatalities due to food allergy. Bock described in 2001 and 2007, 26 and 23 fatal reactions, respectively, in patients older than 12 years of age over a five year period (35,36). Liew (30) described 3 fatal reactions in patients of older than 10 years of age over a 9-year period. Malmheden (37) reported 6 fatal reactions; three of which were older than 15 years.

The severity of unexpected reactions varied within and between the studies ranging from mild, local complaints (Mueller 0) to severe, vascular complaints (Mueller 4) (21,22,24-26,29,31,33,37). In addition, Comstock (25) and Añíbarro (24) showed percentages of the most severe symptom of a reactions, where 4% and 32%, respectively, were classified as Mueller 4. Three studies reported about treatment of the allergic reactions with emergency medication (21,22,25). In 58% (25) to 100% (21) emergency medication was used (Table 1).

Causes and location of unexpected reactions

The most frequent causes of unexpected reactions were the result of inadvertent ingestion of peanuts, nuts, vegetables/fruit, egg and milk (21-26,29-31,33,35-37). However the allergens fish, shell fish, soy and seeds were also mentioned in more than one study (23-26,29-31,35,37). Peanut and nuts were most often associated with severe reactions (23,26,30,35-37). In four studies, fatal reactions were reported, whereof in three studies peanut was the most frequent cause of fatal reactions (30,35,36).

Unexpected reactions took place in restaurants (21-31%), at school or work (13-23%), at friends' houses (12-35%) or at home (26-37%) (Table 1).

In most studies, unexpected reactions occurred because patients ingested food containing the allergen. However, Comstock (25) and Eriksson (33) also reported unexpected reactions by inhalation or indirect contact as kissing.

Labelling issues related to unexpected allergic reactions

Unexpected reactions could also be related to the way of food labelling. Labelling issues can be divided into three categories, namely readability, clarity and interpretation of labels (29,32,38,43). Readability problems, like the use of difficult words or terms or a number of languages without the national language of the consumer, were mentioned by 40% (32) to 70% (29) of the patients (43). Clarity issues were due to the layout of the ingredients list or allergy advice box, the amount of information and the changes of recipes (32,43), were reported by 30% (32) of the patients.

Interpretation issues like the interpretation of precautionary or so-called 'may contain' labelling (29,32,38,43), were reported by 40% (32) to 85% (29) of the patients (Table 2).

Attitude and behaviour and unexpected allergic reactions

Attitude and behaviour are clearly related to the occurrence of unexpected reactions in patients with a known food allergy. This seems to be influenced by the severity of symptoms (Table 2).

According to Barnett (38), patients estimate the risk of a product based on product brand or name and prior experiences with that product or brand. When this strategy does not lead to a confident decision, printed packet information is used. Patients with severe allergic reactions seemed to take less risk than patients with less severe or inconsistent symptoms (26,43). According to Lämmel (29), 82% of allergic individuals surveyed would not buy a product that may contain the allergen, however; it was not studied whether severity of earlier reactions played a role. Greenhawt (26) reported that 60% of allergic individuals surveyed did not always avoid a product with the allergen: but a higher proportion of students (57%) with less severe symptoms indicated eating food containing the allergen versus 42% of students with a prior history of anaphylaxis.

Four studies specifically addressed attitude and risk taking behaviour of food allergic individuals during puberty and adolescence (11-21 years), the majority of which had a peanut or tree nut allergy (15,39,41,42). These studies reported that teenagers and adolescents take risks with precautionary labelled food (15,39,41,42). Mackenzie (41) and

Sampson (15) showed that not more than 43% to 64% always read labels, were very strict in managing their food allergy and avoided food with precautionary labelling; thereby severity of symptoms and the risk of an unexpected reaction seem to play a role. In another study it was reported that more than 75% of allergic individuals surveyed consumed food with 'may contain' labelling (42). Gallager (39) reported that all adolescents attempt to avoid allergen by checking the label. Reasons for risk taking behaviour among students (26) and teenagers (15) can be summarized as: no previous severe symptoms or inconsistent symptoms, the possibility to self-treat reactions, lack of concern and social circumstances.

In managing their risks, patients with peanut or tree nut allergy are balancing between communication and fear of potential social embarrassment to disclosure of their allergic status (40). Patients restrict themselves in terms of eating out (39,40) and foreign travel (39). Patients avoided particular restaurants that were considered to pose a high risk through self-evident and hidden presence of nuts, and sought familiarity to reduce uncertainty and risks. In addition, availability of medical care nearby played a role in their decision making (40). Teenagers felt that other people could not be trusted to take precautions on their behalf (41).

Discussion

Most food allergic patients are confronted with unexpected allergic reactions to food. Seven studies investigated the frequency of unexpected reactions, but results differ because studies used different time periods and figures were reported in different ways. Peanuts, nuts, vegetables/fruit, egg and milk are the main causal foods. Severe reactions and even fatalities occur. Many reactions occur in patients with a well-known food allergy and with products known to be at risk. A major factor attributing to the risk of unexpected allergic reactions is the eating location. Most reactions take place at home, but a significant number also take place when eating at friends' houses or in restaurants. But also labelling issues, and attitude and risky behaviour of patients play an important role.

This systematic review gives a state-of-the art overview of current knowledge of unexpected reactions to food, using an extensive search strategy in six relevant databases. However, generalizability of the results is limited because of the heterogeneity of study populations and methodology and potential bias due to moderate methodological quality. However, we still feel that it is possible to draw important conclusions. Some studies included participants with self-reported food allergy (15,25-27,29,32,33,39,43); while other studies only included people with a doctor diagnosed allergy (21-24,38,40-42,44). It is known that the self-reported rate of food allergy varies from 1% to 35% (45) in contrast to 3% after doctor diagnosis using the double blind food challenge which is the gold standard

(46). Inclusion of patients with self-reported food allergies as well as lack of information about non responders and lack of information about sample size calculation could have led to selection bias in individual studies. This could therefore result in a lower generalizability of our outcomes for the population of patients with a doctor-diagnosed food allergy. It was not possible to analyze if the frequency and severity of reactions differs between studies of patients with self-report versus doctors-diagnosed food allergy, because in none of these studies all patients were diagnosed by food challenge.

The included studies used different ways of classification of severity. To make it easier to compare the results, we classified the severity of the reactions with the adapted version of the Mueller classification (19,20). However, it remained hard to compare the results. A third limitation is the lack of prospective studies with a quantitative design. Most studies used a retrospective or cross-sectional design with self-reported data. It is often hard for patients to remember the exact frequency and severity of their allergic reactions. This increased the risk of recall bias and information bias.

Figures about the frequency of unexpected reactions to food were reported in different ways. Some authors described reactions on specific foods (22,25,34), sometimes in a specific environment, like during flight (25) and others only described fatal reactions (30,35,36). Besides, some studies reported about the actual percentage of patients with recurrent reactions (25,27,34), while others reported the number of unexpected reactions with sometimes the percentage of patients (22,24,28,35,36). For example, Sicherer (34) reported that 58% had a recurrent reaction on sea food; while Añíbarro (26) showed a frequency of two reactions per patient over 5 years. Therefore it is not possible to make a very precise conclusion about the frequency of unexpected reactions. Nevertheless, these data clearly illustrate that unexpected reactions are a significant problem.

The severity of unexpected reactions varied between the included studies. However it can be concluded that severe reactions do occur frequently; varying from 16-96% of the reactions (Table 1) and even fatalities are reported. The one study suggesting that 96% of unexpected reactions are severe (22), included only eleven patients with doctor-diagnosed reactions, which is likely a significant over-estimation of severe reactions due to the limited sample size and selection bias. It might be that there is an underestimation of mild reactions, which might be easier forgotten than severe reactions, increasing the risk of recall bias.

Peanuts, nuts, egg and milk seem to be the most frequent cause of unexpected reactions, which is probably due to the frequency of these food allergies and the fact that these allergens are frequently used in prepared foods (47). Moreover, cross contamination during production of packaged food products can occasionally occur (47).

Unexpected reactions occur at home regularly, for example due to errors in preparation, cross contamination (48) and a variety of problems in readability and clarity

of food labeling. Information on food labels is overwhelming (43), products with advisory labels with tree nut frequently do not specify the type of tree nut, and nonspecific terms (such as spices and natural flavors) are frequently used but are not linked to an allergen or ingredient, in case they do not belong to the 14 allergens to be labeled (49). Besides the compulsory information about allergens on labels, 17-65% of all manufactured food products, contains precautionary labels (49,50). Chocolate, candy and cookies have such a description on more than 50% of the labels (49). But only 10% of the packaged products (2) and 25% of the packaged cookies/chocolates (51) with a precautionary statement about peanuts had a detectable level of this allergen. Such an unwanted restriction of food choices can seriously affect the quality of life (50). In addition, products can contain undeclared allergen concentration reaching levels that trigger allergic reactions (52).

Unexpected reactions often occur in restaurants. This is not surprising, because restaurant personnel deal with a large number of different and potentially allergenic foods in the same facility which could lead to cross contamination during food preparation (53). Moreover, there are deficits in their knowledge about how to provide safe meals to allergic consumers (54).

Also attitude influences the risk of unexpected reactions. Not everyone is as strict in avoiding allergens (15,26,29,41,42). The percentage of patient with risk taking behavior differs between the included studies, and to some extent it depends on disease severity (15,43), the possibility to self-treat reactions or patients' estimation if it is a risky action (26,39). Allergic individuals regularly feel embarrassed about their allergy (40). Therefore they sometimes prefer to take risks instead of asking the restaurant or retail staff about the presence of allergens in food (40). Teenagers and adolescents might show risk-taking behavior more often than adults (41,43). This is consistent with two studies which reported that teenagers are at the greatest risk of food induced anaphylaxis (36,55); Bock (36) showed that among 32 fatalities, 69% occurred in patients aged between 13 and 21 years. It is reported that adolescence is a period of heightened vulnerability to risk taking behavior because of a disjunction between novelty and sensation seeking (both of which increase dramatically at puberty) and the development of self-regulatory competence (which does not fully mature until early adulthood) (56).

To conclude, the exact frequency is not known but unexpected reactions to food occur in a significant number of patients and can be severe and even fatal. Major factors contributing to the risk of unexpected reactions are eating location, labeling issues and attitude and risk taking behavior of patients.

For clinical practice, this means that patient education about the risks of unexpected reactions, emergency medication and instructions when and how to use it are essential and preferably should be tailored to the specific age groups. Moreover, dietary instructions on how to read labels and how to deal with may contain labeling are necessary. Further, attention to

develop a more transparent way of precautionary labeling is needed. In Australia and New Zealand the Vital (Voluntary Incidental Trace Allergen Labelling) system is in use which is a promising approach to address this issue (57). Prospective studies are needed to get more insight in the frequency, severity, quantity of unintended allergen ingested and causes of unexpected allergic reactions to food, to be able to optimize strategies to support patients in dealing with their food allergy; to prevent unexpected reactions as much as possible and to increase awareness and knowledge in food industry and among retail and restaurant staff.

Acknowledgement

A. Versluis, A.C. Knulst, A. Michelsen, J.L. Baumert and H. van Os- Medendorp declared to have no conflicts of interest which are relevant for the subject of this study. A. kruizinga en G. Houben participated in this study within the framework of the Food Safety Knowledge Development programme of TNO, with financial support of the Dutch Ministry of Health.

Funding

Declaration of all sources of funding for the research reported in the manuscript: none declared.

Conflicts of interest

The authors declare no conflict of interest.

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CHAPTER 3

ACCIDENTAL FOOD ALLERGIC REACTIONS ARE ASSOCIATED WITH HIGHER COSTS AND MORE SICK LEAVE BUT NOT WITH QUALITY OF LIFE

Astrid Versluis, André C. Knulst, Anouska D. Michelsen- Huisman,
Geert F. Houben, W. Marty Blom, Thuy-My Le, Harmieke van Os-Medendorp

Published as a letter to the editor in Clin Exp Allergy. 2021;51(4):627-630.

Abstract

Background

A large proportion of the food allergic patients experiences accidental allergic reactions yearly. However, little is known about the impact on economic costs and health related quality of life (HRQL) of accidental allergic reactions.

Objective

To investigate the influence of accidental food allergic reactions on costs, sick leave and HRQL in adult patients.

Methods

In this prospective cohort study, adults with a doctor-diagnosed food allergy were included. Accidental allergic reactions were recorded over a one-year period. At baseline and 12 months patients completed the Food Allergy Quality of Life Questionnaire-Adult Form and RAND-36. The Food Allergy Economic Questionnaire and EQ-5D-3L was completed at 12 months.

Results

Forty-six patients were included, whereof 78% (36/46) experienced a total of 121 accidental allergic reactions during the one-year follow-up. Patients with reactions had sevenfold higher total yearly direct and indirect costs than patients without reactions (mean €1186 (bootstrap 95% CI: €609-1845) vs €158 (bootstrap 95% CI: €68-266), $p=0.01$). Patients with reactions had, on average, higher costs than patients without reactions in all subcategories: primary care consultations, outpatient consultations, hospital admissions, travel costs to health care facilities and sick leave costs due to accidental allergic reactions. Of all patients who experienced reactions, 22% experienced ≥ 1 reactions leading to sick leave. There was no difference in food allergy specific and generic HRQL between patients with and without reactions at baseline, nor after one year follow-up.

Conclusions

Accidental allergic reactions are associated with higher direct and indirect costs and more sick leave, but not with HRQL.

Introduction

The prevalence of food allergy diagnosed by clinical history and positive serology in adults across Europe ranges from 0.3-6% (1). Food allergic patients are advised to follow an elimination diet. However, even when strictly following an elimination diet, many patients are confronted with accidental allergic reactions (2). An important cause of accidental allergic reactions are labelling issues, but also the attitude and risky behavior of patients (2-4). A previous prospective study with one year follow-up showed that 46% of patients had accidental allergic reactions that were moderate-severe in 78% of the reactions (2). Since such a large part of food allergic patients have accidental allergic reactions which are moderate/severe and potentially require treatment, medical help or hospitalization, this can have a high impact on economic costs. And not only on direct health costs, but also on indirect costs due to sick leave from work. It is known that food allergy is associated with higher economic costs (5-7). A previous study in Europe showed a difference of mean annual costs over one year of I\$927 international dollars comparing people with food allergy (mean annual costs: I\$2016) and those without food allergy (mean annual costs: I\$1089) (7). The economic impact of food allergy is mainly due to health care costs and lost opportunity costs (e.g. due to lost labor) (5,6). Costs for patients with severe food allergy are higher compared with patients with mild food allergy (7). However, there is lack of information about the impact of accidental food allergic reactions to economic costs. Understanding the economic costs of a disease is important to development of effective and efficient health care policies and guidelines (8).

Besides the possible impact of accidental allergic reactions on economic costs, they might also influence the health-related quality of life (HRQL) because patients for example live with a constant vigilance due to the risk of accidental reactions and experience restrictions in social activities. It has been shown that having food allergy is a significant burden for patients and impairs health-related quality of life (9). Multiple factors contribute to the impairment of HRQL, for example dietary restrictions, severity of food allergy, type of food allergy, having multiple food allergies, emergency treatment used and sociodemographic factors (10-12). Although the impact of having food allergy has been studied intensively, it is unknown to what extent the manifestation of accidental allergic reactions contribute to the burden of food allergy.

Since accidental allergic reactions regularly occur in food allergic adults (2), it is important to have insight into the impact of these reactions on costs, sick leave and HRQL. Therefore, we investigated the influence of accidental allergic reactions during one year on costs, sick leave and HRQL in adult patients with a doctor-diagnosed food allergy.

Methods

Study design, setting, study population and ethics

A prospective cohort study with one year follow-up was conducted at the Department of Allergology/Dermatology, a tertiary referral center for food allergy in the Netherlands. Inclusion of patients took place from 2016 to 2017. This study was part of a larger study (13) which focused on the food consumption of 73 doctor-diagnosed food allergic patients who had a food allergy for peanut, hazelnut, milk and/or hen's egg. We included those patients who completed the Food Allergy Socio-Economic Questionnaire (FA-ECOQ) after 12 months.

All patients gave written informed consent prior to inclusion. The local Medical Ethics Review Committee confirmed at 5 July 2016 that the Medical Research Involving Human Patients Act (WMO) did not apply to the study (protocol number: 16/421).

Outcome measures and data collection

Outcome measures were mean yearly direct and indirect costs, sick leave and HRQL.

Patients had to report every accidental allergic reaction to food during one year, using an online questionnaire. Each reported reaction was reviewed by the research team determining whether the reaction was compatible with a food allergic reaction. Furthermore, patients had to complete the baseline questionnaire, regarding patient characteristics; the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF) (14) and the RAND-36 (15) at baseline and after 12 months and the FA-ECOQ (16) and EQ-5D-3L (16) after 12 months. The Dutch validated versions of the FAQLQ-AF, RAND-36 and FA-ECOQ were used (14-16).

The online questionnaire about accidental allergic reactions consisted of items about the causes, severity and sick leave due to the accidental reaction. The severity of allergic reactions was classified using an adapted version of the Mueller severity score: local oral symptoms (Mueller 0) were classified as being mild, symptoms from skin and mucous membranes and/or gastro-intestinal tract (Mueller 1-2) were classified as being moderate and respiratory and/or cardiovascular symptoms (Mueller 3-4) were classified as being severe (17,18).

The FAQLQ-AF consisted of four domains (Risk of accidental exposure, Emotional impact, Allergen avoidance-dietary restrictions and Food allergy-related health) including 29 items about food allergy specific HRQL. The total score ranged from 1 'no impairment' to 7 'maximal impairment' (14). The minimal clinically important difference (MCID) was 0.5 (19).

The RAND-36 consisted of eight health concepts (Physical functioning, Social functioning, Physical role limitations, Emotional role limitations, Mental health, Vitality, Pain, General health and Health change), including 36 questions about generic HRQL. The

total score ranged from 0 "maximum disability" to 100 "no disability"(15). The minimal clinically important difference (MCID) is 3-5 (20).

The FA-ECOQ measured direct and indirect costs (16). Costs were calculated based on the Dutch guidelines for economic evaluations in health care (21) and were corrected for inflation using the consumer price index for 2017 (22). (supplemental table 1) Direct costs included costs for primary care consultation, outpatient consultations, hospital admissions, travel costs to health care facilities for all purposes and indirect costs included costs for sick leave due to accidental allergic reactions.

The EQ-5D-3L measures health status and consisted of five dimension: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain had three levels: no problems (level 1), some problems (level 2) and extreme problems (levels 3) (23).

Analysis

In this study 46 patients were included, which was a subgroup of a larger study (13). In the main study a sample size of 70-80 patients was determined to be representative for the aim of the main study; ultimately 73 patients were included (13). For the current study no further sample size calculation was performed.

The FAQLQ-AF, RAND-36 and FA-ECOQ scores were calculated using standardized methods (14-16,23). For outcome data regarding yearly direct and indirect costs, the mean and 95% bootstrap confidence interval were calculated.

Outcome data regarding sick leave due to accidental allergic reactions and HRQL were analyzed using descriptive statistics. To calculate duration of sick leave, the shortest possible duration per answer option (answer options: a few hours, 1 day, 2 days, >2 days) was used (e.g. for answer option >2 days, we assumed 3 days). Based on level of measurement, frequencies (n/%) or median (bootstrap 95% confidence interval) were used.

Differences regarding total yearly direct, indirect and intangible costs, sick leave due to accidental allergic reactions and HRQL (The food allergy specific (total score and domain Risk of accidental exposure) and generic (total score per dimension) HRQL) between patients with and without accidental allergic reactions were analyzed using descriptive statistics and the Mann-Whitney u test. A p-value <0.05 was considered statistically significant.

Data were analyzed using IBM SPSS Statistics 25 (IBM Corporation, Armonk, NY, USA).

Results

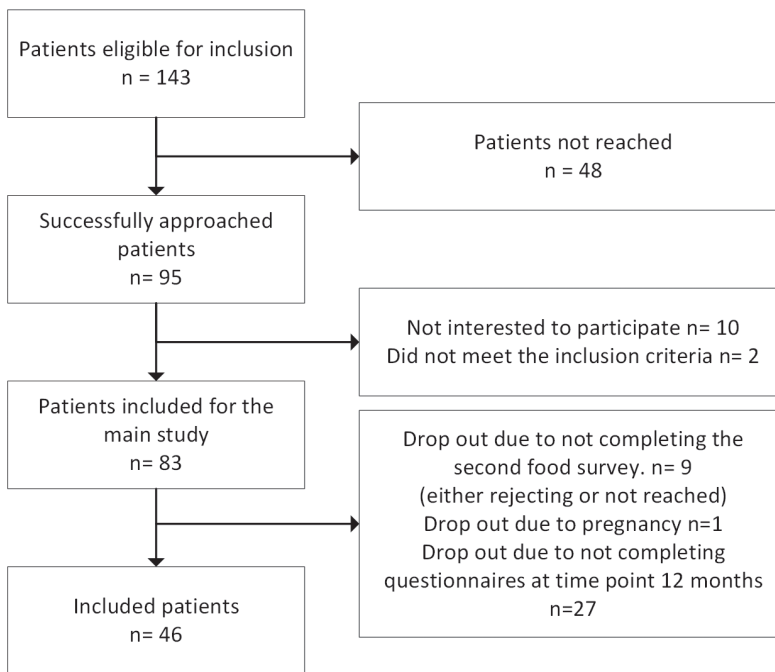
Patient characteristics

In total, 46 patients were included in this study (figure 1). A majority of patients were female (76%, 35/46) and the mean age was 42 years (SD: ±13). Characteristics of the included

patients are shown in table 1. The most common food allergies at baseline were for tree nuts (76%, 35/46), peanut (70%, 32/46) and fruit (52%, 24/46). In 87% (40/46), patients had been diagnosed with a severe food allergy. Most patients already had food allergy for an extended period (mean: 24 years, SD: ± 11 , min-max: 2-50).

A total of 121 accidental allergic reactions were reported during the 1-year follow-up. Of all patients, 78% (36/46) experienced one or more accidental allergic reactions (range: 1-19) during the 1-year follow-up, with varying severity: 22% (27/121) mild, 59% (71/121) moderate and 19% (23/121) severe.

Figure 1. Flowchart of patient inclusion and drop out



Accidental allergic reactions are associated with strongly increased costs

Patients with accidental allergic reactions during the one-year follow-up had higher total yearly direct and indirect costs compared to patients without accidental allergic reactions (mean €1186 (bootstrap 95% CI: €609-1845) vs €158 (bootstrap 95% CI: €68-266), $p=0.01$). In all subcategories (primary care consultations, outpatient consultations, hospital admissions, travel costs to health care facilities and sick leave costs due to accidental reactions) patients with reactions during 1 year follow-up had higher costs than patients without reactions. (table 2)

Table 1. Patient characteristics

	All patients n=46	Patients with reactions n=36	Patients without reactions n=10
	n (%)	n (%)	n (%)
Gender: female	35 (76)	30 (83)	5 (50)
Mean age, in years (SD, min-max)	42 (13, 24-69)	42 (12, 24-67)	43 (16, 26-69)
Education ^a :			
- Low	3 (7)	2 (6)	1 (10)
- Medium	11 (24)	9 (25)	2 (20)
- High	32 (70)	25 (69)	7 (70)
Atopic comorbidities:			
- Allergic rhinitis	38 (83)	30 (83)	8 (80)
- Asthma (missing: n=1)	31 (69)	23 (66)	8 (80)
- Atopic dermatitis (missing: n=1)	33 (73)	30 (86)	3 (30)
Food allergy for:			
- Tree nuts	35 (76)	28 (78)	7 (70)
- Peanut	32 (70)	25 (69)	7 (70)
- Fruit	24 (52)	19 (53)	5 (50)
- Hen's egg	17 (37)	15 (42)	2 (20)
- Cow's milk	16 (35)	14 (39)	2 (20)
- Vegetables	13 (28)	11 (31)	2 (20)
- Soy	8 (17)	6 (16)	2 (20)
- Celery	7 (15)	6 (17)	1 (10)
- Sesame	5 (11)	4 (11)	1 (10)
- Fish, crustaceans and/or molluscs	2 (4)	1 (3)	1 (10)
- Lupin	2 (4)	2 (6)	0 (0)
- Other food allergies	3 (7)	3 (8)	0 (0)
Mean number of confirmed food allergies (SD, min-max) ^b	5 (2, 1-11)	5 (2, 1-11)	4 (3, 1-11)
Years of having food allergy (SD, min-max)	24 (11, 2-50)	24 (11, 2-50)	25 (13, 2-38)
Most severe previous reaction:			
- Mild (Mueller ^c 0)	1 (2)	1 (3)	0 (0)
- Moderate (Mueller 1-2)	5 (11)	4 (11)	1 (10)
- Severe (Mueller 3-4)	40 (87)	31 (86)	9 (90)

^a Educational level: low, elementary education; medium, high school or middle-level applied education; high, higher professional or academic education;

^b Fruit, vegetables, other food allergy each considered as 1.

^c Reactions with local oral allergy symptoms (Mueller 0) were classified as being mild, reactions with symptoms from skin and mucous membranes (Mueller 1) and/or gastro-intestinal tract (Mueller 2) were classified as moderate and reactions with respiratory symptoms (Mueller 3) and/or cardiovascular symptoms (Mueller 4) were classified as being severe (17,18)

The total yearly direct and indirect costs in patients with accidental allergic reactions showed in 3/36 cases extreme values, which was explained by relatively high costs for hospital admissions in two patients and by higher costs for primary care consultations and outpatient consultations for one patient (supplemental table 2). When excluding these three

patients with extreme values, the total yearly direct and indirect costs were still significantly higher in patients with accidental allergic reactions compared to patients without accidental allergic reactions (mean €673 (bootstrap 95% CI: €414-967) vs €158 (bootstrap 95% CI: €69-280)), $p=0.03$).

With regard to intangible costs, patients with accidental allergic reactions reported more problems on all EQ-5D dimensions compared to patients without accidental allergic reactions: mobility (19% vs 0%), self-care (6% vs 0%), usual activities (28% vs 0%), pain/discomfort (50% vs 20%) and anxiety/depression (19% vs 0%).

Table 2. Mean yearly costs in patients with and without accidental allergic reactions

	Total	Patients with allergic reactions (n=36)	Patients without allergic reactions (n=10)
	Mean (bootstrap 95% CI)	Mean (bootstrap 95% CI)	Mean (bootstrap 95% CI)
<i>Total costs</i>	€962 (505-1476)	€1186 (609-1845)	€158 (68-266)
Direct costs			
<i>Consultations</i>			
Primary care consultations	€360 (179-550)	€443 (233-689)	€64 (34-102)
Outpatient consultations	€270 (114-483)	€322 (124-628)	€81 (17-166)
Hospital admissions	€241 (47-522)	€308 (57-663)	€0 (0-0)
<i>Travel costs to health care facilities</i>	€42 (25-59)	€50 (29-74)	€13 (5-24)
Indirect costs			
<i>Sick leave costs due to accidental allergic reactions</i>	€49 (3-115)	€62 (5-149)	€0 (0-0)
	n (%)	n (%)	n (%)
Intangible costs			
<i>Frequency of reporting problems per EQ-5D dimension^a</i>			
Mobility	7 (15)	7 (19)	0 (0)
Self-care	2 (4)	2 (6)	0 (0)
Usual activities	10 (22)	10 (28)	0 (0)
Pain/discomfort	20 (44)	18 (50)	2 (20)
Anxiety/depression	7 (15)	7 (19)	0 (0)

^aReporting problems: EQ-5D level 2 (some problems) + 3 (extreme problems)

Sick leave due to accidental allergic reactions

Of the patients who experienced accidental allergic reactions, 22% (8/36) reported sick leave due to a total of eleven accidental allergic reactions during the 1-year follow-up: five patients reported sick leave for one reaction and three patients for two reactions. Severity of accidental allergic reactions in which sick leave was reported, was in 8 cases moderate (duration of sick leave: few hours (n=6), one day (n=1), >two days (n=1)) and in 3 cases severe (duration of sick leave: few hours (n=1), one day (n=2)).

Accidental allergic reactions have no evident impact on HRQL

At baseline there was no difference in food allergy specific HRQL between patients with and without accidental allergic reactions. After one year follow-up there was still no difference in food allergy specific HRQL between these two patients groups: total score FAQLQ-AF ($p=0.41$), domain Risk of accidental exposure ($p=0.50$).

At baseline there was no difference in generic HRQL between patients with and without accidental allergic reactions. After one-year follow-up there were still no differences in the dimensions of generic HRQL between patients with and without reactions: physical functioning ($p=0.35$), social functioning ($p=0.17$), physical role limitations ($p=0.25$), emotional role limitations ($p=0.72$), mental health ($p=0.72$), vitality ($p=0.34$), pain ($p=0.13$), general health ($p=0.80$) and health change ($p=0.63$). (table 3).

Table 3. Scores FAQLQ-AF and RAND-36 in patients with and without accidental allergic reactions

	Scores at baseline			Scores after 12 months follow-up			Test of difference between patients with vs without reactions	P-value
	Patients with reactions n=33 (missing: n=3)	Patients without reactions n=10	With reactions n=36	Without reactions n=10	Without reactions n=10	Without reactions n=10		
	Median (bootstrap 95% CI)	Median (bootstrap 95% CI)	Median (bootstrap 95% CI)	Median (bootstrap 95% CI)	Median (bootstrap 95% CI)	Median (bootstrap 95% CI)	P-value	
FAQLQ-AF^a:								
Total score	4.3 (3.9-4.7)	3.2 (2.1-5.1)	4.1 (3.4-4.6)	3.7 (2.4-4.9)	3.7 (2.4-4.9)	3.5 (2.6-4.6)	0.41	
Domain Allergen avoidance-dietary restrictions	4.0 (3.5-4.6)	2.6 (2.2-4.5)	3.8 (3.0-4.5)	3.7 (2.3-4.9)	3.7 (2.3-4.9)	4.2 (2.4-5.8)	0.50	
Domain Emotional impact	4.4 (4.1-4.7)	3.1 (2.0-5.3)	4.2 (3.7-4.7)	3.7 (2.3-4.9)	3.7 (2.3-4.9)	4.2 (2.4-5.8)	0.50	
Domain Risk of accidental exposure	5.0 (4.6-5.6)	4.1 (2.4-6.1)	4.8 (4.4-5.3)	4.2 (3.7-4.7)	4.2 (2.4-5.8)	4.2 (2.4-5.8)	0.50	
Domain Food allergy-related health	3.0 (2.7-3.8)	2.3 (1.7-3.7)	3.0 (2.3-3.5)	3.0 (2.3-3.5)	2.5 (1.8-3.7)	2.5 (1.8-3.7)		
RAND-36^b:								
Physical functioning	100 (90-100)	100 (93-100)	95 (90-100)	98 (90-100)	98 (90-100)	50 (38-50)	0.35	
Social functioning	88 (75-100)	100 (44-100)	50 (50-50)	50 (50-50)	50 (38-50)	100 (100-100)	0.17	
Physical role limitations	100 (75-100)	100 (100-100)	100 (75-100)	100 (75-100)	100 (100-100)	100 (100-100)	0.25	
Emotional role limitations	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	0.72	
Mental health	80 (72-88)	80 (68-88)	60 (60-66)	60 (58-64)	60 (58-64)	50 (43-55)	0.72	
Vitality	60 (55-70)	70 (50-90)	45 (43-50)	45 (43-50)	50 (43-55)	5 (0-10)	0.34	
Pain	90 (84-100)	95 (78-100)	20 (0-22)	20 (0-22)	5 (0-10)	50 (45-55)	0.13	
General health	65 (55-75)	73 (60-78)	50 (50-50)	50 (50-50)	50 (45-55)	50 (50-50)	0.80	
Health change	50 (50-50)	50 (38-50)	50 (50-50)	50 (50-50)	50 (50-50)	50 (50-50)	0.63	

^a The total score ranges from 1 "no impairment" to 7 "maximal impairment". MCID: 0.5

^b The total score ranges from 0 "maximum disability" to 100 "no disability". MCID: 3-5

Discussion

In this study we showed that accidental allergic reactions in food allergic adults are associated with higher direct and indirect costs. Furthermore, during the one-year follow-up, 22% of the patients who experienced one or more accidental allergic reaction leading to sick leave. We found no association of accidental allergic reaction with HRQL.

We found that accidental allergic reactions leads to higher direct and indirect costs. Patients with accidental allergic reactions had on average higher costs than patients without accidental allergic reactions in all subcategories, namely: primary care consultations, outpatient consultations, hospital admissions, travel costs to health care facilities and sick leave costs due to accidental reactions. Literature showed that food allergic patients use more health care services leading to higher health care costs (5-7). Patel et al. (6) reported on economic costs of food-induced allergic reactions in the United States and showed that more than half of the costs come from office-based physician visits and that almost half of the costs come from acute treatment. In our study, primary care consultations, outpatient consultations and hospital admissions were responsible for relatively comparable amounts of costs, whereof the highest costs came from primary care consultations. In addition, in the Netherlands the general practitioner is the gatekeeper to hospital and specialist care, and patients visit a general practitioner just as often as an emergency department in case of accidental food allergic reactions (24). Further, we found that the manifestation of accidental allergic reactions is an important factor that further raises health care costs and even leads to sevenfold higher health care costs than in those patients where no accidental allergic reactions occur. Food allergy is a common disease and almost half of the food allergic people experience one or more accidental reactions yearly (2). Assuming that 2.1% of the Dutch adults has food allergy (1) whereof 46% experiences accidental allergic reactions yearly (2), a rough estimation of the total yearly costs for all food allergic Dutch adult residents with accidental allergic reactions would be 160 million euro and without accidental allergic reactions 25 million euro. This shows the large economic burden of accidental allergic reactions. There are several causes for accidental allergic reactions, e.g. not adequately managing the elimination diet (2), incorrect and confusing food labelling caused by e.g. the limited credibility of precautionary labelling (2,3,25) and misunderstandings in restaurants (2,26). Investment in more preventive strategies to avoid accidental allergic reactions, e.g. by giving more dietary advice and by improving regulation of the food industry and restaurants, seems important to reduce the occurrence of accidental allergic reactions and related economic impact.

We demonstrated that patients with accidental allergic reactions reported more problems with regard to mobility, self-care, usual activities, pain/discomfort and anxiety/

depression compared with patients without accidental allergic reactions. This suggests that patients with accidental allergic reactions might have higher intangible costs. More research with a larger sample size is required to confirm this.

We demonstrated that 22% of the patients who experiences one or more accidental allergic reaction per year reports sick leave due to 1-2 accidental allergic reactions. Previous studies have shown that sick leave due to chronic diseases imposes considerable economic burden on society (27-29). There are interventions which support the maintenance of work for people with chronic diseases, like workplace interventions and coaching self-management of patients (30). Some workplace interventions might also be helpful for food allergic patients and employers, thinking of flexible work hours to facilitate attendance at medical appointments and improving knowledge of employees working in eating facilities at workplaces. There is no literature about the extent to which workplace circumstances contribute to accidental allergic reactions. Coaching self-management is known to be important to handling daily life in patients with food allergy (31,32). Further investigation into the need for and benefits of interventions in workplaces would make a valuable contribution to the current knowledge on this subject.

Literature shows that food allergic patients have an impaired HRQL (9-11). The food allergy specific HRQL in our study population was lower, compared with the Dutch food allergic population showed by Goossens et al. (12) ($p=0.04$). This difference might be caused by the higher percentage of milk allergic patients in our study population compared with Goossens et al. (12) (35% vs 15%), which is known as a predictor for greater HRQL impairment (33). Scores of our study population on generic HRQL were comparable with the Dutch food allergic population (34) with exception of the RAND-36 dimension General health which was less impaired in our study ($p=0.037$). We found that experiencing accidental allergic reactions has no additional impact on HRQL. In our study, most patients had food allergy for a long period (mean: 24 years), which probably led to a relatively stable HRQL.

A limitation of this study was the relatively small sample size. Furthermore, our study population had a relatively high percentage of patients with severe food allergy, which might be caused by our third line population. These limitations restrict the generalizability of the data to the general food allergic population. The results were strengthened by the prospective design, use of validated questionnaires and inclusion of a well-defined patient-set. More research in a larger study population is needed to get more insight in the impact of accidental food allergic reactions on economic costs and HRQL.

In conclusion, accidental allergic reactions are associated with higher direct and indirect costs and more sick leave, but not with HRQL.

Acknowledgements

We like to thank Ms. A.M. van Dijk for help with the data collection.

Author contributions

A.C. Knulst, A.D. Michelsen-Huisman, G.F. Houben, W.M. Blom and H. van Os- Medendorp designed the study. A.D. Michelsen-Huisman and H. van Os-Medendorp collected the data. A. Versluis, A.C. Knulst, T.M. Le and H. van Os-Medendorp, analyzed the data and wrote the manuscript. All authors contributed to interpretation of results and manuscript revision. The final version of the manuscript was approved by all authors.

Conflicts of interest

The authors declare no conflict of interest.

Funding

The main study was funded by the TNO Shared Research Program Food Allergy, a non-profit shared innovation initiative. There was no additional funding for the current study.

Data availability statement

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions.

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Supplemental tables

Supplemental table 1. Overview of reference prices used for calculating costs^a

	Reference price (in euros)
Primary care consultations	
General practitioner	€34
General practitioner, consultation at home	€52
Physiotherapy consultations	€34
Outpatient consultations	
Physicians	€95
Dieticians	€34
Hospital admissions (per day)	
Day care	€287
General hospital	€461
Academic hospital	€668
First aid	€269
Travel costs to health care facilities	
Per kilometer	€0.20
Parking per visit	€1.56

^a Costs were calculated based on the Dutch guidelines for economic evaluations in health care (21) and were corrected for inflation using the consumer price index for 2017 (22)

Supplemental table 2. Details of patients with reactions with relatively high costs

	Patients with reactions		
	Patient 1	Patients 2	Patients 3
Total costs	€7553	€4957	€7951
Primary care consultations: costs (frequency)	€2664 (72)	€1734 (51)	€1820 (53)
Outpatient consultations: costs (frequency)	€4560 (48)	€414 (5)	€1140 (12)
Hospital admissions: costs (frequency in days, ambulance)	€0 (0, 0)	€2672 (4, 0)	€4817 (10, 1)
Travel costs to health care facilities	€329	€137	€174
Costs sick leave due to accidental allergic reactions	€0	€0	€0
Age in years	53	50	61
Number of accidental allergic reactions (Mueller scores)	3 (2, 3, 2)	2 (2,3)	1 (2)
Severity of food allergy (Mueller)	3	4	3
Atopic comorbidity ^a	Yes	Yes	Yes
Food allergy specific HRQLQ (total score FAQLQ-AF) at baseline	3.9	4.5	4.9

^a *pollinosis, asthma and/or atopic dermatitis*



CHAPTER 4

COFACTORS IN ALLERGIC REACTIONS TO FOOD: PHYSICAL EXERCISE AND ALCOHOL ARE THE MOST IMPORTANT

Astrid Versluis, Harmieke van Os-Medendorp, Astrid G. Kruizinga, W. Marty Blom, Geert F. Houben, André C. Knulst

Immun Inflamm Dis. 2016;4(4): 392-400.

Abstract

Introduction

Involvement of cofactors, like physical exercise, alcohol consumption and use of several types of medication, are associated with more severe food allergic symptoms. However, there is limited evidence on how often cofactors play a role in food allergic reactions. The study aimed to get more insight into the frequency of exposure to cofactors and how often cofactors are associated with more severe symptoms in food allergic patients.

Methods

A questionnaire was completed by patients visiting the Allergology outpatient clinic. Patients with food allergy were included. Outcome measures were the frequency of medication use of medication groups that might act as cofactor and the frequency that physical exercise, alcohol consumption and use of analgesics are associated with more severe food allergic symptoms.

Results

Four hundred ninety-six patients were included in the study. The frequency with which patients used one or more types of medication that might act as cofactors was 7.7%: antacids/acid neutralizing medication (5%), NSAIDs (2%), beta blockers (0.6%), angiotensin-converting enzyme inhibitors (0.6%) and angiotensin receptor blockers (0.2%). Of all patients, 13% reported more severe symptoms to food after involvement of one or more of the cofactors: physical exercise (10%), alcohol consumption (5%) and use of analgesics (0.6%). Sixty-five percent did not know if these cofactors caused more severe symptoms; 22% reported that these cofactors had no effect.

Conclusions

Only a small percentage of patients (7.7%) used medication that might aggravate food allergic reactions. Physical exercise and alcohol consumption were the most frequently reported cofactors, but occurring still in only 10% or less.

Introduction

Food allergy is an important health problem. The point prevalence of food allergy is estimated to affect around 1-3% of the European population, assessed by clinical history and IgE and/or food challenge (1). Most food allergic patients are confronted with unexpected allergic reactions despite their avoidance diet (2). Managing avoidance of allergenic food to prevent allergic reactions places a psychological burden on patients and has a negative impact on quality of life (3,4). To help patients in managing their diets, European Union regulations prescribe that the fourteen most frequently used ingredients that can cause hypersensitivity or intolerance must be listed on food labels (5).

It is reported that in some patients with food allergy, allergic reactions are more severe if a cofactor is involved (6,7). EAAI guidelines (8) define cofactors as patient-related or external circumstances that are associated with more severe allergic reactions. Cofactors are in literature also referred to as augmentation-, additional or associated factors (6,7,9). In this study the term cofactor is defined as external circumstances that are associated with more severe allergic symptoms.

Cofactors, such as alcohol, physical exercise, infections and use of some types of medication (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), antacids, acid neutralizing medication, beta blockers, angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs)) might influence the occurrence of allergic reactions (6,7,10,11). Literature reports that cofactors are involved in 25.6% to 39% of the anaphylactic reactions to food in adults (10,12). The underlying mechanisms of cofactor in augmenting food allergic reactions are hardly understood. One suggested mechanism is an increased gastrointestinal absorption of protein, caused by underlying processes like gastrointestinal hyperpermeability after physical exercise or intake of NSAID's, or relaxation of tight junctions in gut epithelium after intake of alcohol (6,7,13-15). For intake of alcohol other mechanisms are suggested as well: 1) alcohol has a direct influence on total IgE levels, which is related to the amount of consumption (7,16,17), 2) some patients probably react to ingredients of alcoholic beverages (7). Other mechanisms suggested with respect to physical exercise are: 1) increased blood circulation leading to increased influx of allergen in the gut (7), 2) basophil activation and increased histamine releasability through lowered pH and increased osmolarity (6,7,13), 3) elevated IL-6 upregulates tissue transglutaminase (tTG) enzymes, resulting in peptide aggregation which leads to increased IgE cross-linking (6,7,13), 4) redistribution of blood that transports the allergen from the gut to skeletal muscle and/or skin where phenotypically different mast cells reside, resulting in an altered mediator release (13).

The available evidence on the frequency of involvement of cofactors and the influence on food allergic reactions is scarce. Besides, most studies have been conducted in patients with severe allergic reactions (10,12,18,19). Further, the results of different studies are not consistent in frequency of involvement of cofactors in food allergic reactions. More evidence on the role of cofactors is important for diagnostics and doctors' advice to patients and on population level to help the food industry and regulatory authorities to design appropriate food safety strategies (6,7,20). The aim of this study was to get more insight into the frequency of exposure to cofactors and how often cofactors are associated with more severe symptoms to food in patients with a doctor diagnosed food allergy.

Methods

Study design, setting, data collection and participants

This was a database study. Patients referred to Allergology outpatient clinic of the University Medical Center Utrecht (UMCU) because of a suspected food allergy, were asked to fill in a one-time questionnaire before the first consultation. The questionnaire consisted of topics about food allergy, atopic comorbidities, medication use and if physical exercise, alcohol consumption and use of analgesics within 2 hour after consumption of the suspected food causes more severe symptoms. The results of this questionnaire and conducted diagnostic tests (skin prick tests (SPT), ImmunoCAP and food challenges) were collected in databases between November 2002 and August 2012.

The study population consisted of patients ≥ 16 years of age with a food allergy. The food allergy diagnosis was established based on patient reported allergic symptoms to food and a positive SPT or ImmunoCAP (conducted within a year before or after the reported symptoms) or food challenge for the same type of food. An exclusion criterion was inability to read or write the Dutch language.

Outcome measures and patient demographics

The first outcome measure was the frequency that patients reported an association between physical exercise, alcohol consumption or use of analgesics with increased severity of allergic symptoms to food.

The second outcome measure was the frequency of medication use from medication groups that are suggested in literature as cofactors; namely antacids/acid neutralizing medication, NSAIDs, beta blockers, ARBs and ACEIs (6,7).

Patient characteristics comprised gender, age, atopic comorbidities (asthma, allergic rhino conjunctivitis and atopic dermatitis), type and severity of food allergy, the mean

number of different food allergies and use of medication that could suppress allergic symptoms (systemic corticosteroids, immunosuppressive drugs, antihistamines, inhaled betamimetics and inhaled corticosteroids). Severity of food allergy was classified according to an adapted version of the Mueller allergy severity grading scale. Reactions with local oral symptoms were classified as Mueller 0; with skin and mucosal symptoms as Mueller 1; with gastrointestinal symptoms as Mueller 2; with respiratory symptoms as Muller 3 and cardiovascular symptoms as Mueller 4 (21,22). The different types of food allergy were divided into the fourteen major food allergies and to fruit, vegetables and other types of food allergy (5). A pulmonologist and dermatologist were consulted to diagnose asthma, allergic rhino conjunctivitis and atopic dermatitis based on the available patients' data and international guidelines (23-25). Patients were considered asthmatic if they (ever) had two or more respiratory complaints (dyspnea, coughing and/or wheezing). Patients were considered to have allergic rhino conjunctivitis if they (ever) had eye- and/or nose complaints during a specific season or allergic symptoms to dogs or cats in combination with a positive sensitization (SPT or ImmunoCAP) to the corresponding aeroallergen. The tree/grass pollen season was set on the months January to August, mugwort season in August and September and dust mites season during the entire year. Patients were considered to have atopic dermatitis if they (ever) had pruritus in combination with two or more of the following criteria: (ever) had xerosis, involvement of classical locations (face/neck, elbow crease and/or on the back of the knees) and personal history of asthma or allergic rhino conjunctivitis.

Study size

In order to include a representative group of the available population of patients with food allergy visiting the Allergology outpatient clinic for the first time over a period of 10 years (estimated at 200 per year in the UMCU) the sample size of that group was calculated using the Raosoft Sample Size calculator (26). With a margin of error of 1%, a confidence level of 95% and a response rate of 50%, 499 new patients should be included.

Statistical methods

IBM SPSS Statistics 21 (IBM Corporation, Armonk, NY, USA) was used for data analysis. Descriptive statistics were used to analyze outcome data. Patient demographics on a categorical scale were analyzed by calculating frequency data (n/percentages) and on a ratio scale by calculating the mean and standard deviation. To analyze differences in the frequency of cofactors between patients with mild or more severe allergic symptoms the

chi square test was used (or the Fisher's exact test in case of small numbers). The use of medication was clustered in groups (antacids/acid neutralizing medication, NSAIDs, beta blockers, ARBs, ACEIs, other types of medication). The frequency with which patients used medication of one of these groups was calculated (n/percentage). The chi-square test was used to assess differences between subgroups of age (or the Fisher's exact test in case of small numbers). Because of the explorative design of the study, a P value < 0.05 was considered statistically significant. Missing data was taken into account by coding them as missing and was excluded from analysis.

Ethics

The local Medical Ethics Review Committee confirmed that the Medical Research Involving Human Patients Act (WMO) does not apply to the study (protocol number: 13-520/C).

Results

Patient characteristics

Of the 1173 patients who filled in the questionnaire, 496 patients with a confirmed food allergy were included. In total, 677 patients were excluded because of not having food allergy (n = 671) or being <16 years of age (n = 6).

The mean age of the included patients was 33 years (SD 12.5). Most patients had allergy to several types of food (mean: 2.9 different foods). Of the major food allergies, the most common were hazelnut (43%) and peanut (38%). The severity of food allergy of patients varied from mild/moderate (Mueller 0-2) in 48% of the patients to severe (Mueller 3-4) in 52%. Of all patients, 88% had one or more atopic comorbidities: asthma (62%), atopic dermatitis (67%) and/or allergic rhino conjunctivitis (74%). Medication that could suppress allergic symptoms was used daily or on demand in 67% of the patients; systemic corticosteroids and/or immunosuppressive drugs (9%), antihistamines (56%), inhaled betamimetics (24%) and inhaled corticosteroids (22%). (tables 1 and 2)

Table 1. Patient characteristics, atopic comorbidities and severity of the most severe food allergy

	n (%) (n = 496)
Gender: female (missing values: n = 3)	349 (70%)
Mean age in years (SD, min-max) (missing values: n = 1)	33 (12.5, 16-79)
Atopic comorbidities	
Asthma, atopic dermatitis and/or allergic rhino conjunctivitis	436 (88%)
Asthma (missing values: n = 12)	302 (62%)
Atopic dermatitis (missing values: n = 52)	232 (67%)
Allergic rhino conjunctivitis (missing values: n = 12)	359 (74%)
Medication that could suppress allergic symptoms (on demand and daily use)	
Uses medication from ≥ 1 of the below medication groups	334 (67%)
Systemic corticosteroids and/or immunosuppressive drugs	46 (9%)
Antihistamines	276 (56%)
Inhaled betamimetics	118 (24%)
Inhaled corticosteroids	108 (22%)
Emergency medication prescribed for food allergy¹	
Antihistamines	299 (60%)
Corticosteroids	72 (15%)
Adrenaline auto-injector	154 (31%)
Emergency medication, type unknown	13 (3%)
No emergency medication	143 (29%)
Severity (Mueller) of the most severe food allergy	
Mueller 0	88 (18%)
Mueller 1	86 (17%)
Mueller 2	64 (13%)
Mueller 3	194 (39%)
Mueller 4	64 (13%)

¹ This data is reported by patients before the first consultation at the outpatient department Allergology.

Table 2. Distribution and mean number of food allergies

Distribution of food allergies		n (%)	Positive CAPs N (min-max, median) (n = 496)	Positive SPTs N (range wheal, median) (n = 496)	n (%) Mueller 0-2 (n = 238)	n (%) Mueller 3-4 (n = 258)
List of 10 out of 14 major food allergens¹						
-	Cow's milk	34 (7%)	31 (0.40-101, 2.02)	11 (1-4, 2)	12 (5%)	22 (9%)
-	Hen's egg	29 (6%)	26 (0.40-101, 2.38)	11 (1-4, 2)	14 (6%)	15 (5%)
-	Peanut	191 (39%)	114 (0.39-101, 4.32)	136 (1-5, 2)	75 (32%)	116 (45%)
-	Tree nuts	283 (57%)				
-	- Hazelnut	212 (43%)	127 (0.36-100, 6.64)	156 (1-4, 2)	93 (39%)	119 (46%)
-	- Almond	125 (25%)	30 (0.4-5.70, 1.69)	105 (1-4, 2)	61 (26%)	64 (25%)
-	- Walnut	115 (23%)	48 (0.4-45.10, 1.95)	84 (1-4, 2)	48 (20%)	67 (26%)
-	- Brazil nut	9 (2%)	9 (0.73-42, 2.68)	Not determined	0	9 (4%)
-	- Pistachio	24 (5%)	24 (0.4-100, 1.44)	Not determined	6 (3%)	18 (7%)
-	- Cashew nut	41 (8%)	28 (0.39-57, 3.55)	23 (1-4, 2)	11 (5%)	30 (12%)
-	Fish ²	4 (1%)			3 (1%)	1 (0.4%)
-	Cod		3 (0.5-10.90, 6.30)	2 (2-4, 3)		
-	Crustaceans ²	29 (6%)			9 (4%)	20 (8%)
-	- Shrimp		21 (0.4-61, 2.23)	16 (1-4, 2)		
-	- Lobster		14 (0.36-55, 2.12)	5 (1-3, 2)		
-	- Crab		13 (0.39-52, 1.70)	6 (1-3, 1)		
-	Sesame	33 (7%)	22 (0.5-82, 4.85)	22 (1-4, 2)	9 (4%)	24 (9%)
-	Soy	46 (9%)	25 (0.4-12.7, 1.14)	33 (1-4, 2)	14 (6%)	32 (12%)
-	Lupin	2 (0.4%)	2 (3.86-19.90, 11.88)	Not determined	1 (0.4%)	1 (0.4%)
-	Celery	36 (7%)	4 (0.5-4.87, 2.33)	34 (1-4, 2)	16 (7%)	20 (8%)
Other allergens, not belonging to the major allergens:						
-	Fruit (all) ³	338 (68%)			175 (74%)	163 (63%)
-	Fruit (top 3):					
-	- Apple	270 (54%)	154 (0.38-58.10, 3.73)	215 (1-5, 3)		
-	- Kiwi	171 (35%)	45 (0.36-31.10, 1.20)	147 (1-5, 3)		
-	- Peach	124 (25%)	40 (0.44-70.20, 2.60)	110 (1-2, 2)		
-	Vegetables (all) ^{3,4}	154 (31%)			72 (30%)	82 (32%)
-	Vegetables (top 3):					
-	- Tomato	82 (17%)	20 (0.4-26.10, 1.55)	73 (1-4, 2)		
-	- Carrot	73 (15%)	17 (0.82-45.2.78)	67 (1-4, 2)		
-	- Paprika	44 (9%)	5 (0.40-3.53, 0.71)	41 (1-3, 2)		

Table 2. Continued

Distribution of food allergies	n (%) All patients (n = 496)	Positive CAPs N (min-max, median) (n = 496)	Positive SPTs N (range wheat, median) (n = 496)	n (%) Mueller 0-2 (n = 238)	n (%) Mueller 3-4 (n = 258)
Other food allergies	6 (1%)			1 (0.4%)	5 (2%)
Mean number of food allergies ³ (SD, min-max)	2.9 (1.87, 1-9)			2.6 (1.74, 1-9)	3.1 (1.95, 1-9)

¹Of the fourteen major allergens sulphur dioxide, cereals containing gluten, molluscs and mustard were not specifically evaluated in the questionnaire. Of the tree nuts, pecan nut and macadamia nut were not specifically addressed in the questionnaire. The questionnaire contained an item 'other food allergies'.

² Allergy to any species

³ Allergy to one or more fruits considered as 1 food allergy, allergy to one or more vegetable(s) considered as 1 food allergy and other food allergies considered as 1 food allergy

⁴ Celery not included

Use of medication in the total food allergic population

Medication use was analyzed to gain insight into the frequency that patients used medication previously suggested in literature as a cofactor.

Of all patients, 7.7% (95% CI: 5-10%) used medication that might act as a cofactor. The most commonly used types of medication were antacids/acid neutralizing medication (5%) and NSAIDs (2.2%). Beta blockers, ACEIs, ARBs were used by $\leq 0.6\%$ of the patients.

Patients above 21 years of age used significantly ($p=0.028$) more frequent medication that could function as a cofactor (9%) compared with adolescents (16-21 years of age) (3%). There was no significant difference in use of medication from the individual medication groups between the two age-groups, whereas beta blockers, ACEIs and ARBs were only used by patients above 21 years of age (table 3).

Table 3. Frequency of medication use from medications groups might act as cofactors

Medication use	n (%) All patients (n = 496)	n (%) ≤ 21 years of age (n = 108)	n (%) > 21 years of age (n = 387)	p-value ≤ 21 years of age vs > 21 years of age (n = 495)
Uses medication from ≥ 1 of the below medication groups	38 (7.7%)	3 (3%)	35 (9%)	0.028
- Antacids/acid neutralizing medication	25 (5.0%)	1 (0.9%)	24 (6%)	0.025
- NSAIDs	11 (2.2%)	2 (1.9%)	9 (2.3%)	1.000
- Beta blockers	3 (0.6%)	0	3 (0.8%)	1.000
- Angiotensin-converting enzyme inhibitors (ACEIs)	3 (0.6%)	0	3 (0.8%)	1.000
- Angiotensin-receptor blockers (ARBs)	1 (0.2%)	0	1 (0.3%)	1.000

Frequency of physical exercise, alcohol consumption and use of analgesics as cofactor in food allergic reactions

Of all patients, 13% (95% CI: 10-16%) reported experiencing more severe symptoms to food after involvement of one or more of the cofactors: physical exercise in 10%, alcohol consumption in 5% and use of analgesics in 0.6%. Of the patients reporting the cofactor physical exercise, one patient had FDEIA (to chicken meat and hen's egg). Sixty-five percent of all patients reported that they did not know if involvement of one of these cofactors caused more severe symptoms. Twenty-two percent of the patients reported that cofactors had no effect on their allergic symptoms.

Patients with mild or moderate food allergy (Mueller 0-2) reported significantly ($p=0.037$) less frequently that involvement of cofactors caused more severe symptoms, in comparison with patients with severe food allergy (Mueller 3-4), resp. 10% versus 16%. There was no significant difference between patients with mild or moderate food allergy and patients with severe food allergy, with regard to the frequency of the involvement of physical exercise and use of analgesic, the frequencies were resp. 7% versus 12% and 0% versus 1%. The involvement of alcohol consumption causing more severe symptoms was reported in 5% of the patients in both groups.

The frequency of cofactors between adolescents (16-21 years of age) and adults above 21 years of age was resp. 16% versus 12%. Physical exercise was more frequently reported as a cofactor in adolescents (13%) in comparison with patients above 21 years of age (9%). Alcohol consumption and use of analgesics were reported less frequently in adolescents compared with adults above 21 years of age, resp. 3% versus 5% and 0% versus 1%. None of the differences were statistically significant (table 4).

Table 4. Frequency of cofactors in all patients and subgroup analyses regarding severity of food allergy and age

Cofactors	n (%) All patients (n = 491)	n (%) Mueller 0-2 (n = 236)	n (%) Mueller 3-4 (n = 255)	p-value vs Mueller 3-4 (n = 491)	n (%) ≤ 21 years of age (n = 108)	n (%) >21 years of age (n = 382)	p-value vs > 21 years of age (n = 490)
Physical exercise, alcohol consumption and/or analgesic use	64 (13%)	23 (10%)	41 (16%)	0.037	17 (16%)	47 (12%)	0.349
- Physical exercise	47 (10%)	17 (7%)	30 (12%)	0.086	14 (13%)	33 (9%)	0.178
- Alcohol consumption	24 (5%)	12 (5%)	12 (5%)	0.846	3 (3%)	21 (5%)	0.248
- Analgesic use	3 (0.6%)	0	3 (1%)	0.250	0	3 (1%)	1.000
Unknown to the patient	317 (65%)	156 (66%)	161 (63%)	0.493	62 (57%)	255 (67%)	0.073
No effect	110 (22%)	57 (24%)	53 (21%)	0.371	29 (27%)	80 (21%)	0.192

Discussion

This study illustrates the presence and role of cofactors in patients with a doctor diagnosed food allergy. In this population, 7.7% of patients used medication that might act as a cofactor, whereof antacids/acid neutralizing medication and NSAIDs were most frequently used. This study further showed that 13% of the food allergic patients reported more severe allergic symptoms to food after involvement of one or more of the following cofactors: physical exercise (10%), alcohol consumption (5%) and use of analgesics (0.6%). More than half of the patients (65%) indicated not to have known if one of these cofactors had been associated with their allergic symptoms to food.

In this study, 7.7% of the patients used medication that might act as a cofactor. Antacids and acid neutralizing medication were used in 5% of the patients, NSAID's in 2.2% and beta blockers, ACEIs and ARBs in $\leq 0.6\%$. This is lower than the use of this medication in the general Dutch population. In 2012 Dutch pharmacies delivered antacids to 15-20%, NSAID's to 20% and beta blockers and ACEIs together to 15%-20% of the general Dutch population (27). It is probable that these results manifested as a result of the study population having a lower mean age than the Dutch population as a whole; 33 years versus 40-41 years (28). It is likely that the frequency of medication intake increases with age.

This study reported about the frequency with which patients use medication that might act as a cofactor in food allergy. Evidence about the role of this cofactor is scarce and there is discrepancy in outcomes. Only a study in mice showed that the use of proton-pump-inhibitors increases the risk of anaphylaxis (29). Untersmayr et al. (30) suggested that in long-term acid-suppressed patients the anti-ulcer treatment primes the development of IgE toward dietary compounds. Further, the CICBAA (French food allergy network) demonstrated that in 0.9%-4.7% of the anaphylactic reactions to food, beta blockers played a role and ACEIs and ARBs in respectively 0-0.1% and 0.9-2.4% (10). In conclusion, based on available evidence, involvement of these types of medication might cause more severe food allergic reactions. However, additional studies are needed to confirm the relative contribution of these drugs to the severity of food allergic reactions. Given that these types of medication are used in 7.7% or more of food allergic patients, it is important that physicians inform patients about the potential influence on their food allergy and check this during follow-up.

This study demonstrated that 13% of the patients reported to experience more severe allergic symptoms to food after involvement of a cofactor. In patients with severe food allergy, the frequency of involvement of cofactors was significantly higher than in patients with mild or moderate food allergy (16% versus 10%). The most frequently involved cofactor was physical exercise. Other studies reported a higher frequency of cofactors in anaphylactic reactions to food, namely 26% to 39% in adults (10,12) and 18.3% in a mixed population of

children and adults (18). Since in our study two-third of the patients indicated not to know if a cofactor influenced their allergic reaction, it can be assumed that patients might be largely unaware of the potential role of cofactors. In literature, it was earlier hypothesized that increased awareness is needed (7,31). On the other hand, most patients in the age group of this study (mean age: 33 years) regularly consume alcohol and perform physical exercise (32,33). We suppose that patients should have noticed it when these cofactors are associated with their allergic reactions, which confirms the low frequency. Another explanation for the lower frequency found, is that our study focused only on three cofactors which were regularly reported in literature, but not on other cofactors like infections, hormonal influence and body temperature (6,7). Still, cofactors seem to be involved in 13% or more of the patients with food allergy. This makes cofactors important to take into account in diagnostic measures and doctors' advice.

With respect to the frequency of involvement of specific cofactors, we demonstrated that 10% of the patients reported physical exercise as a cofactor, 5% alcohol intake and 0.6% intake of analgesics. There is wide range in the frequency of these three cofactors in literature. The frequency of physical exercise as a cofactor was earlier reported in a range of 0% to 15.9% of the anaphylactic reactions in adults (10,12,19). Wolbing et al. (6) reported that alcohol was a cofactor in anaphylaxis in 15.2% of the patients. Kanny et al. (9) demonstrated that 13% of the food allergic patients (children and adults) reported alcohol consumption as a cofactor. The CICBAA (10) showed that NSAIDs are a cofactor in 1.2% to 4.7% of the anaphylactic events. Cardona et al. (31) demonstrated that NSAIDs are involved in 58% of cofactor-enhanced food allergic reactions. Kanny et al. (9) reported that alcohol or NSAID intake is significantly more frequent in anaphylactic shocks than in mild reactions to food. These differences may be caused by the differences in population and differences in method of data collection.

Physical exercise is a well-known cofactor in food-dependent exercise induced anaphylaxis (FDEIA). In FDEIA, physical exercise is a prerequisite to induce allergic reactions to food (6,7). FDEIA is accepted as a separate clinical entity. Wheat is the most prevalent cause. Until now the precise mechanism is still unclear (13,15,34). It was demonstrated that patients with WDEAI often have IgE reacting to omega-5 Gliadin and HMW-Glutenin (15,34-36). In our study only one patient had FDEIA, but not related to wheat but to chicken meat and hen's egg.

Our study demonstrated that some patients had more severe allergic reactions after alcohol consumption, which is confirmed by Wolbing et al. (6) and Niggeman et al. (6,7). In literature several underlying mechanisms are suggested for this cofactor (7,16,17). It was also shown that a high intake of alcohol is associated with increased total serum IgE levels

and allergic sensitization (16,17). Remarkably the effect was different for pollen (higher degree of sensitization) and house dust mite (lower degree of sensitization) (16). However the underlying mechanism is far from being understood (16,17). We found that the use of alcohol was reported to enhance the severity of a food allergic reaction. Since alcohol was reported to result in relaxation of tight junctions in the gut epithelium, this might lead to increased allergen uptake and in turn to more severe reactions (6,7). More studies are needed to understand the (probably different) pathophysiological mechanisms behind the alcohol as a cofactor.

It is known that allergic reactions could be more severe with unstable asthma and during the pollen season (37,38). So, a combination of unstable atopic comorbidities and involvement of cofactors could lead to even more severe reactions. Since atopic comorbidities are frequently present in the food allergic population it seems important to minimize a potential negative influence by optimizing the treatment of any atopic comorbidity.

In this study many patients (67%) used medication (daily or on demand) that reduces severity of allergic symptoms, whereof antihistamines were most often used (56%). These factors (39), are important to consider as well. Notably, most literature so far only reported about factors that increased the severity of food allergy, but little attention was paid to factors that might decrease the severity of an allergic reaction, which might be at least as important.

This study gives information on the possible frequency in which cofactors might occur in the food allergic population. However, the study provides no information about a possible influence of cofactors on the minimal eliciting dose or individual thresholds of patients nor on the proportion of the food allergic population in which cofactors might influence thresholds or may play another role (not affecting thresholds). No clinical studies have been published yet that systematically studied the influence of cofactors on thresholds. However, in the total population of the present study the frequency of cofactors was only 13% and the frequency that patients use medication that are known as a potential cofactors was low, suggesting that cofactors, if influencing thresholds at all, probably will have limited influence on the dose-distribution of minimum eliciting dose at a population level. Further research is needed to investigate the influence of cofactors on eliciting doses.

A limitation of this study was the self-reported data and the possibility of recall bias and information bias. The diagnosis of food allergy and allergic rhino conjunctivitis was confirmed by the results of diagnostic tests (SPT, ImmunoCAP and food challenge). The criteria of Williams (25) were followed to diagnose atopic dermatitis. However, the criteria 'Onset under the age of 2 years' was excluded because of missing data on this item. For the diagnosis of asthma the criteria of the GINA guidelines (23) were used. However some

criteria were excluded because no data was collected about these items. This makes the diagnoses of atopic dermatitis and asthma somewhat less certain.

In conclusion, the results of this study show that only a small percentage of patients (7.7%) used medication that might aggravate food allergic reactions. Physical exercise and alcohol consumption were the most frequently reported cofactors associated with more severe allergic symptoms in patients with food allergy, but still in only 10% or less. Our results indicated that it is important to increase the awareness both among patients and health professionals.

Author contributions

A. Versluis, H. van Os-Medendorp and A.C. Knulst contributed to study design, data collection, data analysis and interpretation and writing the manuscript. A.G. Kruizinga, W.M. Blom and G.F. Houben contributed to interpretation of results and manuscript revision. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

Conflicts of interest

None declared.

Acknowledgements

The authors thank the nurses of Allergology outpatient clinic of the UMCU for the help with data collection and René C Schweizer pulmonologist at UMCU for his advice concerning asthma diagnosing.

Funding information

No funding information provided.

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CHAPTER 5

POTENTIAL COFACTORS IN ACCIDENTAL
FOOD ALLERGIC REACTIONS ARE
FREQUENTLY PRESENT BUT MAY NOT
INFLUENCE SEVERITY AND OCCURRENCE

Astrid Versluis, Harmieke van Os-Medendorp, W. Marty Blom,
Anouska D. Michelsen- Huisman, Jacqueline J.M. Castenmiller,
Hubert P.J.M. Noteborn, Geert F. Houben, André C. Knulst

Clin Exp Allergy. 2019;49(2):207-215.

Abstract

Background

Cofactors, like physical exercise and alcohol intake, might be associated with the severity or occurrence of food allergic reactions.

Objective

To gain insight into the frequency of presence of potential cofactors in accidental food allergic reactions in adults and to what extent these factors influence the severity and occurrence of allergic reactions.

Methods

A prospective cohort study was conducted, with a one-year follow-up in adult patients with a physician-diagnosed food allergy. Patients were required to fill in a questionnaire after every accidental allergic reactions to food over a one-year period. The primary outcome measure was the frequency that potential cofactors were present in these allergic reactions.

Results

157 patients were included, of which 46% reported a total of 153 reactions during a 1-year follow-up period. In 74% of the reactions ≥ 1 potential cofactor was reported to be present: tiredness (38%), alcohol intake (16%), stress (14%), symptoms of pollinosis (16%), symptoms of asthma (9%), sickness/flu (3%), physical exercise (3%) and use of analgesics (2%). More than one potential cofactor was reported in almost half of all reactions (47%). There was no significant difference in the presence of these factors between mild, moderate and severe reactions ($p=0.522$). In the total study population, 9% of the patients used medication that might act as cofactor (antacids, ARBs, beta blockers and ACEIs) on a daily basis, which however did not influence the occurrence of reactions. Furthermore, 38% daily used allergy suppressing medication.

Conclusions

Although factors suggested to be cofactors were frequently present during accidental food allergic reactions, we found no evidence for an association between the potential cofactors examined and reaction severity, in a population where most reactions were of mild to moderate severity.

Introduction

The point prevalence of food allergy is estimated to be 1-3% of the European population, based on clinical history and IgE and/or food challenge (1). Food allergy has a negative impact on quality of life and places a psychological burden on patients, caused by the daily requirement to avoid potentially offending foods and the risk of accidental allergic reactions (2,3). Despite the effort of health care professionals and patients to prevent allergic reactions, many patients experience accidental allergic reactions to food (4,5).

Literature reports that cofactors, such as infections (6), physical exercise (6-9), use of specific types of medication (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), antacids and beta blockers (9,10) and alcohol intake (6,9), might influence the occurrence and severity of food allergic reactions (11,12). There is limited evidence about the frequency of presence of these potential cofactors in food allergic reactions in adults and to what extent cofactors influence the severity and occurrence of allergic reactions. Data from anaphylaxis registers in Europe report the presence of potential cofactors in respectively 25.6% and 39% of the anaphylactic reactions to food in adults (13,14). Physical exercise, alcohol intake and use of medication were reported most often in anaphylactic reactions to food in adults (13,14). Infection, stress and use of specific types of medicine (e.g. aspirin/NSAIDs, beta blockers, angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs)) were present in only a few of the anaphylactic allergic reactions (13,14). The underlying mechanisms of how these potential cofactors could influence food allergic reactions are still not fully understood. Several mechanisms are suggested, for example an increased gastrointestinal permeability and absorption of proteins after physical exercise or intake of NSAIDs (12,15). And in case of acute infections, fever causing an elevated blood circulation and subsequent influx of food allergens is suggested (11).

Our previous, retrospective study suggested that 13% of the food allergic adults experience more severe allergic symptoms if a cofactor (physical exercise and/or alcohol consumption and/or use of analgesics) was present. Patients with severe food allergy reported more often that the presence of cofactors caused more severe reactions, when compared with patients with mild/moderate food allergy (16).

There are also allergic reactions to food where additional factors are crucial for the onset of the symptoms. For example, in food-dependent exercise-induced anaphylaxis (FDEIA), an accepted separate clinical entity, where physical exercise is crucial for the onset of allergic symptoms to food. The best characterized form is wheat-dependent exercise-induced anaphylaxis (WDEIA), where measurement of specific IgE to omega-5 Gliadin and HMW-Glutenin is important for diagnosis (15,17). Further, it has been suggested that in lipid transfer protein (LTP) allergic reactions, involvement of cofactors like NSAIDs, alcohol and

physical exercise may play an eliciting role (18-21). Also, influence of cofactors on severity of LTP allergic reactions was described, where patients had severe anaphylactic reactions when cofactors were present and only mild reactions when no cofactors were present (19).

EAACI guidelines (22) define cofactors as “patient-related or external circumstances that are associated with more severe allergic reactions”. In literature, cofactors are also referred to as additional-, associated- or augmentation factors (11,12,23). In this study cofactors are defined as external circumstances and patient-related factors that have influence on occurrence and severity of allergic symptoms.

Studies into the frequency of presence of potential cofactors and the influence of these factors on severity and occurrence of food allergic reactions have been predominantly conducted in children or in a mixed population consisting of children and adults, with severe food allergy and carried out with a retrospective design. More evidence about this subject is needed for better treatment and advice to patients (11,12).

The aim of this prospective study was to gain deeper insight into the frequency of presence of potential cofactors in accidental food allergic reactions in adults with a physician-diagnosed food allergy and to what extent these factors influence the severity and occurrence of allergic reactions.

Methods

Study design and setting

A longitudinal prospective cohort study was conducted from 2012 to 2015 at the University Medical Centre Utrecht in the Netherlands. This study was part of a study concerning accidental allergic reactions to food in adults (5,24). Patients had to fill in a questionnaire after every accidental allergic reactions to food over a one-year period.

Participants and ethics

Patients ≥ 18 years with physician-diagnosed food allergy, based on patient’s convincing history, and positive skin prick test, IgE and/or food challenge, were included. Patients were excluded from participation if they did not have the ability to read or write the Dutch language or if they did not have computer or internet access. Additionally, patients with established FDEIA, based on convincing history and where possible on serology, were not included, because in FDEIA, presence of physical exercise is crucial for the onset of allergic symptoms to food (15).

All patients gave written informed consent prior to inclusion. The local Medical Ethics Review Committee confirmed that the Medical Research Involving Human Patients Act (WMO) did not apply to the study (protocol number: 11-309/C).

Data collection

At baseline, data about history and severity of food allergy, atopic comorbidities and medication use was collected by means of a structured interview combined with information from the patients' medical records. Additionally, an online questionnaire was completed by the patients about demographics (sex, age, education).

Further, during one year, patients were required to complete an online questionnaire after every accidental allergic reaction to food. This questionnaire included questions about the causes and severity of the accidental reaction and about the presence of potential cofactors: tiredness, alcohol intake, stress, symptoms of pollinosis, symptoms of asthma, sickness/flu and physical exercise. Patients were contacted for further clarification if necessary.

Outcome measures

The primary outcome measure was the frequency that potential cofactors were present shortly prior to, during and/or shortly after an allergic reaction. Factors of interest were tiredness, alcohol intake, stress, symptoms of pollinosis, symptoms of asthma, sickness/flu, physical exercise and use of analgesics (NSAIDs or opioids). Physical exercise was considered as potential cofactor if performed within a time period of 30 minutes before till 2 hours after eating the suspected food (15). Alcohol intake and use of analgesics were considered as potential cofactor when used within eight hours prior the reaction, symptoms of asthma and sickness/flu when being present the day of the reaction, and tiredness, stress and symptoms of pollinosis when present directly prior to the reaction. To avoid over- or underestimation of the frequency of potential cofactors due to patients with multiple reactions, we looked into all reactions and every first reaction of patients.

Secondary outcome measures compared the severity of reactions in the presence or absence of potential cofactors and the number of these factors present, and the extent to which patients reported reactions with and without presence of these factors. Also the influence of asthma, pollinosis, age and gender was determined, on the basis of the likelihood that one or more cofactors were present in every first reaction.

Further, the frequency of daily used medication types in patients with and without reactions and in all, mild, moderate and severe reactions was determined and compared to investigate whether there were differences between these groups/reactions. Medication types suggested in literature as potential cofactors (11,12) and that were analyzed in this study were antacids, ARBs, beta blockers and ACEIs. Also included was the use of medication that could suppress allergic reactions, e.g. antihistamines, systemic corticosteroids/

immunosuppressive drugs, inhaled corticosteroids, corticosteroids/betamimetics and tricyclic antidepressants (TCAs). Some items for this outcome measure were added at a later time in the study, resulting in missing data in n=67 of the study population.

The patient characteristics and food allergy related data included: gender, age, atopic comorbidities and distribution and severity of food allergy. Severity of food allergy and accidental food allergic reactions was classified using an adapted version of the Mueller classification (25,26). Reactions with local oral symptoms (Mueller 0) were classified as mild, reactions with skin- and mucosal or gastro-intestinal symptoms (Mueller 1 and 2) as moderate and reactions with respiratory or cardiovascular symptoms (Mueller 3 and 4) as severe. Further, the Ewan and Clark grading (27,28) was used to classify severity, because there is no agreed consensus on how to measure severity of reaction in food allergy. According to this grading system, reactions with oral pruritus, skin symptoms, angio-oedema, gastrointestinal symptoms and rhino conjunctivitis were classified as mild, laryngeal edema and mild respiratory symptoms as moderate and dyspnea and hypotension as severe.

Data analysis

The study population consisted of 157 patients, based on the primary outcome of the other part of this study, published by Michelsen- Huisman et al. (5). Data were analyzed with descriptive analyses, using IBM SPSS Statistics 21 (IBM Corporation, Armonk, NY, USA).

Patient characteristics, frequency of presence of potential cofactors in allergic reactions and use of medication were analyzed using frequency data (n/percentage). A 95% confidence interval of the primary outcome of this study was calculated to provide a precise estimation. Differences in severity of reactions between reactions with and without potential cofactors, in severity of reactions as a function of the number of present potential cofactors, and in patients with and without allergic reactions with regard to daily medication use were analyzed using the chi square test (or the Fisher's exact test in case of small numbers).

We carried out multiple testing. Bonferroni correction was applied resulting in a p-value <0.01. Univariate logistic regression analyses were used to assess the influence of asthma, pollinosis, age and gender on the likelihood that one or more potential cofactors were present in every first allergic reaction of all patients.

Only full cases were used, missing data were excluded from analysis.

Results

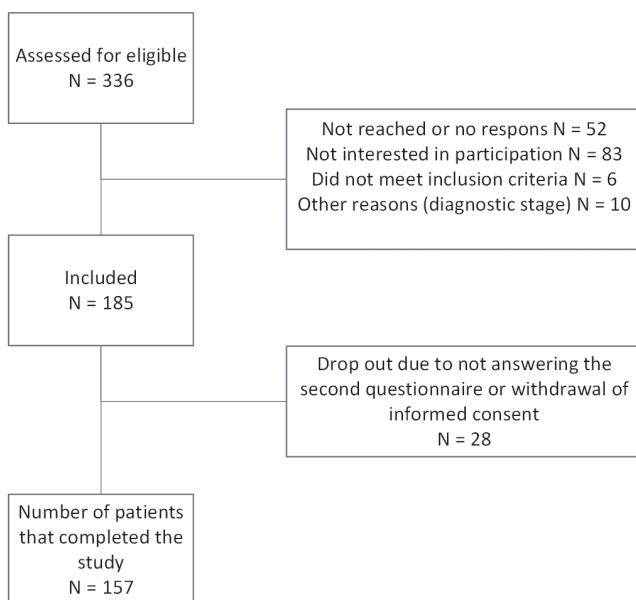
Patient characteristics and frequency of allergic reactions

Of the 336 patients who were eligible for inclusion, 157 were included (figure 1). The majority of patients were female (74%). The mean age was 35 years (range 18-70). Frequency of

atopic comorbidities was: pollinosis (76%), atopic dermatitis (59%) and asthma (54%). Most patients had a moderate (Mueller 1-2) (23%) or severe (Mueller 3-4) (73%) food allergy. The mean number of confirmed food allergies per person was 3.5 (range 1-10). The most common allergies were fruit (61%), hazelnut (55%), other nuts (excluding hazelnut) (48%), peanut (47%) and vegetables (32%).

Of these patients, 73 (46%) patients reported a total of 153 reactions during a 1-year follow-up period; 0.97 (range 0-11) reactions were reported per person. These reactions were caused by: prepacked foods (41%), meals outside the home (24%), fresh products (20%), products or meals in a foreign country (9%) and whilst having a meal at home (7%) (5). In 19 out of 51 analyzed products the culprit food allergen was found: cow's milk (n=8), peanut (n=6), hazelnut (n=5) were the most common (noningredient) allergens (24).

Figure 1. Flowchart of patient inclusion



Frequency of presence of potential cofactors in allergic reactions

One or more potential cofactors were reported to be present in 74% (95% CI: 66% – 81%) of the accidental allergic reactions to food (figure 2). The most common potential cofactor in accidental allergic reactions was tiredness (38%), followed by alcohol intake (16%), stress (14%), symptoms of pollinosis (16%), and symptoms of asthma (9%).

More than one potential cofactor was reported to be present in almost half of all allergic reactions (47%). In these reactions, two (30%) or three (14%) of these factors were

present. Less frequent were reactions in the presence of four (1%) and five (3%) factors. Of the twenty-eight patients reporting more than one allergic reaction (in four patients, data about potential cofactors were missing), 15 patients (54%) reported only reactions in the presence of potential cofactors (ranging from one up to five factors), 12 (43%) reported reactions both with and without presence of these factors and one patient (who reported four allergic reactions) only had reactions in absence of these factors.

In every first accidental allergic reaction per patient, one or more cofactors were reported to be present in 78% of the patients.

Logistic regression analysis were performed to assess the influence of asthma, pollinosis, age and gender univariate on the likelihood that one or more potential cofactors were reported to be present in every first allergic reaction. No significant influence was found of asthma (OR: 0.61, CI: 0.17-2.20), pollinosis (OR: 1.61, CI: 0.36-7.17), age (OR: 0.97, CI: 0.92-1.01) and gender (OR: 2.34, CI: 0.58-9.43).

Daily used medication that might act as cofactor and occurrence of allergic reactions

For 157 allergic patients, data about daily used medication that might act as cofactor was available in n=90 patients. Daily use of these types of medication was reported by eight patients (9%): antacids (4%), ARBs (3%), beta blockers (2%) and ACEIs (1%) (table 1). In this patient group there was no significant difference between the number of patients that reported no or one or more allergic reactions ($p=0.286$).

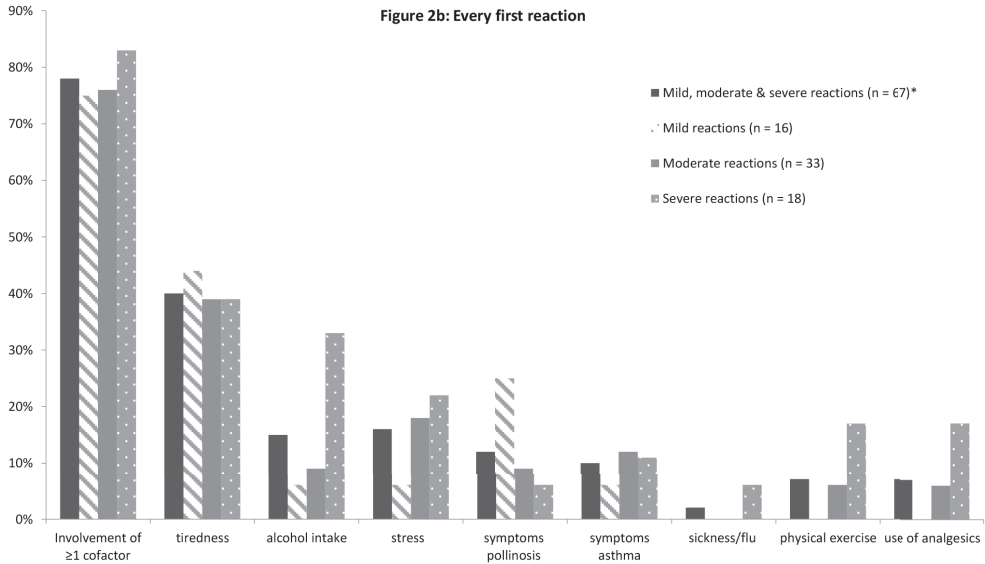
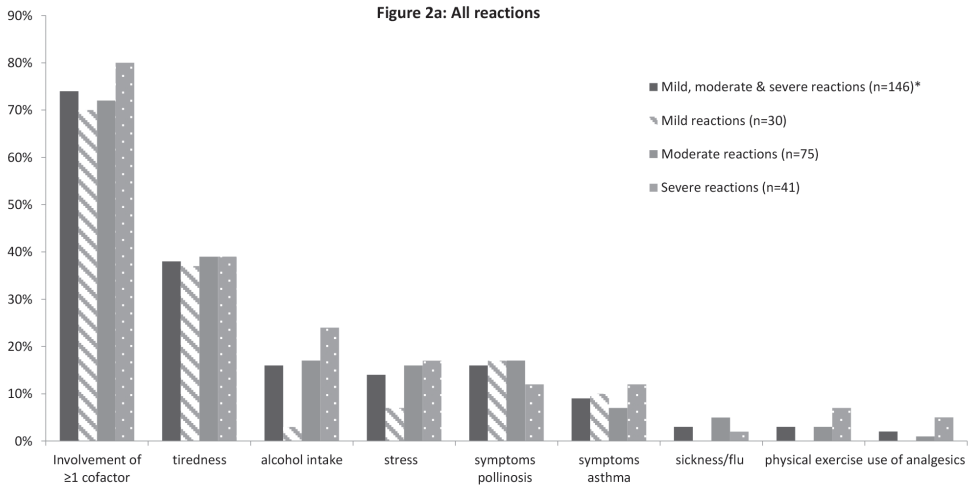
Six patients (7%) used antacids on demand, whereof two patients reported allergic reactions. None of the patients used ARBs, beta blockers and ACEIs on demand.

Daily used allergy suppressing medication

Of all 157 patients, 38% daily used medication that could suppress allergic symptoms (table 1). Antihistamines were most frequently used (29%). The use of medication that suppresses allergic symptoms was 10% lower in the group of patients that did not report any allergic reaction; however this was not significantly different ($p=0.239$).

Of the eight patients who daily used medication which is suggested as potential cofactor (antacids, ARBs, beta blockers and ACEIs), four did not use medication that could suppress allergic symptoms.

Figure 2. Frequency of presence of potential factors in accidental allergic reactions to food in all reactions (figure 2a) and every first reaction (figure 2b)



* Reactions with local oral allergy symptoms (Mueller 0) were classified as being mild, reactions with symptoms from skin and mucous membranes (Mueller 1) and/or gastro-intestinal tract (Mueller 2) were classified as moderate and reactions with respiratory symptoms (Mueller 3) and/or cardiovascular symptoms (Mueller 4) were classified as being severe (25,26)

Table 1. Medication use that might act as cofactor or that could suppress allergic symptoms

Total patient group	Patients with no allergic reactions		Patients with allergic reactions		All allergic reactions		Mild allergic reaction (Mueller 0) ^c		Moderate allergic reactions (Mueller 1-2)		Severe allergic reactions (Mueller 3-4)	
	Patient level	Patient level	Patient level	Patient level	Reaction level	Reaction level	Reaction level	Reaction level	Reaction level	Reaction level	Reaction level	Reaction level
Daily use of medication that could act as cofactor	N = 90 (missing: n=67) ^a	N = 51 (missing: n = 18)	N = 39 (missing: n=34)	N = 79 (missing: n=74)	N = 20 (missing: n=13)	N = 38 (missing: n=39)	N = 21 (missing: n=22)					
Uses daily medication from ≥1 of below medication groups	8 (9%)	3 (6%)	5 (13%)	7 (9%)	3 (15%)	2 (5%)	2 (10%)					
- Antacids	4 (4%)	3 (6%)	1 (3%)	1 (1%)	1 (5%)	0	0					
- ARBs	3 (3%)	1 (2%)	2 (5%)	2 (3%)	1 (5%)	1 (3%)	0					
- Beta blockers	2 (2%)	0	2 (5%)	2 (3%)	1 (5%)	1 (3%)	0					
- ACEIs	1 (1%)	0	1 (3%)	3 (4%)	0	1 (3%)	2 (10%)					
Medication that could suppress allergic symptoms (daily use)^b	N = 157	N = 84	N = 73	N = 153	N = 33	N = 77	N = 43					
Uses medication from ≥1 of below medication groups	59 (38%)	28 (33%)	31 (43%)	83 (54%)	16 (49%)	45 (58%)	22 (51%)					
- Antihistamines	45 (29%)	21 (25%)	24 (33%)	71 (46%)	13 (39%)	37 (48%)	21 (49%)					
- Inhaled corticosteroids	13 (8%) (missing: n=1)	4 (5%)	9 (12%)	21 (14%)	5 (15%)	12 (16%)	4 (9%)					
- Combination inhalers (corticosteroids/betamimetics)	10 (6%) (missing: n=1)	3 (4%)	7 (10%) (missing: n=1)	20 (13%) (missing: n=2)	1 (3%)	14 (18%)	5 (16%) (missing: n=2)					
- Inhaled betamimetics	9 (6%)	5 (6%)	4 (6%)	11 (7%)	0	7 (9%)	4 (9%)					
- Systemic corticosteroids/immunosuppressive drugs	4 (3%)	3 (4%)	1 (1%)	4 (3%)	0	4 (5%)	0					
- TCAs	3 (3%) (missing: n=67)	0	3 (8%) (missing: n=34)	4 (5%) (missing: n=74)	0 (missing: n=13)	3 (8%) (missing: n=39)	1 (5%) (missing: n=22)					

Abbreviations: ARBs, Angiotensin-receptor blockers; ACEIs, Angiotensin-converting enzyme inhibitors; TCAs Tricyclic antidepressants

^a The items for this outcome measure were added at a later moment in the study, resulting in relatively many missing data

^b In case of methotrexate: one dose weekly

^c Reactions with local oral allergy symptoms (Mueller 0) were classified as being mild, reactions with symptoms from skin and mucous membranes (Mueller 1) and/or gastro-intestinal tract (Mueller 2) were classified as moderate and reactions with respiratory symptoms (Mueller 3) and/or cardiovascular symptoms (Mueller 4) were classified as being severe (25,26)

Alcohol intake, physical exercise and analgesics use

When alcohol consumption was reported (16% of reactions), alcohol intake was in most patients limited to 1-2 alcoholic consumptions (71%) and often the time interval between alcohol intake and the reaction was 0-2 hours (83%) (table 2). Physical exercise was reported in five (3%) allergic reactions, varying between ½-0 hours prior eating to ½-2 hours after eating the suspected food. All three patients that used analgesics reported a reaction within 4 hours of the intake of analgesics.

Cofactors and severity of allergic reactions

In mild, moderate and severe reactions, potential cofactors were present in 70%, 72% and 80% of the reactions respectively; and absent in 30%, 28% and 20% of the reactions respectively (figure 2). There was no significant difference in the presence of these factors between mild, moderate and severe allergic reactions in all reactions ($p=0.522$) and in every first reaction per patient ($p=0.792$) and also no difference was found between mild, moderate and severe reactions in the presence of individual potential cofactors: tiredness ($p=0.977$ and 0.949), alcohol intake ($p=0.058$ and 0.036), stress ($p=0.396$ and 0.423) symptoms of pollinosis ($p=0.759$ and 0.170) and symptoms of asthma ($p=0.582$ and 0.424). Using an alternative scoring system for severity, namely that according to Ewan and Clark grading (27,28), also showed no significant differences (supplement table 1). Furthermore, there was no significant difference in the number of present potential cofactors between mild, moderate and severe allergic reactions ($p=0.171$).

In severe reactions, daily use of medication that might act as a cofactor (antacids, ARBs, beta blockers, ACEIs) was not more frequent compared to mild and moderate reactions.

Mild, moderate and severe reactions were reported after a low as well as high amount of alcohol consumption (table 2).

Table 2. The amount/intensity of potential cofactors and the time interval between these factors and allergic reactions: alcohol intake, physical exercise and use of analgesics

Alcohol	Allergic reactions with presence of alcohol. n=24
Total alcoholic consumptions:	
- 1 -2	17 (71%) (Mueller ^a : 0 (n=1), 1 (n=2), 2 (n=8), 3 (n=5), 4 (n=1))
- 3 - 4	4 (17%) (Mueller: 2 (n=2), 3 (n=1) 4 (n=1))
- ≥5	3 (12%) (Mueller: 1 (n=1), 3 (n=1), 4 (n=1))
Time interval between alcohol intake and reaction:	
- 0-2 hours prior reaction	20 (83%) (Mueller: 0 (n=1), 1 (n=2), 2 (n=9), 3 (n=6), 4 (n=2))
- 2-4 hours prior reaction	3 (13%) (Mueller: 1 (n=1), 2 (n=1), 3 (n=1))
- 4-8 hours prior reaction	1 (4%) (Mueller: 4 (n=1))
Physical exercise	Allergic reactions with presence of physical exercise. n=5
Time interval between physical exercise and eating:	
- ½ - 0 hours prior eating	2 (Mueller: 2 (n=1), 3 (n=1))
- 0- ½ hours after eating	2 (Mueller: 3 (n=1), 4 (n=1))
- ½ - 2 hours after eating	1 (Mueller: 2 (n=1))
Use of analgesics (including NSAIDs and opioids)	Allergic reaction with presence of analgesics use. n=3
Type of analgesic:	
- NSAIDs	1 (Mueller: 1 (n=1))
- Tramadol	2 (Mueller: 3 (n=2))
Time interval between intake of analgesic and reaction:	
- 0-2 hours prior reaction	2 (Mueller: 3 (n=2))
- 2-4 hours prior reaction	1 (Mueller: 1 (n=1))
- 4-8 hours prior reaction	0

^aMueller classification for severity: Mueller 0: Reactions with local oral allergy symptoms; Mueller 1: reactions with symptoms from skin and mucous membranes; Mueller 2: symptoms from gastrointestinal tract; Mueller 3: reactions with respiratory symptoms and Mueller 4 reactions with cardiovascular symptoms (25,26)

Discussion

This study is to date the only prospective study on this subject. It showed that in 74% of the accidental allergic reactions to food, one or more potential cofactors were reportedly present. The most common potential cofactor was tiredness, followed by alcohol intake, stress, symptoms of pollinosis, and symptoms of asthma. However, there were no differences in severity of reactions with and without these factors. Daily use of medication that might act as cofactor, was also found not to influence the occurrence either.

We found that in most allergic reactions (74%) one or more potential cofactors were present, with differences in frequency per specific factor, ranging from 2% to 38%. Retrospective data from anaphylaxis registers (13,14) reported the presence of these

factors in 25.6% and 39% of the anaphylactic reactions to food in adults, with differences in frequency per specific factor ranging from 1.3% to 15.9%. We found that tiredness (38%), alcohol intake (16%), stress (14%) and symptoms of pollinosis (16%) were the most frequently present potential cofactors. Less frequently present were sickness/flu (3%), physical exercise (3%) and use of analgesics (2%). Remarkably, in the anaphylaxis registers exercise was the most frequently present factor (9.6% and 15.9%) (13,14). However, the anaphylaxis registers made no distinction between physical exercise as potential cofactor influencing severity of reactions and FDEIA in which physical exercise is crucial for the onset of allergic symptoms. In our study, patients with FDEIA were excluded, which could partly explain the lower frequency of physical exercise reported. Other potential cofactors that were reported in the anaphylaxis registers were alcohol intake in respectively 3.7% (14) and 9.6% (13) of anaphylactic reactions, stress (4.5%) (13), NSAIDs (4.7%) (14), (other) drugs (3.7% (14) and 21.2% (13)) and infection (1.3%) (13). Remarkably, tiredness (the 1st most frequent potential cofactor in our study) was not reported in the anaphylaxis registers (13,14). No other studies have been published about the frequency of tiredness in food allergic reactions. The differences in frequency that potential cofactors are present in allergic reactions between our study and the anaphylaxis register studies, could be explained by differences in study design. The prospective design of our study with a one-year follow-up period likely resulted in less recall and information bias than studies based on an online registry with questionnaires filled in by many different physicians. Besides, in our study, patients with mild, moderate and severe reactions were included, probably resulting in other outcomes compared with the anaphylaxis registries in which only patients with anaphylactic reactions (severe reactions involving respirator and/or cardiovascular tract) were included (13,14).

We found no differences in severity of reactions between those with and without potential cofactors. Also when using the Ewan and Clark grading (27,28), which resulted in a higher number of mild reactions as compared with the Mueller classification (25,26), no differences were found in severity of reactions between those with and without potential cofactors. Further, daily use of medication that might act as cofactor, was found not to influence the occurrence either. This seems to be in contrast with literature. Wölbing et al. (12) carried out a review about cofactors in anaphylactic reactions and concluded these factors seem to have an important role in elicitation and severity of anaphylactic reactions, however that underlying mechanisms are still not fully understood and further research is needed. One study following twenty-two children during peanut oral immunotherapy reported that more than half of them (12/22) often developed unexpected allergic reactions after ingestion of a previously tolerated dose when a potential cofactor was present, including

exercise, excessive tiredness, exposure to inhalant allergens, infection and menstruation (29). However, the small sample size in this study limits the generalizability from patient level to population level. A database study with 382 cases of anaphylaxis showed that severe and uncontrolled asthma is a risk factor for severe anaphylactic reactions (30). In our previous retrospective study, 13% of the food allergic patients reported experiencing more severe reactions after physical exercise (10%), alcohol intake (5%) and/or use of analgesics (0.6%) (16). Further, patients with severe food allergy reported significantly more often that the presence of cofactors caused more severe reactions, when compared with patients with mild/moderate food allergy (16). The prospective design of the current study with data collected by questionnaires filled in per accidental allergic reactions, likely resulted in better recall and more precise data than our previous retrospective study with data collected with a questionnaire administered at one point in time.

Insight into the underlying mechanisms of the different potential cofactors would help to understand the relevance of these potential cofactors in food allergic reactions. Several mechanisms are suggested, for example increased blood circulation after physical exercise leading to increased influx of allergen in the gut, and relaxation of the tight junction of the gut epithelium after alcohol intake leading to increased gastro-intestinal absorption of protein. However the amount of evidence differs per cofactor and the significance of these suggestions is still not clear. (11,12,31)

This study further showed that about one third of the food allergic patients used medication (such as antihistamines and corticosteroids) that likely suppresses allergic symptoms. Patients used these types of medication regularly for other atopic comorbidities such as asthma and pollinosis. Although it is suggested in literature that unstable asthma and active pollinosis can act as potential cofactors in food allergy, adequate treatment might result in suppression of severity of reactions (32-34). We found no significant difference in use of allergic symptoms suppressing medication comparing patients who did or did not report any allergic reaction.

A limitation of this study was that the accidental allergic reactions were reported by the patient, which could lead to information bias and response bias, possibly resulting in over- or underestimation of the presence of potential cofactors in reactions and of severity of reactions. In addition, the experience of symptoms of an allergic reaction might differ per person, which could lead to bias in data when it is self-reported. However, a study in young children showed that self-reported data about severity of allergic reactions were not biased (35), suggesting that the role of bias in self-reported data might be limited. Besides, all reported reactions were reviewed by the research team within one week and if necessary the patient was called by phone for further clarification.

Tiredness and stress were often present during the reported allergic reactions. We did not measure the degree of tiredness and stress, so we could not make a differentiation between e.g. mild and severe tiredness and stress. This limits the strengths of our conclusion.

We did not study hormonal changes during the premenstrual and ovulatory phase as a potential cofactor, which has been suggested by others (36,37). However, we did not find any evidence for the influence of gender on the likelihood that one or more cofactors were present in allergic reactions.

Alcohol consumption was considered to be a potential cofactor when used within eight hours prior the reaction. Literature describes several factors that influence the time interval by which alcohol is eliminated from the body; for example the amount of alcohol, gender, age, food and biological rhythms (38). This makes it impossible to determine if alcohol was actually present during the accidental allergic reaction. In our study, in most reactions alcohol was consumed within 2 hours prior the reaction (83%). This suggests that alcohol had influence on the occurrence of the reaction.

Further, it needs to be mentioned that use of medication that could act as cofactor was only questioned in part of the study population which limits the generalizability.

In conclusion, although factors suggested to be cofactors were frequently present during accidental food allergic reactions, we found no evidence for an association between the potential cofactors examined and reaction severity, in a population where most reactions were of mild to moderate severity.

Acknowledgments

This study was financially supported by the Netherlands Food and Consumer Product Safety Authority, Utrecht, The Netherlands.

Author contributions

H. van Os- Medendorp, A. Michelsen- Huisman, J. J.M. Castenmiller, G.F. Houben and A.C. Knulst designed the study. A. Versluis, H. van Os- Medendorp and A. Michelsen- Huisman collected the data. A. Versluis, H. van Os-Medendorp and A.C. Knulst analyzed the data and wrote the manuscript. All authors contributed to interpretation of results and manuscript revision. The final version of the manuscript was approved by all authors.

Conflicts of interest

All authors declare that they have no conflict of interest.

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Supplemental tables

Supplemental Table 1. Frequency of presence of potential factors in accidental allergic reactions to food – Ewan and Clark grading

Cofactors	Mild reactions (Ewan and Clark grading 1-3)*	Moderate reactions (Ewan and Clark grading 4)	Severe reactions (Ewan and Clark grading 5)	P-value mild, moderate and severe reactions vs. whether or no presence of cofactor(s)
	n = 71 (missing: n = 4)	n = 40 (missing: n = 1)	n = 35 (missing: n = 2)	
Involvement of ≥ 1 of the cofactors below	51 (72%)	28 (70%)	29 (83%)	0.381
Tiredness	27 (38%)	15 (38%)	14 (40%)	0.973
Alcohol intake	9 (13%)	6 (15%)	9 (26%)	0.225
Stress	9 (13%)	5 (13%)	7 (20%)	0.554
Symptoms of pollinosis	12 (17%)	8 (20%)	3 (9%)	0.373
Symptoms of asthma	6 (9%)	3 (8%)	4 (11%)	0.856
Sickness/flu	1 (1%)	3 (8%)	1 (3%)	NA
Physical exercise	0	2 (1%)	3 (1%)	NA
Use of analgesics (NSAIDs or opioids)	0	1 (3%)	2 (6%)	NA

**Oral pruritus/erythema/urticaria/angio-oedema/gastrointestinal symptoms/rhino conjunctivitis = mild; laryngeal edema/mild respiratory symptoms = moderate; dyspnea/hypotension = severe (27, 28)*



CHAPTER 6

LOW DIETARY ADHERENCE AFTER A POSITIVE FOOD CHALLENGE IN FOOD ALLERGIC ADULTS

Astrid Versluis, Thuy-My Le, Francine C. van Erp, Mark A. Blankestijn, Geert F. Houben, André C. Knulst, Harmieke van Os-Medendorp

Clin Transl Allergy. 2022;12(2):e121119.

Abstract

Background

After a positive food challenge (FC), patients receive dietary advice regarding avoidance of the culprit food. We examined the frequency and variables associated with dietary adherence after a positive FC in adults.

Methods

In this prospective daily practice study, adults with a positive FC were included. After every FC, dietary advice was given consisting of three options: 1) strict avoidance, 2) avoidance but products with precautionary allergen labelling (PAL) allowed and 3) (small) amounts allowed. Questionnaires about dietary adherence and associated variables were completed prior to and six months after the FC(s).

Results

Forty-one patients (with 58 positive FCs) were included. Overall, patients adhered to the advised diet after 31% of the FCs. After 33 FCs, the advice was strict avoidance, whereof 82% followed a less strict diet. After 16 FCs, the advice was avoidance but products with PAL allowed, whereof 19% followed a less strict and 25% a stricter diet. In nine FCs with the least strict advice, "(small) amounts allowed", 67% followed a stricter diet. Three variables were associated with adherence: misremembering dietary advice, impaired health-related quality of life (HRQL) on domain "Emotional impact" and the need for dietary change after the FC.

Conclusion

After one third of the positive FCs, patients adhered to the dietary advice. Variables associated with adherence were misremembering dietary advice, impaired HRQL on domain "Emotional impact" and the need for dietary change after the FC. It seems important that healthcare professionals should more frequently apply adherence-enhancing strategies to improve dietary adherence.

Introduction

Food allergy is an adverse immune response to food proteins that can cause symptoms involving skin, mucous membranes, gastro-intestinal and respiratory tracts and the cardiovascular system (1). Diagnostics in patients with a suspected food allergy includes a detailed medical history, assessment of sensitization and a food challenge. A double-blind placebo-controlled food challenge is the gold standard for diagnosing food allergy (2). After a positive food challenge, dietary avoidance of the culprit food is the key intervention (1). The dietary restrictions should be tailored to the individuals specific allergic and nutritional needs (1). For example, in patients with pollen-food syndrome, which is common in adults, different fruits, nuts and vegetables may cause symptoms when eaten raw, but are tolerated when eaten cooked (3). It is necessary for each patient to receive counselling and education to manage the elimination of the culprit food(s) from their diet (1).

Following the dietary advice is important to prevent accidental allergic reactions, unnecessary dietary restrictions, impairment of quality of life, costs and nutritional deficiencies (1,4-6). Previous studies showed, remarkably, that food allergic children and adolescents often fail to adhere to dietary advice to avoid the culprit foods (7-9). In parents of children with a doctor-diagnosed sea-food allergy, it was shown that only one third adhered to the given dietary advice (7). In college students with self-reported food allergies, only half of them always avoid the culprit food (9). And in adolescents (13-19 years of age) with a severe, doctor-diagnosed food allergy, it was reported that 85% of them generally tried to avoid the food; however, less than half enquired about ingredients in restaurants (42%) or at friends' houses (35%). Only 16% of the adolescents were adherent to all aspects of self-care investigated (8). Further, it has been shown that approximately half of adults with a doctor-diagnosed food allergy experience on average two accidental allergic reactions per year, in some cases due to incorrect management of the advised dietary advice (10).

Information about frequency and variables associated with adherence to dietary advice in adults with a doctor-diagnosed food allergy is scarce. Therefore, this study investigated the frequency and variables associated with dietary adherence after a positive food challenge in adults.

Methods

Study design, setting, study population and ethics

A daily practice study with a quantitative prospective design was carried out from 2014 till 2017 at the Department of Allergology/Dermatology of a tertiary referral center for food allergy in the Netherlands.

All patients (≥ 18 years) who underwent a positive food challenge with at least one of the 13 EU regulated allergenic foods (cereals containing gluten, crustaceans, eggs, fish, peanuts, soybeans, milk, nuts, celery, mustard, sesame seeds, lupin, molluscs) were included.

All patients gave written informed consent prior to inclusion. The Medical Ethics Review Committee of the University Medical Centre Utrecht confirmed on October 15, 2013 that the Medical Research Involving Human Patients Act (WMO) did not apply to the study (protocol number: 14-237/C).

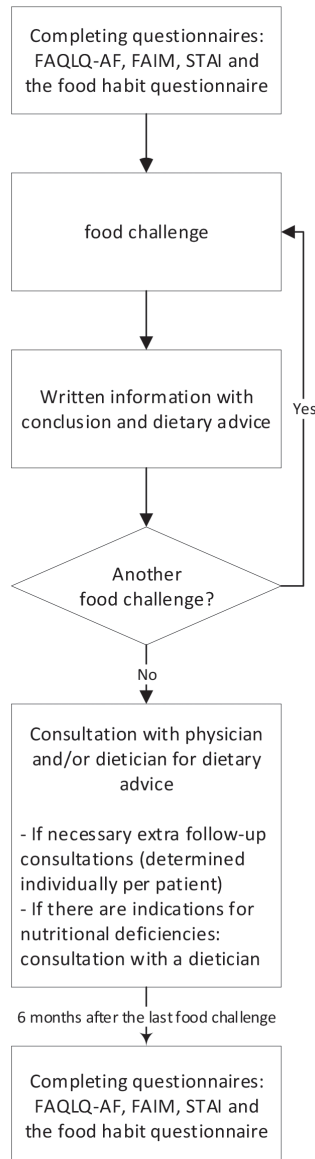
Standardized methods for food challenges and follow-up care

Every patient underwent a standardized allergy work-up. The first step included collection of a detailed medical and dietary history and assessment of sensitization (specific IgE and / or skin prick testing). Secondly, a food challenge was conducted, to confirm or rule out a food allergy, to assess severity of symptoms or to investigate thresholds (1). The food challenges were performed in an open or blinded manner and all ended with a daily normal dose of that food (1). Food challenges were conducted and interpreted by experienced staff, consisting of an allergy nurse, clinical nurse specialist, dietician and dermatologist in accordance with standardized procedures (11). Dietary advice was determined individually per patient by the experienced staff, based on sensitivity and severity of symptoms during the food challenge and each individual patient's history regarding intake of the challenged food in daily diet (12). There were three dietary advice options. Option 1: strict avoidance of the allergenic food and ingredients (including products with precautionary allergen labelling (PAL)). Option 2: avoidance of the allergenic food and ingredients but products with PAL allowed. Option 3: (small) amounts of the allergenic food or ingredients allowed with dose adjustment based on complaints and on careful and complete evaluation (only in case of mild (mainly oral allergy) symptoms during food challenge and/or mild reaction to only a high dose).

After each positive food challenge, patients received a standardized follow-up consisting of written information about the conclusion and dietary advice, and a consultation with the physician and/or dietician when all tests had been performed. If indicated, additional follow-up consultations could be scheduled (figure 1).

Outcome measures

The primary outcome measure was frequency of dietary adherence. Dietary adherence was defined as 'consequently following dietary advice'.

Figure 1. Flowchart of research procedure and standardized follow-up care after a positive food challenge

The secondary outcome measure was the association of a number of variables with dietary adherence, including: consultation with a dietician instead of a physician during follow-up, accurate recollection of the prescribed dietary advice at follow-up, the need for a dietary change after the food challenge (if the habitual diet prior to the food challenge differed from

the advised diet after the food challenge), if the type of food challenged was nuts/peanuts vs. other foods, if the patient experienced accidental allergic reactions during follow-up, the method of food challenge (single/double blind vs. open), age (adolescent vs. adult), the number of positive food challenges (one vs more than one), health-related quality of life (HRQL) at baseline and state and trait anxiety at baseline. Furthermore, reasons for non-adherence were studied in patients who consciously failed to adhere to the advised diet.

Data collection

Patients were asked to complete four questionnaires prior to and 6 months after the last food challenge, consisting of: the food habit questionnaire, the Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF) (13), the Food Allergy Independent Measure (FAIM) (14) and the State-Trait Anxiety Inventory (STAI) (15) (figure 1). The food habit questionnaire included items about avoidance of the challenged food(s). This questionnaire was developed by a multidisciplinary team consisting of an allergist, dietician, nurse scientist and clinical nurse specialist. Feasibility of the questionnaire was achieved by conducting a pilot in small group of patients who underwent a food challenge at the day care unit. The questionnaire filled in six months after the last food challenge included additional items about what dietary advice patients thought they had received after the food challenge, whether patients experienced accidental food allergic reactions during the follow-up period and patients' reasons in the event that they consciously chose not to adhere to the received dietary advice. The FAQLQ-AF consisted of four domains (Risk of accidental exposure, Emotional impact, Allergen avoidance-dietary restrictions and Food allergy-related health) comprising a total of 29 items about food allergy specific quality of life. The total score ranged from 1 (no impairment) to 7 (maximal impairment) (13). The FAIM consisted of 4 items about patients' perceived food allergy severity and food allergy related risks. The total score varies from 1 (limited severity perception) to 7 (greatest severity perception) (14). The STAI consisted of 40 items and covered aspects of state anxiety (in the specific situation of eating the food the patient is allergic to) and trait anxiety (feelings of stress, worry, discomfort, etc. that a person experiences on a daily basis). The score varies from 20 (minimal anxiety) to 80 (maximal anxiety) in both state and trait anxiety (15). The Dutch validated versions of the FAQLQ-AF, FAIM and STAI, were used and the scores were calculated using standardized methods (13-15).

Additionally, patients completed a questionnaire about atopic comorbidities and educational level. Other characteristics of patients and food challenges were collected from the patients' medical records. The severity of allergic reactions was classified based on type of symptoms: local oral symptoms were classified as "mild", symptoms from skin and

mucous membranes and/or gastro-intestinal tract as “moderate” and respiratory and/or cardiovascular symptoms as “severe”.

Sample size and statistical methods

We did not carry out a sample size calculation, but all patients undergoing one or more positive food challenges over a period of 3 years and who met the inclusion criteria were asked to participate in the study.

Outcome data regarding frequency, variables associated with dietary adherence and reasons for non-adherence, were analysed using descriptive statistics. Depending on level of measurement, frequency (n/%) or mean (SD) were used.

Differences between patients who adhered to the dietary advice, followed a stricter diet than advised or followed a less strict diet than advised with regard to variables associated with dietary adherence were analysed using the Fisher-Freeman Halton test or Kruskal-Wallis test depending on level of measurement and data distribution. Some variables were analyzed per patient (instead of per food challenge). In these factors, group classification (follows diet as advised, follows a stricter diet than advised and follows a less strict diet than advised) was based on dietary adherence after the most severe (and in case of similar severity, the first) food challenge of the patient.

A p-value <0.05 was considered statistically significant. Data were analyzed using IBM SPSS Statistics 25 (IBM Corporation).

Results

Characteristics of patients and food challenges

In this study, a total of 41 patients were included, who underwent a total of 58 food challenges with a positive outcome, confirming the food allergy. The majority of patients were female (71%) and the mean age was 33 years (SD: ± 12 , min-max: 19-61). Most patients had atopic comorbidity: asthma (68%), atopic dermatitis (58%, 23/40, n=1 missing) and/or allergic rhino conjunctivitis (88%). The majority of the patients underwent one positive food challenge (71%), and the other patients underwent 2 (17%,) to 3-4 (12%) positive food challenges. The mean time between food challenge and evaluation of dietary adherence was seven months (SD: ± 3 , min-max: 5-16, missing: n=3).

Of the total 58 positive food challenges, most commonly challenged foods were nuts (54%) and peanut (17%). The allergic reactions during the food challenges were mainly moderate (48%) or severe (35%; table 1).

After almost two thirds of the food challenges (66%), patients received dietary advice via standardized follow-up care (via written information and consultation with a physician

and/or dietician) and in the other food challenges, only via consultation with a physician and/or dietician (17%) or only via written information (17%).

Table 1. Characteristics of food challenges

	All food challenges n=58
	n (%)
Food challenged:	
- Nuts ¹	31 (54)
- Peanut	10 (17)
- Hen's egg	5 (9)
- Sesame	4 (7)
- Cow's milk	4 (7)
- Other ²	4 (7)
The method of the food challenge:	
- Single/double blind	42 (72)
- Open	16 (28)
Severity of reaction during food challenge ³ :	
- Mild	10 (17)
- Moderate	28 (48)
- Severe	20 (35)

¹ Nuts includes: walnut (n=12), hazelnut (n=11), cashew nut (n=5), almond (n=3)

² Other includes: shrimp (n=1), grains (n=2) and soy (n=1)

³ Mild: local oral symptoms, moderate: symptoms from skin and mucous membranes and/or gastrointestinal tract and severe: respiratory and/or cardiovascular symptoms

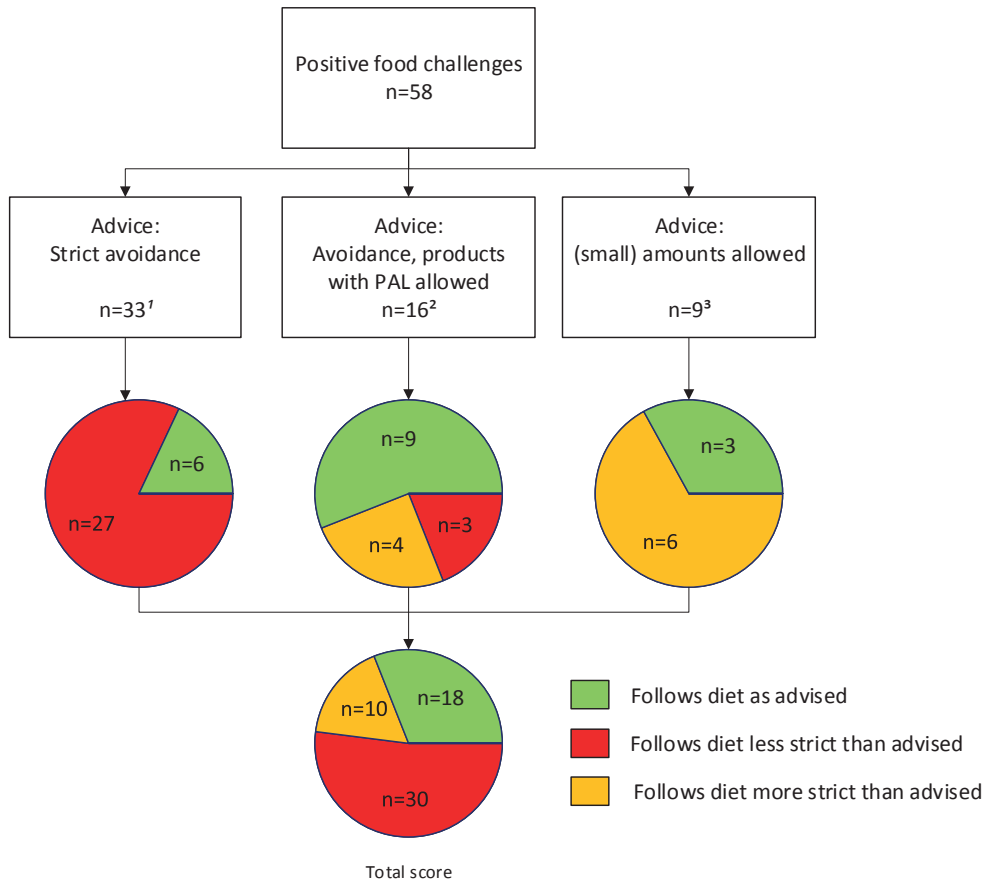
Only one third of the patients adhered to the dietary advice

After the positive food challenges, patients received dietary advice, consisting of the three options: 1) strict avoidance of the culprit food, 2) avoidance but products with PAL allowed and 3) (small) amounts allowed. Patients adhered to the advised diet after 31% (18/58, 95% CI: 20%-45%) of all food challenges.

After 33 food challenges, the dietary advice was strict avoidance of the allergenic food and ingredients. In the vast majority of this group (82%, 27/33), a less strict diet was followed (figure 2). After 16 food challenges, advice to follow a less strict diet was given, namely to avoid the allergenic food and ingredients, but not products with PAL. In almost half of these cases (44%, 7/16), the dietary advice was not followed: in 19% (3/16) a less strict diet was followed and 21% (4/16) a stricter diet.

In nine food challenges with mild allergic reactions, the dietary advice was that (small) amounts of the allergenic food or ingredients were allowed because of the mildness (mainly oral allergy) of the symptoms during food challenge and/or mild reaction only in the event of a high dose. In this group, after two-thirds (6/9) of the food challenges a stricter diet than advised was followed.

Figure 2. Dietary adherence



¹ Types of food allergen: peanut: n=7, hazelnut: n=3, nuts (excl. hazelnut): n=12, cow's milk: n=3, hen's egg: n=5, sesame: n=3

² Types of food allergen: peanut: n=3, hazelnut: n=4, nuts (excl. hazelnut): n=6, cow's milk: n=1, shrimp: n=1, grain: n=1

³ Types of food allergen: hazelnut: n=4, nuts (excl. hazelnut): n=2, soy: n=1, sesame: n=1, grain: n=1

Variables associated with adherence to dietary advice

We examined which variables were associated with dietary adherence. Table 2 shows the association between different variables and adherence to dietary advice, comparing the patient groups who: (a) followed diet as advised, (b) followed a stricter diet and (c) followed a less strict diet. Comparing these three groups gives insight as to whether these variables are associated with dietary adherence and whether it might lead to a less or more strict diet.

The first variable investigated was accurate recollection of the prescribed dietary advice.

Figure 2 shows the prescribed dietary advice. In the follow-up questionnaire, patients self-reported the dietary advice they received per food challenge. Almost one third of all patients (29%, 16/56, missing n=2) misremembered the prescribed dietary advice. Patients who followed a stricter diet most often misremembered the diet (67%), compared to patients who adhered to the diet (33%) and patients that followed a less strict diet (14%) ($p=0.01$).

Secondly, the variable “the need for a dietary change after the food challenge” was investigated. In more than two thirds of the food challenges (72%, 24/33, missing n=15) the advised diet after the food challenge differed from the habitual diet prior to the food challenge. In patients following a stricter diet and also in patients who followed a less strict diet, the advised diet after the food challenge more often differed from the habitual diet prior to the food challenge, compared to patients who adhered to the advised diet (88% and 86% vs 46%, $p=0.08$).

Further, the variable HRQL and anxiety at baseline was investigated, measured with the FAQLQ-AF, FAIM and STAI. In patients following a less strict diet, the baseline score of FAQLQ domain Emotional impact was more impaired compared to patients who adhered to the advised diet or followed a stricter diet ($p=0.02$). No differences between the three patient groups was found in the other FAQLQ-AF domains, FAIM and STAI (table 2).

No difference was found between the three patient groups with regard to the healthcare professional that gave dietary advice (dietician vs. physician, $p=1.00$), occurrence of accidental food-induced allergic reactions during follow-up ($p=0.36$), the type of food challenged (peanuts/nuts vs. other foods) ($p=0.59$), the method of food challenge (single/double blind vs. open, $p=0.45$), age (adolescent vs. adult, $p=1.00$) and the number of positive food challenges (one vs. more than one, $p=0.61$).

Table 2. Variables associated with adherence to dietary advice

Variables	Follows diet as advised	Follows diet stricter than advised	Follows diet less strict than advised	Comparison of group: adherence, stricter diet and less strict diet
	Per food challenge			
	N (%)	N (%)	N (%)	p-value ¹
Was the prescribed dietary advice accurately recollected at follow-up (n=56):				
- Yes	12 (67)	3 (33)	25 (86)	0.01
- No	6 (33)	6 (67)	4 (14)	
Was a dietary change was needed after the FC (n=33)				
- Yes	5 (46)	7 (88)	12 (86)	0.08
- No	6 (54)	1 (13)	2 (14)	

Table 2. Continued

Variables	Follows diet as advised	Follows diet stricter than advised	Follows diet less strict than advised	Comparison of group: adherence, stricter diet and less strict diet
	Per food challenge			
	N (%)	N (%)	N (%)	p-value ¹
Follow- up consultation with (n=48) ² :				
- Dietician	11 (73)	6 (75)	19 (76)	1.00
- Physician	4 (27)	2 (25)	6 (24)	
Type of food challenged (n=58):				
- Peanut or nuts	11 (61)	8 (80)	22 (73)	0.59
- Other foods	7 (39)	2 (20)	8 (27)	
Method of the food challenge (n=58):				
- Single/double blind	12 (67)	9 (90)	21 (70)	0.45
- Open	6 (33)	1 (10)	9 (30)	
	Per patient, adherence after FC with most severe outcome			
	N (%)	N (%)	N (%)	p-value ¹
Did a food-induced allergic reaction(s) occur during follow-up (n=41):				
- Yes	5 (33)	5 (63)	10 (56)	0.36
- No	10 (67)	3 (38)	8 (44)	
Age (n=40) ³				
- Adolescent (≤24 years of age)	4 (27)	2 (25)	5 (29)	1.00
- Adults	11 (73)	6 (75)	12 (71)	
Number of positive food challenges (n=41)				
- 1	10 (67)	7 (88)	6 (33)	0.61
- >1	5 (33)	1 (13)	12 (67)	
HRQL and anxiety before food challenge(s)	Mean (SD) N=14-15 ⁴	Mean (SD) N= 6-7 ⁵	Mean (SD) N = 16-18 ⁶	p-value ⁷
Food allergy related quality				
- Total score	4.0 (1.4)	3.7 (1.2)	4.4 (1.3)	0.30
- Domain Risk of accidental exposure	4.2 (1.6)	3.6 (1.7)	4.6 (1.3)	0.44
- Domain Emotional impact	4.1 (1.5)	3.5 (1.2)	4.9 (1.3)	0.02
- Domain Allergen avoidance-dietary restrictions	3.8 (1.5)	4.0 (1.3)	4.0 (1.6)	0.84
- Domain Food allergy-related health	4.3 (1.8)	3.6 (1.4)	4.1 (1.7)	0.62
FAIM	3.4 (1.0)	3.0 (0.6)	3.6 (1.0)	0.22
STAI: State anxiety	35.1 (12.1)	33.0 (12.1)	30.6 (9.7)	0.69
STAI: Trait anxiety	35.0 (8.3)	29.2 (9.3)	36.2 (9.0)	0.17

¹ Statistical test used: Fisher-Freeman-Halton Test² Patients who received dietary advice via consultation³ Missing: n= 1⁴ Missing: n= 0-1⁵ Missing: n=1-2⁶ Missing: n=0-2⁷ Statistical test used: Kruskal Wallis test

Non-adherence was a conscious choice in more than one third of the patients

Of the patients who did not adhere to the dietary advice, more than one third (35%, 13/37, n=3 missing) reported that this was a conscious choice. The other patients (65%, 24/37) did not mention such a conscious choice for non-adherence.

Most of the patients who made this conscious choice, received advice to strictly avoid the food but followed a less strict diet (77%, 10/13) with two different reasons: a strict diet led to too many restrictions in diet (4/10) and using products with PAL was expected to be safe (4/10). In two cases, no reason was recorded. The other three patients (23%), received the advice that (small) amounts were allowed but they consciously chose to avoid the food, because they expected allergic complaints upon consuming the food.

Discussion

In this study, we showed that in only one third of the positive food challenges, patients adhered to the dietary advice. Variables associated with adherence were: misremembering dietary advice, an impaired HRQL on domain Emotional impact and the need for a dietary change after the food challenge.

It is remarkable that dietary adherence after a positive food challenge in adults is low, despite all patients having been given dietary advice. Two previous studies investigating dietary adherence in children and adolescents with a doctor-diagnosed food allergy showed that only one third of the parents of children with a sea-food allergy adhered to the dietary advice and that less than half of the adolescents enquired about ingredients in restaurants or when visiting the house of a friend (7,8). To our knowledge, this is the first study to show low dietary adherence in food allergic adults. The low frequency of dietary adherence is a major concern because of the risk of accidental allergic reactions in case of a less strict diet and the risk of unnecessary product avoidance and social impairment in case of a stricter diet than advised (5,6,10). Non-adherence is also a well-recognized problem in other types of medical advice; for example in adherence to medication and in following dietary and lifestyle changes in other diseases (16-18).

In our study, dietary adherence was lowest in patients who received advice to strictly avoid a food. Strict avoidance meant that the culprit food including products with PAL should be avoided. Several factors might negatively influence the adherence to the advice to avoid these products. First, patients are confronted with unstandardized presentation of information on food labelling, which is often unclear, with low readability and clarity and consequently difficulty in interpretation (19,20). Second, PAL is increasingly present on products, strongly restricting food choices (4). Third, some patients estimate the risk, based on product name and brand and prior experiences (21). Finally, even for products without

PAL, there is no guarantee that these are without allergens, adding to the confusion (22). Overall, patients who have to avoid products with PAL face many obstacles, so healthcare professionals should guide and support patients to better-deal with these difficulties. Regulations of food labelling and PAL would help food allergic patients to better manage their diet.

In general, food allergic patients are advised to strictly avoid the culprit food (23). However, it is not necessary for all food allergic patients to completely avoid the culprit food. Sicherer et al. (12) reported in a review, that, in patients who are not highly allergenic, options such as usage of products with PAL or allowing a small amount of the culprit food may be considered individually per patient. In our study one of the following options for dietary advice was given after the food challenge: 1) strict avoidance (33/58), 2) avoidance but products with PAL allowed (16/58) and 3) (small) amounts allowed (9/58). Option 2 is mainly advised to patient with mild/moderate complaints who already use products with PAL for a longer period, without complaints. Currently, the Ad Hoc Joint FAO/WHO Expert Consultation on Risk Assessment of food allergens works on a more accurate way of precautionary food labelling (24), which is already implemented by some food producers. Due to this developments, it seems more and more needed to advise a strict diet in patients who previously received the advice to avoid the food but who were allowed to use products with PAL.

We identified three variables that are associated with dietary adherence. The first was “misremembering the advised diet”. In our study 29% misremembered the prescribed dietary advice. A previous study in children with a sea-food allergy showed that almost one-quarter of the parents were unable to correctly recall the dietary advice (7). Poor and inaccurate patient recollection of medical information is a well-known problem (25,26). The second variable was the need for a dietary change after the food challenge. Our results indicate that this is a factor in both patients who follow a stricter and a less strict diet as advised. It is known that changing dietary behavior is challenging (27). Conducting a qualitative study in which patients are interviewed about this topic seems valuable to generate more insight in this variable. The third variable we found was that the HRQL domain Emotional impact was more impaired in patients who followed a less strict diet than advised. However, most patients who followed a less strict diet had a severe food allergy. So, HRQL might be indirectly associated with dietary adherence via having a severe food allergy, which itself is shown to negatively impact HRQL (28). Furthermore, it is reported that food challenges are associated with improvement of HRQL (29). Therefore, future research on this topic with repeated measures of HRQL seems valuable to get more insight into the relation between HRQL and dietary adherence. The sample-size of our study was

too small to further analyze the relationship between adherence, HRQL and severity using a multivariate model. Remarkably, no association was found between accidental allergic reactions and dietary adherence. However, we do not know if patients adapted their diet after experiencing a reaction, which would bias this result. In addition, literature showed that accidental allergic reaction often occur after not following the advised diet (10,20). In summary, several variables might be associated with dietary adherence. It seems important that healthcare professionals consider these variables when giving advice and guidance about dietary restrictions. Future research should give more insight into additional variables that could be associated with dietary adherence, e.g. methods used for diagnostics, the indication for the food challenge, severity of (accidental) reactions and the type of food allergen. Moreover, future research on the occurrence of accidental food-induced allergic reactions during follow-up seems needed, excluding the possible bias of patients adapting their diet after experiencing a reaction.

Our results indicate that patients who receive standardized follow-up care after a positive food challenge(s), still frequently fail to adhere to dietary advice. This is disappointing and it indicates that the given follow-up care is not sufficient. The follow-up care given in our study was largely consistent with the international food allergy guideline of Muraro et al. (1) which reports that education about risky situations, reading labels, the regulation of precautionary labels and possible substitute food products is essential for an effective long-term elimination diet in food allergic patients. Different intervention strategies could be useful. It has been shown that parents of food allergic children benefit from food allergy management curriculums, with preferably a variety of educational materials (30,31). An online self-management program for food allergic patients can be used in addition to face-to-face consultations (32). Combined interventions seem to be most beneficial in achieving adherence. For example, education, supporting, building a trusting relationship, personalized care, shared decision-making, evaluation and use of different tools (e.g. mobile apps, video, written materials) (33-37). With regard to dietary advice after a positive food challenge, more frequent follow-up consultations mainly focusing on imparting knowledge, supporting patients to adhere to their diet and discussing obstacles and barriers seem important, preferably always with the same healthcare professional (1,35,36). More insight about intervention strategies which are effective in enhancing dietary advice in food allergic adults is needed.

A limitation of this study was that it was conducted in a tertiary center with patients with a history of more severe food allergic reactions. This could have the effect of restricting the generalizability of our data to the general food allergic population. Furthermore, one third of the patients did not receive dietary advice via the standardized follow-up care (i.e.

17% only via written information and 17% only via consultation with a physician and/or dietician). However, when comparing patients who had received standardized follow up care versus those who had not with regard to dietary adherence, no differences were found. Furthermore, our definition of dietary adherence was strict. If we had defined dietary adherence as 'not following dietary advice one or less times per month', dietary adherence would have been slightly higher: in patients with a strict diet 21% instead of 18% and in patients with dietary advice to avoid the food but products with PAL allowed 75% instead of 56%. A study about dietary adherence in parents of sea-food allergic children also used the stricter definition that dietary advice should be followed all the time (7). Furthermore, the small sample size limits the power of the subgroup analysis and the generalizability of the results. A strength of this study was the prospective study design and use of validated questionnaires (with the exception of the food habit questionnaire), which contributed to the reliability of our results. An additional advantage of this study was that diagnosis and dietary advice was based on a food challenge. If only one third of the patients that experienced the severity of the reaction during a food challenge adhered to the dietary advice, it is the question whether dietary adherence is even worse in patients that are only diagnosed by history and sensitization. It would be interesting to investigate this in future studies.

In conclusion, patients adhered to the dietary advice after only one third of the positive food challenges. Variables associated with adherence were misremembering dietary advice, an impaired HRQL on domain Emotional impact and the need for a dietary change after the food challenge. Our results indicate that it is important for healthcare professionals to more frequently apply adherence-enhancing strategies in order to improve dietary adherence.

Acknowledgements

We would like to thank the nurses of the Allergology outpatient clinic of the University Medical Centre Utrecht for their help with the data collection. The authors received no financial support for the research, authorship and publication of this article.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Author contributions

Astrid Versluis: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Writing – original draft. Thuy-My Le: Supervision; Writing

– review & editing. Francine C. van Erp: Conceptualization; Methodology; Writing – review & editing. Mark A. Blankestijn: Data curation; Writing – review & editing. Geert F. Houben: Supervision; Writing – review & editing. André C. Knulst: Conceptualization; Investigation; Methodology; Supervision; Writing - review & editing. Harmieke van Os- Medendorp: Conceptualization; Formal analysis; Methodology; Supervision; Validation; Writing - review & editing.

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CHAPTER 7

REINTRODUCTION FAILURE AFTER NEGATIVE FOOD CHALLENGES IN ADULTS IS COMMON AND MAINLY DUE TO ATYPICAL SYMPTOMS

Astrid Versluis, André C. Knulst, Francine C. van Erp, Mark A. Blankestijn,
Yolanda Meijer, Thuy-My Le, Harmieke van Os-Medendorp

Clin Exp Allergy. 2020;50(4):479-486.

Abstract

Background

Reintroduction of a food after negative food challenge (FC) faces many obstacles. There are no studies available about this subject in adults.

Objective

To investigate the frequency, reasons and risk factors of reintroduction failure in adults.

Methods

In this prospective study, adult patients received standardized follow-up care after negative FCs including a reintroduction scheme and supportive telephone consultations. Data were collected by telephone interview (2 weeks after FC) and questionnaires (at baseline and 6 months after FC(s)): food habits questionnaire, State-Trait Anxiety Inventory, Food Allergy Quality of Life Questionnaire-Adult Form and Food Allergy Independent Measure. Frequency and reasons of reintroduction failure were analyzed using descriptive statistics and risk factors with univariate analyses.

Results

Eighty patients were included with, in total, 113 negative FCs. Reintroduction failed on short term (2 weeks after FC) in 20% (95% CI: 13%-28%). Common reasons were symptoms upon ingestion during the reintroduction scheme (50%) and no need to eat the food (23%). On the long term (5-12 months after FC(s)), reintroduction failure increased to 40% (95% CI: 28%-53%). Common reasons were atypical symptoms after eating the food (59%) and fear for an allergic reaction (24%). Five risk factors for long-term reintroduction failure were found: if culprit food was not one of the 13 EU regulated allergens, reintroduction failure at short-term, atypical symptoms during FC, a lower quality of life and a higher state anxiety.

Conclusions & clinical relevance

Reintroduction failure after negative FCs in adults is common, increases over time, and is primarily due to atypical symptoms. This stresses the need for more patient-tailored care before and after negative food challenges.

Introduction

The prevalence of food allergy diagnosed by clinical history and positive serology in Europe ranges from 0.3-6% (1). The prevalence of self-reported food allergy is much higher and ranges from 2-37% (2). Therefore, adequate diagnostic testing is of key importance. A double blind food challenge is the gold standard to confirm or rule out food allergy (3,4). After a negative food challenge, patients are advised to reintroduce the food in their daily diet. This is important because it helps to reduce unnecessary restrictions in the diet. Dietary restrictions were shown to be associated with nutritional deficiencies, increased costs, and a negative impact on quality of life (5-7). Moreover, the importance of exposure in decreasing the risk of developing food allergy has been demonstrated in children (8-10). Remarkably, patients frequently do not succeed in reintroducing the food after negative food challenge. Studies in children show that even up to 44% fail to reintroduce the food (11-15). Reasons for reintroduction failure in children are (atypical) symptoms during reintroduction, ongoing fear for an allergic reaction, being not convinced by the challenge test result, aversion, habit of avoiding the food, and having family members who also eliminate the food (11,13-18). Several factors are associated with a higher chance of reintroduction failure in children, e.g. being a girl (13,17), lower age (17), not receiving advice about food reintroduction (17), symptoms occurring during FC (17), symptoms during reintroduction (17) and the type of allergen (14).

There are no studies found about reintroduction failure after negative food challenges in adults. Therefore, we investigated the frequency, reasons and risk factors of reintroduction failure in adults after a negative food challenge.

Methods

Study design, setting, study population and ethics

A daily practice study with a quantitative prospective design was carried out from 2014 till 2017 at the Department of Allergology/Dermatology of a tertiary referral center for food allergy in the Netherlands.

All patients who underwent a food challenge based on a history suspected of type 1 food allergic reactions were included. Patients who had one or more negative food challenges were followed until six months after the last food challenge. Inclusion criteria were: a negative food challenge with any type of food with exception of composite meals, \geq 18 years of age and with the ability to read and write Dutch.

All patients gave written informed consent prior to inclusion. The local Medical Ethics Review Committee confirmed that the Medical Research Involving Human Patients Act (WMO) did not apply to the study (protocol number: 14-237/C).

Standardized methods for food challenges and follow-up care

Food challenges were conducted and interpreted by experienced staff, consisting of a trained allergy nurse, clinical nurse specialist, dietician and dermatologist in accordance with standardized procedures (19). The criteria for conducting an blinded food challenge were: 1) the availability of good recipe, 2) risk of non-specific complaints, 3) risk of false positive or unclear result and 4) patient preferences. The food challenge protocols differed per type of food and all ended with an estimated daily normal dose of that food. For example a blinded hazelnut challenge and blinded peanut challenge consisted of a placebo day and active day and occurred with the following incremental protein doses: for hazelnut 1.5 mg, 10 mg, 30 mg, 100 mg, 300 mg, 1000 mg and 3000 mg and for peanut 1 mg, 10 mg, 30 mg, 100 mg, 300 mg, 1000 mg, 3000 mg and 5000 mg. In case of fruits an open challenge was performed with the following dose series: 1 g, 3 g, 10 g, 30 g and 100 g.

After negative food challenges, patients received standardized follow-up care to support reintroduction in daily diet. Since there were no guidelines about follow-up care, we developed standardized follow-up care based on literature (12,13,16) and expert opinion. If no symptoms occurred during food challenge, patients received a one-day stepwise reintroduction scheme directly after the food challenge. The reintroduction scheme differed per type of food. For example the scheme for hazelnut and peanut was as follows: ½ nut, 1 nut, 2 nuts and 5 nuts and for fruits 1/8 portion, 2/8 portion and 5/8 portion, all with time intervals of 30 minutes, at the same day. This was followed by telephonic consultation the next day to evaluate if no late symptoms occurred after the food challenge and to give permission to start reintroduction at home. If symptoms occurred, these were first evaluated by a physician before advice was given about reintroduction. Two weeks after this advice, telephone consultation took place to evaluate reintroduction. If reintroduction was successful, patients were advised to continue eating the food in their daily diet. If reintroduction failed, a patient tailored follow-up based on reasons of failure was provided. In case of mild to moderate (atypical) symptoms patients were advised to repeat the reintroduction scheme. In the case of (repeated) symptoms during reintroduction, the food challenge outcome and diagnosis were re-evaluated by experienced staff. Six months after the food challenge(s), reintroduction in the daily diet was evaluated. The follow-up care was carried out by a clinical nurse specialist.

Outcome measures

Primary outcome measures were the frequency of short-term and long-term reintroduction failure. Short-term reintroduction failure was defined as “never started with or not able to successfully complete the reintroduction scheme”. Long-term reintroduction failure was defined as “not eating the food, eating only products that might contain traces of the food

or eating the food at a frequency of <1 occasion per month (in case of seasonal products: < once a month when the food was regularly available), 6 months after the last food challenge”.

Secondary outcome measures were patient reported-reasons for short- and long-term reintroduction failure. Furthermore, we studied the influence of a number of potential risk factors on long-term reintroduction failure, namely consisting of patient characteristics (gender, educational level, atopic comorbidities, sensitization to negatively challenged food, sensitization to any food), duration of the pre-challenge elimination diet, patients purpose of food challenge, factors related to food challenge (food challenge method, symptoms during food challenge, if culprit food was a major allergen (i.e. one of the 13 EU regulated allergens: cereals contain gluten, crustaceans, eggs, fish, peanuts, soybeans, milk, nuts, celery, mustard, sesame seeds, lupin, molluscs) and patients’ conviction about the conclusion from food challenge), short term reintroduction failure, if patient underwent one or more positive food challenges, food allergy related quality of life and state and trait anxiety. Only risk factors for long term reintroduction failure were analyzed, because continued reintroduction in daily diet is the final purpose of reintroduction.

Data collection

Patients were asked to complete in four questionnaires prior to and 6 months (time that questionnaires were returned varied from 5-12 months) after the food challenge(s), including the food habit questionnaire, State-Trait Anxiety Inventory (STAI) (20), Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF) (21) and Food Allergy Independent Measure (FAIM) (22). The food habit questionnaire consisted of items about avoidance of the challenged food(s). The questionnaire that was filled in six months after the food challenge(s) included additional items about patients’ conviction to the conclusion of the food challenges and reasons for avoiding the food(s). The STAI consisted of 40 items and covered aspects of state anxiety (in the specific situation of eating) and trait anxiety (feelings of stress, worry, discomfort, etc in situations that everyone experiences on a daily basis). The score varies from 20 (minimal anxiety) to 80 (maximal anxiety) in both state and trait anxiety (20). The FAQLQ-AF consisted of four domains (Risk of accidental exposure, Emotional impact, Allergen avoidance-dietary restrictions and Food allergy-related health) including 29 items about food allergy specific quality of life. The total score ranged from 1 “no impairment” to 7 ‘maximal impairment’ (21). The FAIM consisted of 4 items about patients’ perceived food allergy severity and food allergy related risks. The total score varies from 1 (limited severity perception) to 7 (greatest severity perception) (22). The Dutch validated versions of the STAI, FAQLQ-AF and FAIM were used and the scores were calculated using standardized methods (20-22).

Additionally, patients completed a questionnaire about atopic comorbidities (asthma, allergic rhino conjunctivitis and atopic dermatitis) and educational level.

Two weeks after the advice to reintroduce a food, data about frequency and reasons of short term reintroduction failure were collected during telephone consultation. If patients did not answer the telephone, then an attempt was made to reach the patient in the following weeks.

Data about gender, age, sensitizations to food (skin prick tests, immunoCAP and ImmunoCAP ISAC), type/method of food challenge, patients purpose of food challenge and additional information about reintroduction were collected from patients' records.

Sample size and statistical methods

To include a representative sample of the available population of patients undergoing one or more negative food challenges over a period of 35 months (estimated at 52 negative FCs in 42 patients per year), the required sample size of that group was calculated using the Raosoft Sample Size calculator (23). Since there were no comparable studies to estimate the expected frequency of reintroduction failure after negative food challenges in adults, we conservatively assumed a frequency of 50%. With a margin of error of 5%, a confidence interval of 95% and assuming a response distribution of 50%, 94 patients should be included.

Outcome data regarding frequency and reasons for reintroduction failure were analysed using descriptive statistics. Based on level of measurement, we used frequencies (n/%) or mean (sd). A 95% confidence interval was calculated for the primary outcome.

Differences regarding risk factors between long-term reintroduction failure and success and between patients who did and did not respond with regard to patient characteristics and risk factors for long-term reintroduction failure were analyzed by comparing the first performed food challenge of every patient using chi square test, Fisher's exact test, Fishers-Freeman Halton test or independent-samples t-test depending on level of measurement and data distribution. A p-value <0.05 was considered statistically significant.

Data were analyzed using IBM SPSS Statistics 25 (IBM Corporation).

Results

Characteristics of patients and diets

In total 170 patients were included, of which 80 patients underwent a total of 113 negative food challenges and were followed. The 90 patients included, but not evaluated were patients with a positive outcome of the food challenge and thus considered allergic.

Patient and food challenge characteristics of the followed patients are shown in table 1. A majority of patients were female (66%, 53/80) and the mean age was 32 years (SD: ±13). Of all patients, 82% (55/67) had one or more atopic comorbidity; 78% (56/72) had allergic rhinitis, 56% (40/72) asthma and 55% (37/67) atopic dermatitis. In 76% (61/80) patients were sensitized to any food.

The number of negative food challenges per patients ranged from 1 (69%, 55/80) to 2 (20%, 16/80) to 3-4 (11%, 9/80).

The duration of the pre-challenge elimination diet varied from: <1 year (32%, 35/109), 1-10 years (19%, 21/109) to >10 years or lifelong (44%, 48/109) and in 5% (5/109) of the food challenges this was unclear (table 1).

Table 1. Patient and food challenge characteristics

	All patients N (%) N=80^a
Gender: female	53 (66)
Mean age in years (SD, min-max)	32 (13, 18-70)
Education level ^b :	
- Low/intermediate	46 (64)
- High	24 (33)
- Other	2 (3)
Asthma, atopic dermatitis and/or allergic rhino conjunctivitis:	55 (82)
- Allergic rhinitis	56 (78)
- Asthma	40 (56)
- Atopic dermatitis	37 (55)
Sensitization for any type of food	61 (76)
	All food challenges N (%) N=113^c
Food challenged:	
- Hazelnut	29 (26)
- Nuts (excl. hazelnut)	23 (20)
- Peanut	14 (12)
- Fruits and vegetables (excl. celery)	13 (12)
- Fish, crustaceans and/or molluscs	8 (7)
- Cow's milk	8 (7)
- Grains (incl. buckwheat)	7 (6)
- Hen's egg	5 (4)
- Seeds and kernels	3 (3)
- Soy	2 (2)
- Celery	1 (1)
Sensitization to the negatively challenged food:	
- Sensitized	63 (62)
- Not sensitized	38 (38)
Duration of the pre-challenge elimination diet:	
- <1 year	35 (32)
- 1-10 years	21 (19)
- >10 years or lifelong	48 (44)
- Unclear	5 (5)

^aNumber of missings varied per outcome from n= 0-13

^bLow: Primary school, pre-vocational Secondary Education. Intermediate: senior general secondary education, Pre-university education, secondary vocational education. High: Higher professional education, university education

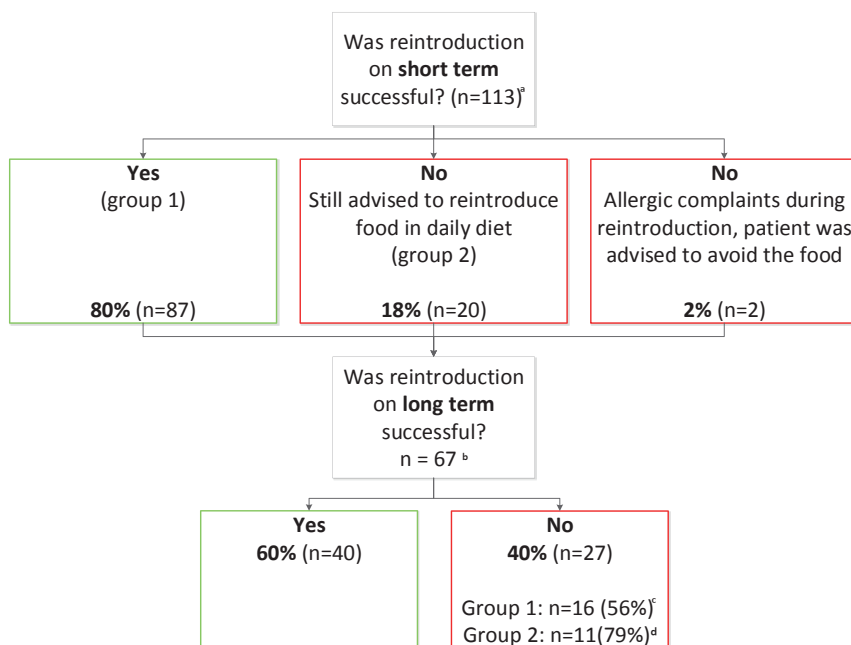
^cNumber of missing varied per outcome from n=0-11

Short term reintroduction failure occurred in 20% for various reasons

After a negative food challenge, patients were advised to reintroduce the food using a reintroduction scheme. Figure 1 shows a flowchart of the frequency of reintroduction failure. In 20% (95% CI: 13%-28%) (22/113) of the negative food challenges, patients failed to reintroduce the food using the reintroduction scheme. Of the patients who failed short term reintroduction, 23% (5/22) failed before even to start the reintroduction scheme.

Figure 2 shows the patient reported reasons for short term reintroduction failure. The most common reason, reported by 50% (11/22), was having symptoms during reintroduction. In 9 out of these 11, the patients had atypical symptoms, mainly atypical gastro-intestinal and skin/mucosal symptoms. In the remaining two, there were typical allergy symptoms, namely itchy mouth, mild coughing, mild rhinitis and mild hoarseness. Both patients were considered allergic after re-evaluation. Another common reason for short term reintroduction failure was feeling no need to eat the food (23%, 5/22).

Figure 1. Flowchart of the frequency of short- and long-term reintroduction failure



^a N = 4 short term success unknown, not reached by telephone to evaluate reintroduction

^b Loss to follow up: n = 46

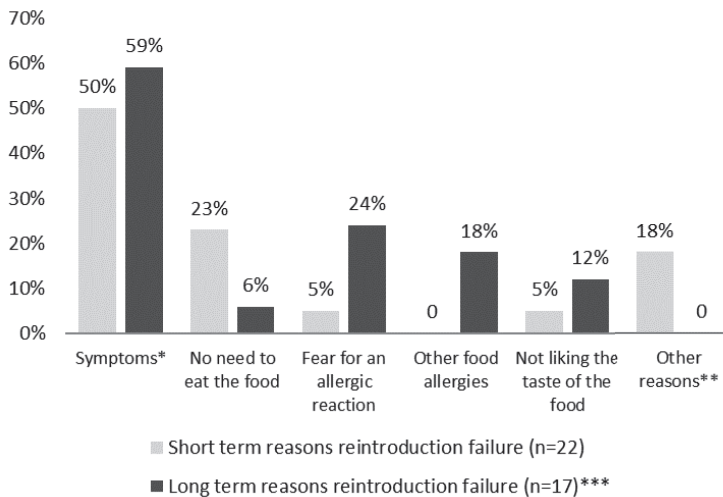
^c Loss to follow up: n = 34

^d Loss to follow up: n = 6

Long term reintroduction failure occurred in 40% partly due to similar reasons

On the long term (data available in 67 food challenges, carried out in 47 patients) reintroduction failure increased to 40% (95% CI: 28%-53%) (27/67). The most common reason for long term reintroduction failure (data available for 17 food challenges) was having atypical symptoms after eating the food (59%, 10/17), mainly atypical gastro-intestinal and skin/mucosal symptoms. Other reasons were fear of an allergic reaction (24%, 4/17), having other food allergies (18%, 3/17), not liking the taste of the food (12%, 2/17) and feeling no need to eat the food (6%, 1/17; figure 1 and 2).

Figure 2. Patient-reported reasons for reintroduction failure



*Short-term: 82% atypical symptoms, 18% typical allergy symptoms. Long-term: 100% atypical symptoms.

**Other reasons were (n = 4) as follows: (a) abdominal problems cause other than food allergy, (b) first wanted advice about other non-allergic symptoms to the food, (c) seasonal food product, not available anymore when patient had to repeat the reintroduction scheme and (d) wanted to reintroduce but it just did not happen.

***More than one answer possible

Daily diet on the long term after successful and failed reintroduction

In the 40 cases in which long-term reintroduction was successful, the frequency at which the food was consumed differed from daily (30%, 12/40) to weekly (28%, 11/40) to monthly (43%, 17/40), either as ingredient (100%, 40/40) or as pure food (70%, 28/40).

Long term reintroduction failure was defined as “not eating the food, eating only products that might contain traces of the food or eating the food at a frequency of <1 occasion per month

(in case of seasonal products: < once a month when the food was regularly available), 6 months after the last food challenge". Of the food challenges where long-term reintroduction failed (data available for 25 food challenges), in 64% (16/25) the food was not strictly avoided: in 40% (10/25) the food (pure and/or as ingredient) was used at a frequency of less than once a month and in 24% (6/25) only products with precautionary allergen labelling (PAL) were used.

Risk factors for long-term reintroduction failure

Comparing successful and failed long term reintroduction, five possible risk factors for long-term reintroduction failure were found, namely: if culprit food was not a major allergen (7% vs 42%, $p=0.01$), a higher mean baseline score of FAQLQ-AF domain Risk of accidental exposure (mean score 4.0 (sd: 1.1) vs. 5.0 (sd: 1.1), $p=0.01$), a higher mean baseline score of state anxiety (mean score 27.9 (sd: 7.4) vs 35.6 (sd: 10.5), $p=0.01$), short term reintroduction failure (11% vs 42%, $p=0.03$) and atypical symptoms during food challenge (48% vs 79%, $p=0.04$; Table 2 and Supplemental Table 1).

If patients did undergo one or more positive food challenge was not a risk factor for negative food challenges (successful reintroduction 23% vs failed reintroduction 29%, $p=0.642$).

Table 2: Potential risk factors of long term reintroduction failure on long term of the first performed food challenge of every patient

Factors	Success N (%)	Failure N (%)	p-value
Food challenge and reintroduction			
Food challenge method (n=46)			0.58
- Open	12 (44)	10 (53)	
- Blind	15 (56)	9 (47)	
If culprit food was a major allergen* (n=46):			0.01
- Yes	25 (93)	11 (58)	
- No	2 (7)	8 (42)	
Non-specific symptoms during food challenge (n=46)			0.04
- Yes	13 (48)	15 (79)	
- No	14 (52)	4 (21)	
Patients conviction about the conclusion from food challenge (n=45)			0.01
- Very convinced	19 (70)	5 (28)	
- Pretty, little or not convinced	8 (30)	13 (72)	
Short term reintroduction (n=46)			0.03
- Successful	24 (89)	11 (58)	
- Failure	3 (11)	8 (42)	
Underwent one or more positive food challenges			0.642
- Yes	6 (23)	5 (29)	
- No	20 (77)	12 (71)	

Table 2. *Continued*

Factors	Success Mean (SD)	Failure Mean (SD)	p-value
FAQLQ-AF, FAIM and STAI			
Food allergy related quality of life, before food challenge (n=43)			
- Total score	4.1 (1.1)	4.8 (0.9)	0.05
- Domain Risk of accidental exposure	4.0 (1.1)	5.0 (1.1)	0.01
- Domain Emotional impact	4.3 (1.4)	4.8 (1.1)	0.20
- Domain Allergen avoidance-dietary restrictions	4.0 (1.3)	4.6 (1.1)	0.14
- Domain Food allergy-related health	4.3 (1.4)	4.7 (1.6)	0.35
FAIM before food challenge (n=43)	3.5 (1.0)	4.0 (0.9)	0.10
STAI: state-anxiety, before first food challenge (n=43)	27.9 (7.4)	35.6 (10.5)	0.01
STAI: trait-anxiety before food challenge (n=43)	31.3 (7.6)	34.9 (8.1)	0.14

**The 13 EU regulated allergens includes: cereals contain gluten, crustaceans, eggs, fish, peanuts, soybeans, milk, nuts, celery, mustard, sesame seeds, lupin, molluscs*

Discussion

This is the first study addressing frequency and reasons for reintroduction failure in adults after a negative food challenge. Reintroduction failed on short term in 20% (95% CI: 13%-28%) and on long term in even 40% (95% CI: 28%-53%). Common reasons were atypical symptoms (both on short and long term), no need to eat the food (short term) and fear of an allergic reaction (long term). Five risk factors for long-term reintroduction failure were found: a culprit food other than the major food allergens, short-term reintroduction failure, atypical symptoms during FC, a lower quality of life and a higher state anxiety.

Reintroduction failure rate in adults appeared to be in the same range as in children: 8% to 44% (11-15,17). We based the definition of long-term reintroduction failure on the assumption that the foods that are challenged were eaten at least once a month in the general Dutch population (24), which was the case for almost all negatively challenged foods (data not shown). In literature, the definition for successful reintroduction varied from eating the food regularly (11,14), to at least once a month (25) to occasionally (13,17). This makes comparison of the studies difficult. If we would adapt our definition for long term failure, and consider the 10 patients who used the food at a frequency of less than once a month as successful, then the result would be that 50 patients (77%) would be successful and 15 (23%) failed introduction. The high frequency of reintroduction failure and the increase over time stresses the need for improved and more patient-tailored care after negative food challenges, not only in the first weeks after negative challenge but also thereafter. This should lead to less elimination diets, reduced social impairment (26), decreased fear of accidental reactions (27), decreased nutritional deficiencies (28) and improved quality of life (29,30).

The most common reason for reintroduction failure both on short and long term was having atypical symptoms. In children this was reported in 7% (16). This difference between adults and children might be caused by the fact that young children are less capable of reporting (subjective) symptoms. It is important that professionals give specific attention to such symptoms by explaining that such symptoms are not due to food allergy and therefore are not a reason to stop reintroduction or avoid the food and to discuss other potential explanations for these symptoms.

Another common reason for reintroduction failure was that patients felt no need to eat the food. Two studies in children showed that this was a reason for reintroduction failure in 3 to 13% of children (11,17). Recent literature indicates the importance of (early) introduction of food and continued exposure in preventing food allergy in children (8-10). We saw that patients who failed reintroduction more often reported 'expansion of diet and to experience fewer limitation in daily life' as purpose of the food challenge compared with patient who successfully reintroduced, however this was not a significant difference. If patients purpose of a food challenge is not to reintroduce the food after a negative food challenge it is still important to discuss the benefits from a food challenge. An important reason for a food challenge is to better estimate the chance of severe allergic reactions to a food and the need for an adrenalin auto injector. Professionals should discuss the purpose of the challenge from patients and professionals perspective before proceeding to food challenges, to assess the added value of carrying out a food challenge.

Fear of allergic reactions was another common reason, as was previously shown in children (11,14,17). This was illustrated by the relatively higher score on state anxiety (anxiety in the specific situation of eating) before food challenge in the group who failed reintroduction. Adequately addressing anxiety appears another important issue to be integrated in the follow-up care, e.g. by identifying the presence, discussing the impact and considering counseling by a psychologist.

Typical allergic symptoms during reintroduction were also reported, but only in two patients. Symptoms were never severe, confirming the strong diagnostic value of the food challenge procedure (3). Literature in children shows a somewhat higher frequency of typical allergic symptoms upon reintroduction, namely in 3-12%, but in line with our data, the reported symptoms are not severe (12,13). Dambacher et al. (12) suggested that the explanation for this false negative result of the food challenge is that the threshold dose for the allergic reaction is higher than the dose reached at the food challenge. This was however not the cause in our study, where typical allergic symptoms occurred during following the reintroduction schema which did not exceed the highest dose of the food challenge. Another explanation might be the influence of the matrix of the food challenge on the threshold

dose (31) or the presence of cofactors during reintroduction in daily life (32). In these (rare) cases it is important to reconsider the challenge result and adjust the dietary advice. Since no severe allergic symptoms were reported, we feel that the reintroduction procedure can be performed at home.

Three of the risk factors for long term reintroduction failure are measured before food challenge, namely if culprit food was no major allergen, a higher mean baseline score of FAQLQ-AF domain risk of accidental exposure and a higher mean baseline score of state anxiety. In daily practice, measuring these risk factors will give insight in the chance of reintroduction failure and might be helpful for tailoring follow-up care to the patients' needs.

A limitation of this study was that part of the results on the long term were missing because of non-response to the questionnaires. Comparing completers versus non-responders with regard to patient characteristics and risk factors for long-term reintroduction failure, the only difference was that in patients who did respond, the culprit food was significantly more frequently not a major allergen (data not shown), which was a risk factor for reintroduction failure. This might lead to overestimation of the frequency of long-term reintroduction failure. The strength of this study was the prospective design, which minimizes the risk of recall bias.

In conclusion, this study shows that despite careful standardized follow-up care, reintroduction failure after a negative food challenge in adults is common and increases over time, with a major impact of atypical symptoms. This stresses the need for more patient-tailored care before and after negative food challenges.

Acknowledgements

We are thankful for the help with data collection of the nurses of Allergology outpatient clinic of the University Medical Centre Utrecht. Also, we like to thank prof. G.F. Houben and dr. H.M. Kansen for their critically reviewing the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

A. Versluis, A.C. Knulst, F.C. van Erp, Y. Meijer and H. van Os- Medendorp designed the study. A. Versluis and M.A. Blankestijn collected the data. A. Versluis, H. van Os-Medendorp and A.C. Knulst analyzed the data and wrote the manuscript. All authors contributed to interpretation of results and manuscript revision. The final version of the manuscript was approved by all authors.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

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Supplemental tables

Supplemental Table 1. Potential risk factors of reintroduction failure on long term of the first performed food challenge of every patient

Factors	Success N (%)	Failure N (%)	p-value
Patients characteristics, food habits and purpose			
Gender (n=46):			0.61
- Male	9 (33)	5 (26)	
- Female	18 (67)	14 (74)	
Educational level (n=45):			0.06
- Low/Intermediate	15 (58)	16 (84)	
- High	11 (42)	3 (16)	
Atopic comorbidity (n=46)			0.25
- Yes	24 (89)	14 (74)	
- No	3 (11)	5 (26)	
Sensitization for negatively challenged food (n=40)			0.70
- Not sensitized	11 (41)	6 (32)	
- Sensitized	14 (52)	10 (53)	
- Not tested	2 (7)	3 (16)	
Sensitization for 1 or more type of food (n=46)			0.36
- Sensitization	18 (67)	15 (79)	
- No sensitization	9 (33)	4 (21)	
Duration of the pre-challenge elimination diet (n=33)			0.23
- 0-12 months	5 (29)	8 (50)	
- >1 year	12 (71)	8 (50)	
Patients purpose of food challenge (n=46)			0.14
- 1: Expansion of diet and to experience fewer limitations in daily life	7 (26)	10 (53)	
- 2: Less anxiety	2 (7)	3 (16)	
- 3: Clarification of previous reaction(s) and (severity of) food allergy	13 (48)	4 (21)	
- 4: Both purpose 1, 2 and 3	5 (19)	2 (11)	
Age in years (n=45) (Mean, SD)	31.6 (10.7)	35.3 (15.3)	0.4





CHAPTER 8

GENERAL DISCUSSION

Astrid Versluis, Thuy-My Le, Geert F. Houben, André C. Knulst,
Harmieke van Os-Medendorp

A modified version is submitted for publication as a perspective article

Food allergy affects 0.3-6% of the adults in Europe (1). At present, no curative treatment is available. The key interventions after diagnosing a food allergy are prescribing an elimination diet and emergency medication to treat accidental allergic reactions (2). Despite specific dietary advice, even with instruction from a trained dietician on how to avoid the culprit food, accidental reactions to food still occur in the daily life of food allergic individuals. This thesis describes the frequency, severity and impact of accidental reactions, factors related to the occurrence of these reactions and aspects of adherence to dietary advice after a food challenge-supported diagnosis.

The **main findings** of this thesis are:

- Accidental allergic reactions occur frequently and often are severe (**Chapter 2**).
- Accidental allergic reactions in food-allergic adults are associated with higher costs due to higher need for primary care consultations, outpatient consultations, hospital admissions, travel to health care facilities and sick leave costs due to the reaction (**Chapter 3**).
- Occurrence of accidental allergic reactions are affected by several factors, which can be grouped into three categories: 1) patient-related factors, 2) health care-related factors and 3) food-related factors (**Chapter 2, 4, 5, 6 and 7**).
- Cofactors are regularly present in daily life, but the influence on severity and threshold of accidental reactions seems to be limited (**Chapter 4 and 5**).
- Patients frequently do not adhere to dietary advice, neither after a positive nor negative food challenge (**Chapter 6 and 7**).

This general discussion consists of three parts.

1. The first part discusses the frequency and severity of accidental allergic reactions and their impact on costs and health-related quality of life (HRQL).
2. The second part focusses on factors affecting the occurrence of accidental allergic reactions. These factors are classified into 3 categories, related to: 1) the patient, 2) health care and 3) the food. Per category, the factors are discussed and implications for prevention of accidental allergic reactions described.
3. The final part gives conclusions and implications for clinical practice and future research.

1. Accidental allergic reactions occur frequently, are severe and are associated with higher costs

Our literature review (**Chapter 2**) on food allergic patients aged > 12 years showed that accidental allergic reactions occur frequently in daily life. The frequency differed per included study. For example, Sicherer et al. (3) carried out a cross-sectional random telephone survey in patients with sea food allergy (66% ≥ 18 years of age) and reported that 58% had recurrent reactions during lifetime, whereof 21% had experienced more than six recurrent reactions, whereas Anibarro et al. (4) showed in a retrospective study with food allergic adults a frequency of only two reactions per patient over 5 years. An exact estimation of frequency of accidental reactions was difficult, since the designs of the included studies differed, for example with regard to circumstances and characteristics of the investigated reactions (e.g. reactions to a specific type of food or in a specific environment like during a flight). A more recent and prospective study from our center (5) showed a relatively high frequency of accidental reactions: approximately half of all included food allergic adults experienced on average two accidental reactions per year. The prospective design of this study likely reduced recall bias, resulting in more reactions being reported compared with Anibarro et al. (4).

The severity of accidental allergic reactions varies from mild to severe, and was sometimes even fatal (**Chapter 2**). Anibarro et al. (4) and Comstock et al. (6) showed, respectively, that 32% and 57% of the accidental reactions were severe (respiratory and/or cardiovascular symptoms). Four studies reported fatalities due to accidental reactions. For example, Bock et al. (7,8) described respectively 26 and 23 fatal reactions in patients older than 12 years of age over two 5-year periods based on cases reported in a registry in the United States (US) and Liew et al. (9) reported three fatal reactions over a 9-year period based on a national database in which anaphylactic deaths are registered in Australia. The more recent and prospective study of Michelsen-Huisman et al. (5) showed that 28% of the accidental reactions were severe. This study reported no fatal reactions.

The foods causing accidental reactions most frequently were peanut, nuts, hen's egg and cow's milk (**Chapter 2**). This may be due to the widespread use of these foods or ingredients derived thereof in a large variety of products and food production facilities, which also increases the risk of cross contamination (10). Peanut and nuts were most often associated with occurrence of severe reactions (**Chapter 2**). This may be associated with the fact that unintended presence of peanut and nut in food products will be often in the form of particulates. Furthermore, in peanut and nut allergy, sensitization to seed storage proteins occurs frequently, which are allergens that more often cause severe symptoms due to stability of the protein resulting in resistance to heat and proteolysis (11). **Chapter 6**

showed that there is no difference in adherence to dietary advice after food challenges with peanut/nuts and other types of food, indicating that non-adherence is not the reason that peanut and nuts are a frequent cause of accidental reactions.

Patients often do not (adequately) use their emergency medication following their accidental reactions (**Chapter 2**). Even after severe reactions, patients often do not use their emergency medication, in particular the first choice drug (adrenaline), and do not visit an emergency department (**Chapter 2**). This increases morbidity and the risk of fatal reactions (12). The EAACI guidelines (2) recommend that adrenaline must be administered in case of reactions with respiratory and cardiovascular symptoms and that the patient should be evaluated at an emergency department. Our recent prospective study (5) showed that in 86% of the cases with severe reactions, emergency medication was used, but in only 5% of the cases adrenaline was used and in only 14% medical care was sought. Despite this, no fatal reactions were reported. However, it can be assumed that recovery took longer without optimal treatment. Also other studies report that adrenaline auto-injectors are under-used (13,14). It is worrying that patients not optimally manage potentially life-threatening situations. Patients need to be aware of the importance of adequate emergency treatment, which requires careful and repeated instruction about how and when to use emergency medication when needed, especially the adrenaline auto injector. Health care professionals should be aware that emergency management is a challenge for patients and needs to be a recurring topic of discussion during consultation. Furthermore, it might help if patients always carry their emergency plan with them, on paper or as an emergency treatment app (15).

Another important aspect is the impact of accidental reactions on costs. This thesis showed that adult patients (mostly with a severe food allergy [87%]) who experience accidental reactions had sevenfold higher direct (medical) and indirect (non-medical) costs than patients without reactions (mean €1186 (bootstrap 95% CI: €609-1845) vs €158 (bootstrap 95% CI: €68-266)) (**Chapter 3**). The costs of all examined subcategories were higher in patients with reactions compared to patients without reactions: primary care consultations (mean: €443 vs. €64), outpatient consultations (mean: €332 vs. €81), hospital admissions (mean: €308 vs. €0), travel costs to health care facilities (mean: €50 vs. €13) and sick leave costs due to the reaction (mean: €62 vs. €0). Assuming that 2.1% of the Dutch adults has food allergy (1) whereof, 46% experiences accidental reactions yearly (5), a rough estimation of the total yearly costs for all food-allergic Dutch adults with accidental reactions would be 160 million euro and 25 million euro for those without accidental reactions, illustrating the large economic burden of accidental reactions. Patel et al. (16) showed in a retrospective study in the US that costs due to food-induced allergic reactions

are estimated on half a billion dollars per year; ambulatory visits were responsible for more than half of the costs (52%). Due to differences in healthcare financing systems and the role of the general practitioner between our country (the Netherlands) and the US, and in study design, it is difficult to make an adequate comparison of costs (17,18). However, it is notable that both the results of Patel et al. (16) and our study (**Chapter 3**) showed that emergency visits and hospital admissions are responsible for less than half of the costs. It is known that patients often do not seek adequate medical care at the emergency department even when a reaction is severe (5), which might explain the relatively low costs of emergency visits and hospital admissions. This implies that the costs for emergency department visits (and thereby the total costs) would be considerably higher if all patients were to adequately manage their accidental reactions.

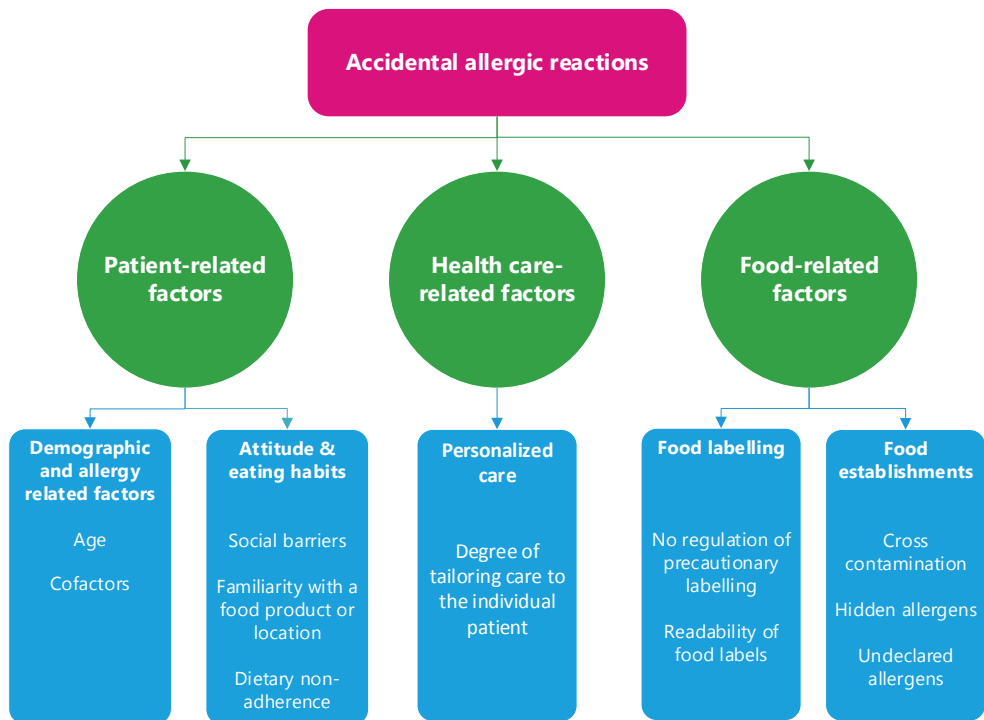
In **Chapter 3** we showed that experiencing accidental reactions in the preceding year has no additional impact on the already impaired health-related quality of life (HRQL) of food allergic patients. Most patients included in the study had a food allergy already for a very long period (mean: 24 years), which probably led to a relatively stable impaired HRQL. It is known from literature that having a food allergy impairs HRQL and causes anxiety (15,16). Multiple factors affect the impairment of HRQL, including: dietary restrictions, severity of the food allergy, type of food allergy, having multiple food allergies, emergency treatment used and sociodemographic factors (17-20). Polloni et al. (19) showed that severe life threatening reactions might even lead to a post-traumatic stress reaction.

In conclusion, accidental reactions occur frequently, are often severe, and often inadequately treated. Severe reactions are associated with sevenfold higher costs but do not further decrease the already strongly impaired HRQL in individuals with a long lasting history of their food allergy. Therefore, prevention of accidental reactions is very important. To this end, better understanding factors that affect the occurrence and severity of accidental reactions is crucial. In the following section, these factors are discussed.

2. Many factors affect the occurrence of accidental allergic reactions

To be able to prevent accidental allergic reactions, it is important to identify factors that affect their occurrence. This thesis identified several factors which can be grouped into three categories: 1) patient-related factors, 2) health care-related factors and 3) food-related factors (figure 1). With regard to category 1 (the patient) the most important factors are age-related factors and factors related to attitude and eating habits. With regard to the other two categories (health care and food), the most important factors are the extent to which health care is tailored to patients' individual needs and issues related to food labelling. In the following paragraphs, the factors are discussed per category.

Figure 1. Factors affecting the occurrence of accidental allergic reactions



2.1 Patients related factors affecting the occurrence of accidental reactions

This paragraph describes patient-related factors which can affect to the occurrence of accidental reactions, including age-related factors, factors related to attitude and eating habits and cofactors.

2.1.1 Age-related factors

Age-related factors impact the occurrence of fatal accidental reactions. Bock et al. (8) showed that adolescents are at high risk of fatal reactions: among 32 fatalities, 69% occurred in patients between 13-21 years of age. This high percentage can be due to higher risk-taking behavior with regard to the management of the elimination diet by teenagers and adolescents (**Chapter 2**). Also other literature reports that adolescence is a period of heightened vulnerability to risk-taking behavior (20,21). Sampson et al. (22) reported that only 61% of the adolescents always carry their adrenaline auto-injector, meaning that 39% do not. Also in other chronic diseases it is reported that adolescents are particularly vulnerable to poor health outcomes (23,24). For example, adolescents with asthma have a lower treatment adherence than people in other age groups, which negatively affects morbidity and even mortality (23,25). Adolescence is the period in which dietary management transition from parents to child takes place. Specific strategies for this transition for food allergic individuals are important (26,27), such as early start of the transition process (11-13 years), using a multidisciplinary approach, discussing self-management in everyday contexts such as school/work and actively evaluating adherence (27). Using these strategies might reduce risk-taking behavior, and result in less accidental reactions.

2.1.2 Attitude and eating habits: social barriers, familiarity with food/location and dietary change

With regard to the attitude and eating habits of the patient, several factors appeared to play a role. We observed that patients often experience social barriers to disclosing their allergy when eating outside their home, due to (fear of) potential social embarrassment (**Chapter 2**). It is important that patients give information about the food allergens they avoid, because then the person who prepares or provides the food can take this into account. Our literature review (**Chapter 2**) showed that accidental reactions often occur at locations outside the home (63-74%). This is comparable with a recent study based on the national Food Allergy Research & Education (FARE) registry in the United States, showing that 65% of the allergic reactions to food in adults occur outside the home (28). This study also reported that in 46% of the allergic reactions that occurred in restaurants, patients did not disclose their allergy status to the restaurant staff (28). A qualitative interview study showed examples of social embarrassment: food allergic patients fear situations in which they feel that their communication would attract undue attention whereby they could be seen as a fussy eater (29). It is reported that patients who have an highly open personality (the desire for novel ideas or experiences) experience more issues with social occasions, including greater feeling of embarrassment, than patients with lower levels of

openness (30). In general food legislation is not very helpful in allergic consumers' everyday life. A recent positive development was that since 2014 mandatory information about the presence of the 14 major allergens in non-prepacked foods, also in restaurants and cafés (31) is required. Begeen et al. (32) showed that this legislation provides food-allergic patients with a sense of empowerment. This applies especially to those who felt embarrassed about asking restaurant staff questions. However, this feeling of empowerment was not manifest in all patients. Therefore it is hugely important that patients are supported and encouraged to disclose their allergy status to others. Healthcare professionals and patients should openly discuss social embarrassment, by helping patients understand the effect of their own personality on their food allergy experiences in daily life.

Another factor related to eating habits, is when they use familiarity with a food product or eating location as a strategy to judge the safety of food. **Chapters 2 and 6** showed that allergic consumers estimated the risk of eating a certain food product based on the type of food product or brand in combination with prior experiences, instead of reading the complete food label. This way the individual might miss possible changes in ingredients, which can lead to an accidental reaction. Furthermore, allergic consumers considered high-risk eating locations, like cafés, fast food restaurants, ice cream shops and Asian restaurants, where allergic reactions occur more often, as safe when the eating venue was familiar. Therefore, it is important that risk assessment of a food product or eating location should not be based on familiarity, since actual risks might be missed, leading to accidental reactions.

Non-adherence to the advised elimination diet is also important (**Chapter 6**). Following a less strict diet than advised, puts patients at higher risk of accidental reactions. In **Chapter 6** we found two factors that led to non-adherence to dietary advice: 1) patients who were advised to change their diet following a positive food challenge and 2) patients who were advised to strictly avoid the culprit food (meaning avoidance of the allergenic food and ingredients, including products with precautionary allergen labelling (PAL)). But also dietary change after a negative food challenge often fails; in 40% of the cases with negative food challenges, patients fail to reintroduce the negatively challenged food into their daily diet (**Chapter 7**). Barriers of changing dietary behavior might play a role. It has been shown in other chronic diseases, like coeliac disease, cardiovascular diseases and obesity, that adherence to specific dietary patterns is challenging because of many barriers, such as: higher costs, overall restrictive nature of the diet, the patient's food environment, medical comorbidities, social support and practical factors, for instance developing cooking skills (33-35). Tapsell (33) reported that encouraging dietary behavior change to improve nutritional quality and health outcomes requires more than information about healthy foods, because psychological factors will influence food choices regardless of knowledge

about food. This study suggests that an interdisciplinary effort including combining diet and psychological support is needed to support individuals in making appropriate changes within their complex life circumstances (33). Patients who were advised to strictly avoid the culprit food more often failed to adhere to dietary advice. This might be explained by the fact that a strict elimination diet has more impact on food choices than a less strict diet. Another aspect might be that many patients do not consider PAL credible and therefore ignore these labels (36,37). This is discussed in more detail in paragraph 2.3.1. The high frequency of non-adherence to dietary advice, indicates that more guidance with regard to dietary behavior is needed. This seems especially important in patients who are advised to strictly avoid the food, since these patients are at higher risk of non-adherence and mostly have a severe food allergy.

2.1.3 The influence of cofactors on the severity and threshold of accidental allergic reactions seems to be limited

Cofactors are often present during accidental allergic reactions (74%), but appear to be a minor factor with regard to the severity of these reactions (**Chapter 5**). In literature, cofactors are reported as factors influencing the severity and/or threshold of allergic reactions in some patients (38,39). Frequently suggested cofactors are physical exercise, use of nonsteroidal anti-inflammatory drugs (NSAIDs), use of alcohol and active infectious diseases (39). Cofactors might have different underlying mechanisms, for example an increased gastrointestinal permeability and absorption of proteins after physical exercise or intake of NSAIDs (38,39) and in case of acute infections, fever causing an elevated blood circulation and subsequent influx of food allergen (38). However, the exact influence and impact of cofactors is unclear. **Chapter 4** showed that only 13% of the patients reported experiencing more severe symptoms after accidental reactions in combination with one of the examined cofactors (physical exercise, use of alcohol and/or analgesics). In addition, **Chapter 5** showed no significant difference in the presence of potential cofactors between mild, moderate and severe accidental reactions, indicating that cofactors do not influence the severity of accidental reactions. In **Chapter 5**, the data was collected prospectively, likely resulting in less recall bias and more precise data than the retrospective study presented in **Chapter 4**. In contrast, Wölbing et al. (39) and Niggeman et al. (38) both carried out a literature review about cofactors in anaphylactic reactions and concluded that these factors play a role in elicitation and severity of reactions. However, both literature reviews reported that underlying mechanisms are not fully understood and that further research was needed. Recently, Dua et al. (40) published a prospective study in peanut-allergic participants who underwent three open peanut challenges: combined with exercise, with sleep deprivation,

and with no intervention. This study reported that both sleep deprivation and exercise caused only a limited reduction of the individuals' threshold to peanut. Turner et al. (41) assessed the results of this study and concluded that this decrease is equivalent to a single dosing interval when using a PRACTALL-style semilogarithmic dosing regimen and is well within the intraindividual variation in reaction threshold reported by Patel et al. (42). Furthermore, Turner et al. (41) argued that the factor with the largest impact in threshold variability was the clinical center at which patients were evaluated. Moreover, exercise was only identified as a significant factor in one of the two clinical centers (40). Therefore, although cofactors can have some effect on threshold and severity of the reaction in some individuals, this does not appear to be any greater than the inherent shift in both clinical thresholds and risk of anaphylaxis identified in the wider food-allergic population, nor does it appear that such effects are predictable. The limited impact of cofactors is also indicated by the fact that population Eliciting Dose (ED) values calculated from reaction thresholds in the presence of the cofactors (40) were not lower than those based on the world wide largest threshold dataset as published by Remington et al. (43) and Houben et al. (44), indicating that the variability caused by these cofactors may not outrange that already covered in such a large database. Another important issue that is strongly underestimated is that, on a daily basis, more than one third of the food allergic patients (38%) use medication that suppresses allergic symptoms (e.g. antihistamines and corticosteroids) (**Chapter 5**), possibly limiting the potential influence of cofactors. In conclusion, cofactors are very regularly present in daily life, but the influence on severity and threshold of accidental reactions seems to be limited. Still, cofactors need to be considered when assessing a patient's medical history. If there is any suspicion of a role of cofactors in occurrence of (severe) accidental reaction, it is advisable to inform patients about the possible role that cofactors can have in accidental reactions and how to manage these factors in daily life.

2.1.4 Implications: take into account which factors apply to the individual patient

The previous paragraphs showed that several patient-related factors affect the occurrence of accidental reactions. It is important to highlight that the factors involved differ per patient. Therefore, in clinical practice, it is important that health care professionals investigate which factors apply for the individual patient. The following paragraph discusses strategies for clinical practice to tailor care to the individual patient.

2.2 Health care-related factors: a more patient-tailored approach is needed

As illustrated in the previous paragraphs, accidental reactions are a significant problem in the daily life of food allergic patients. In **Chapters 6 and 7** we reported that after a food challenge

with either a positive or a negative outcome, adherence to dietary advice was poor (resp. 31% and 60%), despite dietary advice via standardized follow-up after the food challenges. Standardized follow-up after diagnosing a food allergy consisted of written information about the diagnoses and dietary advice, and a consultation with the physician and/or dietician when all tests had been performed. If indicated, additional follow-up consultations could be scheduled. During consultations, patients received support and education with regard to their food allergy, allergen avoidance, symptoms recognition and indication for treatment. Our standardized follow-up is largely consistent with the recommendation of the international EAACI guidelines (2). The poor dietary adherence after diagnostics with food challenges shown in **Chapter 6** indicates that current standardized care for food allergic patients is not sufficient. The previous paragraphs discussed the multiple factors related to the patient which affect the occurrence of accidental reactions. Not every factor applies to every patient. For instance, not every patient has a strict diet or is advised to change the diet after diagnostics, which are factors affecting the occurrence of accidental reactions. This suggests that clinical practice must be tailored to the individual patient. Based on previous research, we formulated the following recommendations to tailor health care to the individual patient:

1. **Education:** The international EAACI guideline (2) reports that education is the key intervention for an effective elimination diet. The type of education materials can be tailored to the individual patient. Face-to-face consultations seem an appropriate moment to discuss which tools best suit the patient. Different tools can be combined, such as group sessions, written materials, mobile apps, video and online self-management programs (45-51). During this process it is important to take into account health literacy (see point 5). Furthermore, education of family and close relatives about risk situations should be considered (2).
2. **Behavioral aspects:** It is important that support regarding behavioral aspects is tailored to the individual patient. For instance, specific attention and guidance is needed for patients who are advised to change their diet after diagnosis, and therefore need to change their dietary behavior. In these patients, extra follow-up consultations are important for supporting dietary and behavioral change (33). Furthermore, extra attention is needed for adolescents due to higher risk taking behavior. The international EAACI guidelines (52) recommend that adolescents should be positively encouraged to self-manage their condition whilst still in a 'semi-protected' environment, in preparation for adulthood. There are several ways to support this transitional process (27), see paragraph 2.1.1..
3. **Psychosocial aspects:** It is important to recognize psychosocial aspects like anxiety and social embarrassment, and tailor interventions to patients' needs. It is reported that there

are mental health concerns in some food allergic patients (53). Health care professionals can support patients with psychosocial aspects/issues by: 1) paying attention to education, 2) enhancing self-efficacy for instance by practicing assertiveness about avoidance of allergens, 3) assessing social concerns, for example discussing problems that patients and family encounter with regard to managing the food allergy and 4) meaning making, for instance by reflecting on the positive growth patients make due to the challenges of managing food allergy (54). Mental health professionals can help to address psychosocial concerns in case there is a greater need for support (55).

4. **Decision making:** During the process of diagnosis and treatment, many decisions have to be made. Involvement of the patient in this process of decision making (shared decision making) is important. Shared decision making is a process wherein health care professional and patient work together. A mutual discussion between health care professional and patient regarding diagnostics and treatment options helps to make decisions based on both the options and the patient's individual preferences. This will empower patients to make decisions that they find most acceptable (51,56,57). Within the care for patients with food allergy this can be applied, for instance, when deciding whether or not to undertake a food challenge, whether or not to schedule a consultation with the dietician, or about the type of tools used for education.
5. **Health literacy:** An important aspect to take into account is health literacy. Health literacy is patient's ability to obtain, process, and understand the basic health information and services needed to make appropriate health decisions and to effectively communicate with health care providers. A low health literacy is linked to poor health behavior and outcomes (58). Approaches to address health literacy are: shared decision making, use of patient-friendly education material (e.g. simple pictures, key points), using eHealth intervention (video's, interactive self-help tools), avoiding jargon, focusing on the key messages and repeating, use of the "teach-back" method (ask the patient to recall what they have been told), and group education (59-62).
6. **Multidisciplinary team:** A multidisciplinary team helps to organize and coordinate all health care aspects to meet the different needs of the individual patients. In our clinical practice the multidisciplinary team includes food allergy specialists, specialized dieticians, clinical nurse specialists and nurses. Furthermore, in some cases, a mental health professional, pulmonologist or internist is consulted. In a multidisciplinary team, it is important that every discipline has its own responsibility and is aware of each other's role (48). A dietician specialized in food allergy, can identify possible food-symptom relationships based on detailed nutrition history, can provide personalized counseling regarding food allergen avoidance and adequate nutrient intake while following an

elimination diet (63). In our practice, the clinical nurse specialist has a role in diagnosing, treating and supporting patients within a specialty area and integrating new knowledge and innovation into the system of care. This matches with the professional profile of the clinical nurse specialist in our country (64). To have an effective multidisciplinary team, attention to inter-professional collaboration is important; for instance, working on good relationships between team members, managing possible conflicts within teams effectively and ensuring equality and inclusiveness of team participation (65,66).

Applying the previous recommendations will help to ensure that health care is more tailored to the individual patient. For future research, it would be interesting to evaluate the effectiveness of these recommendations with regard to the occurrence of accidental reactions.

2.3 Food-related factors: better regulation of food labelling and food establishments needed

This paragraph describes food-related factors affecting to the occurrence of accidental allergic reactions. The first subparagraph describes factors with regard to food labelling of prepackaged food products. The second subparagraph addresses the role of food establishments.

2.3.1 Food labelling issues are a main cause of accidental allergic reactions

In **Chapter 2** we showed that two food labelling issues affect the occurrence of accidental allergic reactions, i.e. 1) the absence of regulation regarding when and when not to use a precautionary allergen labeling (PAL) statement and 2) interpretability, clarity and readability of food labels. These findings further elucidate the results of our recently published study (5) reporting that prepackaged food products were the main cause of accidental reactions.

A major issue is the absence of regulation regarding when and when not to use a PAL statement on prepackaged foods. In **Chapter 6** we showed that there are different reasons that patients consciously choose not to adhere to their strict avoidance diet, i.e.: 1) a strict avoidance diet leads to too many restrictions and 2) products with PAL are considered to be safe. PAL is used by manufacturers to give information about the possible occurrence of allergen contamination during the production process of food products. PAL is however voluntary and the decision to either use or not use PAL and the presentation of PAL differs per manufacturer. It is reported that 17-68% of all manufactured foods contains PAL (67,68). Chocolate, candy and cookies have such a description on more than 50% of the labels (67). But only 10% of the prepackaged food products (37) and 25% of the prepackaged cookies/

chocolates (69) with a precautionary statement about peanuts had a detectable level of this allergen. This corroborates the notion that avoidance of products with PAL leads to huge and unwanted dietary restrictions, with all their nutritional and societal consequences. On the other hand, it was reported that there are prepackaged food products with high levels of unlabeled allergens, which is a major concern because of the risk of severe accidental reactions (70,71). We analyzed food products which caused accidental reactions, and detected in 37% of the products a non-ingredient allergen (72), which is higher than previously reported 10-25% (37,69) most likely because these were random samples. We showed that milk protein concentrations in unlabeled products reached such high levels that they might elicit allergic reactions in up to 68% of the adult cow's milk allergic consumers (71). Usage of PAL on prepackaged food products is often not based on a standardized risk assessment process. The current practice of deciding on and the way of using PAL has resulted in non-uniform application of PAL and generated more confusion and uncertainty for food allergic patients than benefit (73,74). Many patients do not consider PAL credible and therefore ignore these labels (36,37). In 2007, the Voluntary Incidental Trace Allergen Labelling (VITAL) Program was launched, which aimed to make a simple, standardized precautionary allergen statement related to the presence of an unintended allergen (75). This program recommends the use of so-called reference doses to guide the risk management and the decision to either apply or not apply a PAL statement on prepackaged food products (75). Furthermore, recently the Ad Hoc Joint FAO/WHO Expert Consultation on Risk Assessment of food allergens (74) gave promising recommendations to the United Nations Codex Alimentarius Commission for improvement of PAL, including the recommendations to only use PAL when the allergen may be present at levels that may result in intakes in excess of a relevant reference doses. In addition they advised to choose a clear uniform wording, and to let food business operators document evidence of compliance to a harmonized guidance and their risk assessment for unintended allergen presence. Adoption of the recommendations of the Ad Hoc Joint FAO/WHO Expert Consultation on Risk Assessment of food allergens (74) will strongly contribute to global harmonization of risk based allergen management and PAL. The Expert Consultation however also noted that education of allergic consumers (or those providing food for them, including food business operators) and other relevant stakeholders (e.g. risk assessors, risk managers, healthcare providers) is critical, to ensure understanding of the applied principles and the implications of the chosen phraseology (74).

In addition, **Chapter 2** showed that issues with interpretability, clarity and readability of food labels affects the occurrence of accidental reactions. A recent study from our group (76) showed that less than 50% of patients considered allergy information to be clear. Furthermore, patients attributed different risk levels of unintended presence of allergens

in prepackaged food products to different wordings of PAL, especially patients with higher levels of health literacy (76). In another study, nearly 300 food labels were studied and a wide variety in ways of communication on allergen presence was found (77), increasing the risk of misinterpretation. Six recommendations were given to improve allergen information on food labels: ensure readability of food information, presenting allergens in the ingredient list in bold, uniform topic order on the label, providing an allergen information section, use of one uniform PAL wording, and use of allergen icons (77). The Ad Hoc Joint FAO/WHO Expert Consultation on Risk Assessment of food allergens (74) also strongly recommended the use of one single clear wording of PAL that would unambiguously convey the message that a product carrying a PAL is not suitable for individuals allergic to the allergen warned about. In conclusion, standardization of the lay-out of food labels to improve readability and clarity appears to be strongly needed. It is important that steps are taken to improve policies and guidelines, to translate such improvements into practice.

2.3.2 Food establishments

There are two food-related factors with regard to food establishments which affect the occurrence of accidental allergic reactions: cross contamination during preparation and the presence of hidden or undeclared allergens in menus (28,78,79). In **Chapter 2**, we showed that 21-31% of the accidental reactions occur in restaurants. In paragraph 2.1.2., we already reported that patient-related factors (e.g. social embarrassment) can lead to the occurrence of accidental reactions in food establishments. This paragraph discusses the factors related to food establishments. Recently, Oriel et al. (28) showed that only in 14% of the reactions which occurred when dining out, the restaurant staff was informed of the food allergy and allergens were declared on the menu, and the reactions thus were likely caused by other factors related to the food establishments or by patient-related factors.

Firstly, an important food establishment-related factor is cross-contamination of allergens during preparation of food. Such cross-contamination can easily occur, for example due to cross-contact by hands and cooking equipment (78). Radke et al. (80) reported that some restaurant staff think that a small amount of an allergen can be safely consumed by a food allergic consumer. It can be assumed that this lack of knowledge leads to less careful work with regard to prevention measures of cross contact. A study in the United States showed that only 41% of the restaurant staff receives food allergy training while working at their current restaurant (81). The recently published Workgroup report from the American Academy of Allergy, Asthma and Immunology (AAAAI) (78) gives recommendations for food establishments to lower cross-contamination, including: educating staff that minimal cross-contact can cause allergic reactions, providing knowledge about cleaning methods

to remove food allergens, creating a special allergen-free area in the kitchen and creating a separate pick-up area for allergen-free meals. However, several barriers are reported for implementation of food allergy training, for example: high turnover of staff, lack of interest in food allergy training and high costs (78). Since cross contamination still causes a significant proportion of accidental reactions, it seems important that more attention should be paid to the training of restaurant staff.

Secondly, hidden and undeclared allergens in menus results in the occurrence of accidental reactions (28,78,79). It is known that risks are higher in specific types of restaurants, like Asian restaurants, Italian restaurants and ice cream shops (78). Miscommunication and knowledge of restaurant staff appears to be to an important cause of hidden and undeclared allergens (78). For example, a study in the United States showed that only 73% of the servers correctly identified hen's egg as a major allergen (70). In addition a study among restaurant staff in Germany showed that only 30% was able to correctly name three common food allergens (82). Since 2014, information about the presence of the 14 major allergens in non-prepacked foods (including in restaurants and cafés) is mandatory (31). However, it was reported that hidden allergens still cause accidental reactions (32,83). It can be concluded that to properly inform food allergic customers, knowledge of restaurant staff about food allergy is indispensable. Furthermore, it is important that food allergic patients are informed about in which types of restaurants there are higher risks of hidden allergens.

In conclusion, better food allergy training seems important to improve knowledge of restaurant staff. Furthermore, it is recommendable that this food allergy training is repeatedly offered, so that the knowledge of restaurant staff remains up-to-date. To make this feasible for food establishments, it seems necessary to reduce barriers, for example by making food allergy trainings easily accessible e.g. by developing eLearnings or mobile apps.

3. Conclusions

Accidental allergic reactions occur frequently and are associated with high costs. Their occurrence is affected by many factors, related to the patient, health care and food. The most important factors related to the patient are age, social barriers to disclosing their allergy and non-adherence to the elimination diet. Not every factor applies for every individual patient. With regard to health care-related factors, the degree to which clinical practice is tailored to the individual patients is important. It is highly recommendable to tailor health care to the individual patient, for example with regard to education and support of behavioral and psychosocial aspects. A major food-related factor is absence of harmonized regulation regarding precautionary allergen labelling. Therefore it is of great importance that steps are taken to improve policies and guidelines for precautionary allergen labelling.

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CHAPTER 9

ENGLISH SUMMARY

NEDERLANDSE SAMENVATTING

English summary

Food allergy is caused by an IgE-mediated immune response to allergenic proteins in a food. It manifests by symptoms of the skin, mucous membranes, gastrointestinal tract, respiratory tract and/or cardiovascular system. The severity of the symptoms varies per patient and per food from only mild itching in the mouth, to sometimes life-threatening and fatal reactions, by for example, blocking of the airways or a drop in blood pressure and shock. The diagnostic work-up includes inventory of a detailed medical history (interview with the patient), sensitization tests (measurement of specific IgE in the blood or by skin prick tests) and a food challenge. The food challenge is the gold standard for ruling out or confirming food allergy. During a food challenge, the food is eaten by the patient in gradually increasing amounts and it is observed whether this causes allergic symptoms. A food allergy cannot (yet) be cured. Treatment consists of avoidance of the food from the daily diet. Patients with a food allergy are preferably treated by a multidisciplinary team of medical specialists, dieticians, clinical nurse specialists and nurses. Daily practice shows that despite the elimination diet and the support given, many patients still experience accidental allergic reactions to food in daily life. Therefore, patients often receive an emergency kit with medication (such as antihistamines and an adrenaline auto-injector) to treat such a reaction. However, it is known that patients do not always adequately deal with accidental allergic reactions, for example, not always using their adrenaline auto-injector in cases of severe symptoms and also often do not seek medical help.

The aim of this thesis was to gain more insight into: 1) the frequency, severity and impact on costs and quality of life of accidental allergic reactions to food, 2) which factors play a role in the occurrence of these accidental allergic reactions, and 3) the degree to which dietary advice is followed after ruling out or confirming a food allergy and which factors play a role in the degree of adherence to dietary advice.

Accidental allergic reactions occur frequently and are often severe

In **Chapter 2**, a review of literature was conducted to investigate the frequency and severity of accidental allergic reactions to food in patients older than 12 years of age. It showed that accidental reactions occurred in a significant number of patients. A more recent prospective study from our center found that on an annual basis, half of all food allergic patients experienced accidental reactions, with on average two reactions per year.

The severity of accidental allergic reactions generally ranged from mild to severe. Two studies showed that, respectively, 32% and 57% of the accidental allergic reactions were severe. In addition, our more recent prospective study showed that 28% of the reactions was severe. The number of fatal reactions seemed to be limited. It was also shown that patients, even after severe reactions, often failed to adequately use their emergency medication. This increases the risk of a severe or even fatal outcome of the reactions.

It was concluded that food-allergic patients frequently experience accidental allergic reactions, which are often severe. In addition, it is remarkable that patients regularly do not take adequate measures to treat themselves, which indicates that more and better support is needed with regard to the use of emergency medication and when to seek medical care.

Accidental allergic reactions lead to higher costs

Chapter 3 described a prospective study about the impact of accidental allergic reactions on costs and quality of life. This study showed that accidental allergic reactions had a significant impact on costs. Patients who had suffered accidental allergic reactions had sevenfold higher direct and indirect costs on an annual basis compared to patients without these reactions (mean €1186 (bootstrap 95% CI: €609-1845) vs. €158 (bootstrap 95% CI: €68-266)). The costs were higher in all examined subcategories: primary care consultations, outpatient consultations, hospital admissions, travel costs to health care facilities and sick leave costs due to the adverse reaction.

During the course of the study, we saw no change in (the already low) quality of life in patients who experienced accidental allergic reactions. A possible explanation was that the patients already had a food allergy for a very long period (mean: 24 years), with an already impaired quality of life.

Given the impact of accidental allergic reactions on costs and their frequency and severity, better prevention of accidental allergic reactions is needed. Insight into factors which play a role in accidental allergic reactions can contribute to the development and provision of tailored preventive interventions. This is addressed in the following paragraph.

Multiple factors influence the occurrence of accidental allergic reactions

Eating location, food labeling, attitude, risk-taking behavior and age

The literature review in **Chapter 2** described the possible causes of accidental allergic reactions. The first aspect was the eating location. Accidental allergic reactions often occurred at locations outside the home, such as at a restaurant or at the home of a friend. A second aspect were issues with labeling of prepackaged foods, particularly the absence of a warning about an allergen while it was or could be present in a food product. Also, issues with interpretation of food labels were sometimes a problem, for example due to phrases such as, "May contain traces of peanuts and tree nuts", or the use of other languages without the information being stated in the patient's native language. Furthermore, the layout of labels was not always clear with regard to the ingredient list and allergen information. A third aspect was that patients sometimes took risks themselves. Patients sometimes did not provide enough information about their food allergy when eating outside the home, for example due to being too embarrassed to talk about

the subject. In addition, both **Chapters 2 and 6**, found that patients often did not check the label of products which they had used previously without any problems. As a result, possible changes in ingredients might be missed, which further increases the risk of accidental allergic reactions. Some studies found that risk-taking behavior was more common among adolescents and young adults, with the following reasons given: never had severe symptoms before, being able to treat any reactions themselves, influence of social circumstances (e.g., “all my friends ate the food”), and lack of understanding of the severity of their food allergy.

We concluded that multiple factors may influence the risk of accidental allergic reactions. For daily practice, it is important to determine for each individual patient, which factors play a role and to tailor the care plan accordingly. Another important factor is the absence of regulations regarding labeling of food allergens that may be present due to contamination during the production process. Improvement in this respect is strongly recommended.

The influence of cofactors on the severity of accidental allergic reactions seems limited

Cofactors are factors that may lead to more severe symptoms and lower thresholds during allergic reactions to food. Examples of cofactors include use of alcohol, physical exercise, infections, and use of some types of medications [such as non-steroidal anti-inflammatory drugs (NSAIDs)]. **Chapters 4 and 5** provided further insight into the influence of cofactors on the severity of allergic reaction. In **Chapter 4** we found in a retrospective study that physical exercise and use of alcohol were most frequently reported by patients as cofactors for more severe symptoms. However, this was reported by only 10% or less of the patients. Furthermore, only a small percentage (8%) of patients were found to be taking standard medications known to be potential cofactors.

In our prospective study, described in **Chapter 5**, it became clear that potential cofactors were often (in 74% of cases) present in accidental allergic reactions. However, no significant relation was found between the presence of cofactors and the severity of accidental allergic reactions. Some studies found some, but only limited, influence of cofactors on the severity and threshold of allergic reactions to food. We concluded that potential cofactors are commonly present in the daily life of patients, but the influence on the severity and threshold of accidental allergic reactions is limited. The advice for daily practice is to inform patients about cofactors and how to manage their food allergy in view of the potential impact the cofactors may have.

Dietary advice following a food challenge is frequently not adequately followed

Chapters 6 and 7 discussed the adherence to dietary advice after, respectively, a positive and a negative food challenge. **Chapter 6** described a prospective study which investigated if patients after a positive food challenge, which confirmed the diagnosis of a food allergy, followed the

advice of an elimination diet. Depending on the severity of the confirmed food allergy, one of the following dietary recommendations was given: 1) strict avoidance of the allergenic food and ingredients [including prepackaged products with warnings for (possible contaminations with) the allergen], 2) avoidance of the allergenic food and ingredients, but products with warning allowed and 3) (small) amounts of the allergenic food or ingredient allowed. The study showed that after 69% of positive food challenges, patients failed to adhere to the specific dietary advice: 17% followed a more strict diet and 52% a less strict diet than advised. In food challenges after which a strict elimination diet (option 1) was advised, even 82% of the patients followed a less strict diet than advised, which results in an increased risk of (severe) allergic reactions. Three variables were associated with non-adherence to the dietary advice: 1) misremembering the dietary advice, 2) the need for dietary change after the food challenge, and 3) the emotional impact and therefore a reduced quality of life. We concluded that the dietary advice after a positive food challenge is often not adequately followed, indicating that more support, tailored to the individual patient, regarding dietary follow-up, is required.

Similarly, dietary advice given after a negative challenge, which excludes the diagnosis of a food allergy, is often not adhered to. **Chapter 7** described a prospective study on the reintroduction of a food, after excluding the allergy to (a specific) food. The patients received standardized follow-up care after the food challenge, in which a stepwise reintroduction scheme was provided, followed by telephone consultations with a clinical nurse specialist for support. This study showed that in the short-term (2 weeks after the challenge), 20% of the patients failed to reintroduce the food. The most common reasons for this were symptoms upon ingestion during the reintroduction and also, feeling no need to eat the food. In the long-term [5-12 months after the challenge(s)], the number of patients who did not eat the food had increased to 40%. The most commonly reported reasons were having atypical symptoms after eating the food and fear of an allergic reactions. We concluded that despite standardized follow-up care, failure to reintroduce the food frequently occurs and increases over time. It seems important that careful, more tailored coaching is needed both before and after a food challenge.

Conclusions and future perspectives

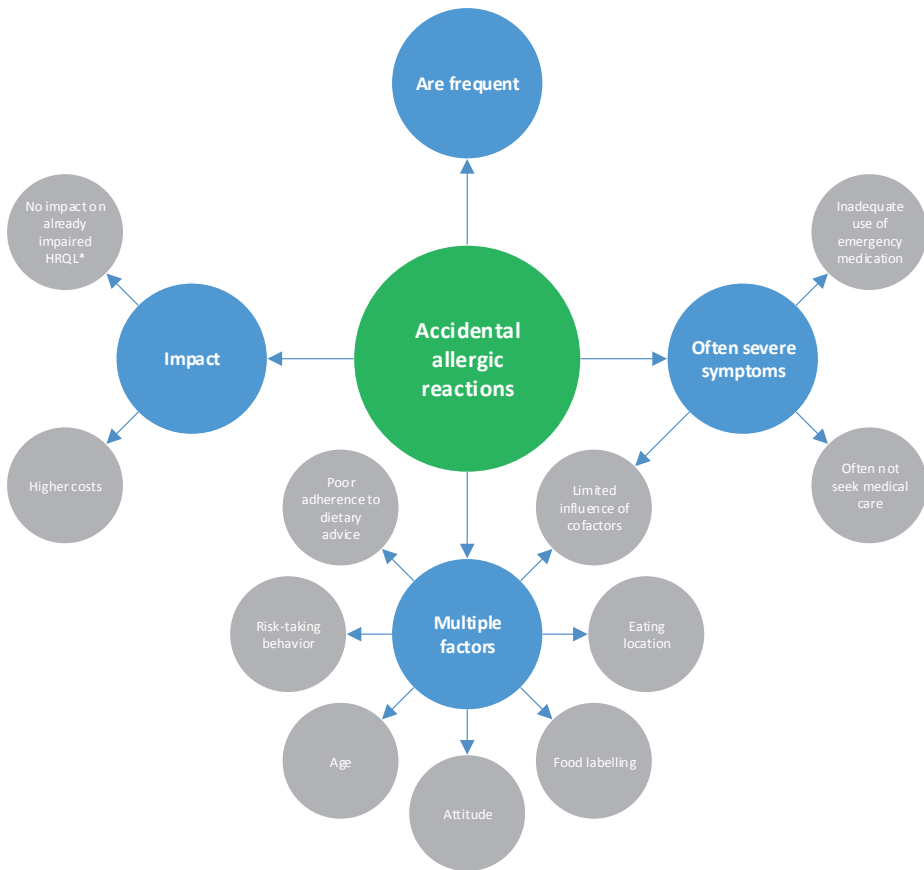
Chapter 8 discussed the main findings of this thesis in the context of the current literature. Figure 1 shows an overview of the different facets of accidental food allergic reactions studied. This thesis showed that accidental allergic reactions occur frequently in the daily lives of adults with food allergy, often causing severe symptoms. These reactions have a significant impact on direct and indirect costs.

Given the frequency of occurrence of accidental allergic reactions, it can be concluded that current standardized care is not sufficiently adequate. Several factors play a role in

accidental allergic reactions, but it is important to note that not every factor applies to every patient. It can be concluded that care for patients with food allergy should be (even) more tailored to the individual. The effect of this will have to be evaluated in future studies.

An important factor is the absence of harmonized regulation regarding labeling of food allergens that may be present due to contamination during the production process. Improving regulations in this respect seems to be a necessary step. Recommendations to improve this have been described by The Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO), consisting of clear standards for when to warn and not to warn for the possible presence of allergens, as well as guidelines on how to apply these in practice. The next step is to implement these recommendations, preferably supported by a legal framework.

Figure 1. Overview of the different facets of accidental allergic reactions studied, as described in the summary



*HRQL = Health-related quality of life

Nederlandse samenvatting

Voedselallergie is een aandoening veroorzaakt door IgE antilichaam-gemedieerde reacties van het immuunsysteem op eiwitten in een voedingsmiddel. Deze uit zich door effecten in huid, slijmvliezen, maagdarmsstelsel, luchtwegen en/of hart- en vaatstelsel. De ernst van de klachten varieert per patiënt en per voedingsmiddel: van alleen milde jeuk in de mond, tot soms levensbedreigende en fatale reacties, bijvoorbeeld door afsluiting van de luchtwegen of bloeddrukval en shock. De diagnose wordt gesteld aan de hand van de anamnese (het gesprek met de patiënt), sensibilisatieonderzoek (meten van specifiek IgE in het bloed of d.m.v. huidpriktesten) en een voedselprovocatie. De voedselprovocatie is de gouden standaard voor het uitsluiten of aantonen van een reactie op voeding. Bij een voedselprovocatie wordt het voedingsmiddel geleidelijk oplopende hoeveelheden door de patiënt gegeten en wordt geobserveerd of dit allergische klachten veroorzaakt. Een voedselallergie kan (nog) niet worden genezen. De behandeling bestaat uit het vermijden van het voedingsmiddel uit het dagelijks dieet. Patiënten met een voedselallergie worden bij voorkeur behandeld en begeleid door een multidisciplinair team van medisch specialisten, diëtisten, verpleegkundig specialisten en verpleegkundigen. Uit de praktijk blijkt dat veel patiënten ondanks het eliminatiedieet en de begeleiding hierbij, in het dagelijkse leven toch onverwachte allergische reacties op voedsel hebben. Patiënten krijgen daarom vaak een noodset met medicatie (zoals antihistaminica en een adrenaline-auto injector) om een dergelijke reactie te behandelen. Het is echter bekend dat patiënten niet altijd adequaat omgaan met onverwachte allergische reacties en bijvoorbeeld hun adrenaline-auto injector niet altijd gebruiken bij ernstige klachten en ook lang niet altijd medische hulp inschakelen.

Het doel van dit proefschrift is om meer inzicht te krijgen in: 1) de frequentie, ernst en impact op kosten en kwaliteit van leven van onverwachte allergische reacties op voeding, 2) welke factoren een rol spelen bij deze reacties, en 3) de mate waarin het dieetadvies wordt opgevolgd nadat een voedselallergie is vastgesteld dan wel uitgesloten en welke factoren hierbij een rol spelen.

Onverwachte allergische reacties komen regelmatig voor en zijn vaak ernstig

In **hoofdstuk 2** is middels een literatuurstudie gekeken naar de frequentie en ernst van onverwachte allergische reacties op voeding bij patiënten van 13 jaar of ouder. Het was niet mogelijk een exacte frequentie vast te stellen, maar het liet wel zien dat onverwachte allergische reacties bij een significant aantal patiënten voorkomen. Een andere retrospectieve studie beschreef dat iedere voedselallergische patiënt gemiddeld twee reacties per 5 jaar heeft. Uit een meer recente, prospectieve studie in ons centrum kwam naar voren dat

op jaarbasis de helft van alle voedselallergische patiënten onverwachte reacties ervaart, waarbij het gemiddeld om twee reacties per jaar gaat.

De ernst van onverwachte allergische reacties bleek te variëren van mild tot ernstig. Twee studies lieten zien dat respectievelijk 32% en 57% van de onverwachte allergische reacties ernstig is. Aanvullend daarop, liet onze meer recente prospectieve studie zien dat 28% van de reacties ernstig is. Het aantal fatale reacties lijkt beperkt. Het werd ook duidelijk dat patiënten, ook na ernstige reacties, vaak niet adequaat hun noodset met medicatie te gebruiken. Dit verhoogt de kans op ernstig verlopende of zelfs fatale reacties.

Geconcludeerd kan worden dat voedselallergische patiënten regelmatig onverwachte allergische reacties hebben, die vaak ernstig verlopen. Daarnaast is opvallend dat patiënten zich regelmatig niet adequaat behandelen, wat aangeeft dat meer en betere begeleiding nodig is ten aanzien van het gebruik van de noodmedicatie en het inschakelen van medische hulp.

Onverwachte allergische reacties gaan samen met hogere kosten

Hoofdstuk 3 beschrijft een prospectieve studie naar de invloed van onverwachte allergische reacties op kosten en kwaliteit van leven. Deze studie liet zien dat onverwachte allergische reacties een significante invloed op kosten hebben. Patiënten met onverwachte allergische reacties hadden op jaarbasis zeven keer meer directe en indirecte kosten dan patiënten zonder deze reacties (gemiddeld €1186 (bootstrap 95% CI: €609-1845) vs. €158 (bootstrap 95% CI: €68-266)). De hogere kosten waren zichtbaar in alle bestudeerde subcategorieën: kosten voor eerstelijns consulten, poliklinische consulten, ziekenhuisopnames, reiskosten naar gezondheidszorginstellingen en kosten door ziekteverzuim.

Tijdens de looptijd van de studie zagen we geen verandering in de (al verlaagde) kwaliteit van leven door het doormaken van onverwachte allergische reacties. Een mogelijke verklaring is dat de bestudeerde patiënten al lange tijd voedselallergie hadden (gemiddeld 24 jaar), met daarbij al een lagere kwaliteit van leven.

Gezien de impact op kosten van onverwachte allergische reacties en de frequentie en ernst ervan, is betere preventie nodig. Inzicht in factoren die een rol spelen bij onverwachte allergische reactie kan bijdragen aan het ontwikkelen en aanbieden van preventieve interventies op maat. Hierop wordt ingegaan in de volgende paragraaf.

Meerdere factoren hebben invloed op het optreden van onverwachte allergische reacties

Eetlocatie, voedsel etikettering, attitude, risicovol gedrag en leeftijd

In de literatuurstudie in **hoofdstuk 2** zijn de mogelijke oorzaken van onverwachte allergische reacties beschreven. Als eerste aspect kwam de eetlocatie naar voren. Onverwachte allergische

reacties komen het vaakst voor als patiënten buitenshuis eten, zoals in een restaurant of bij vrienden thuis. Een andere oorzaak bleek onjuiste etikettering van voorverpakte voedingsmiddelen, in het bijzonder het ontbreken van een waarschuwing voor een allergeen terwijl dat in een product aanwezig is of zou kunnen zijn. Ook bleken etiketten soms moeilijk te interpreteren, bijvoorbeeld door zinnen als: ‘Kan sporen van pinda’s en noten bevatten’, of het gebruik van andere talen zonder dat de informatie in de moedertaal van de patiënt vermeld staat. Ook is de lay-out van etiketten niet altijd overzichtelijk wat betreft de ingrediëntenlijst en allergeneninformatie. Een derde aspect is dat patiënten soms zelf risico's nemen. Patiënten geven soms onvoldoende informatie over hun voedselallergie als ze buitenshuis eten, bijvoorbeeld door schaamte om hierover te vertellen. Ook kwam in zowel **hoofdstuk 2 als 6** naar voren dat patiënten van producten die zij eerder zonder problemen hebben gebruikt, vaak niet meer het etiket controleren. Hierdoor kunnen mogelijke wijzigingen in ingrediënten gemist worden, wat ook weer een risico geeft op onverwachte allergische reacties. Uit enkele studies besproken in **hoofdstuk 2** bleek dat risicogedrag vaker voorkomt bij jongeren en adolescenten, waarbij de volgende redenen naar voren kwamen: nooit eerder ernstige symptomen gehad, de mogelijkheid om eventuele reacties zelf te kunnen behandelen, invloed van sociale omstandigheden (bijvoorbeeld: “al mijn vrienden namen het voedingsmiddel”) en gebrek aan inzicht in ernst van hun voedselallergie.

Meerdere factoren kunnen dus van invloed zijn op het risico op onverwachte allergische reacties. Voor de dagelijkse praktijk is het belangrijk dat per individuele patiënt wordt bepaald welke factoren het meest van toepassing zijn en dat de begeleiding hierop aangepast wordt. Een belangrijke factor is ook de afwezigheid van regelgeving ten aanzien van etikettering van voedselallergenen die mogelijk aanwezig zijn door verontreiniging gedurende het productieproces. Verbetering op dit vlak wordt sterk aanbevolen.

De invloed van cofactoren op de ernst van onverwachte allergische reacties lijkt beperkt

Cofactoren zijn factoren die mogelijk leiden tot ernstiger klachten en lagere drempelwaarde bij allergische reacties op voedsel. Voorbeelden van cofactoren zijn gebruik van alcohol, lichamelijk inspanning, infecties en gebruik van sommige typen medicijnen (zoals non-steroidal anti-inflammatory drugs (NSAIDs)). **Hoofdstuk 4 en 5** geven meer inzicht in de invloed van cofactoren op de ernst van allergische reactie. Uit een retrospectieve studie, beschreven in **hoofdstuk 4**, bleek dat lichamelijk inspanning en alcohol het vaakst door patiënten worden gerapporteerd als cofactor voor ernstiger klachten, echter dit ging maar om een kleine groep van slechts 10% of minder van de patiënten. Verder bleek maar een klein percentage (8%) van de patiënten standaard medicatie te gebruiken die bekend staat als potentiële cofactor.

In onze prospectieve studie, beschreven in **hoofdstuk 5** werd duidelijk dat potentiële cofactoren vaak (in 74% van de gevallen) aanwezig zijn bij onverwachte allergische reacties. Daarbij werd echter geen significante relatie gevonden tussen de aanwezigheid van cofactoren en de ernst van onverwachte allergische reacties. In sommige studies wordt wel enige, maar slechts beperkte, invloed gevonden van cofactoren op de ernst en drempelwaarde van allergische reacties op voedsel. We concludeerden dat potentiële cofactoren vaak voorkomen in het dagelijks leven van patiënten, maar dat de invloed van cofactoren op de ernst en drempelwaarde van onverwachte allergische reacties beperkt lijkt te zijn. Het advies voor de dagelijkse praktijk is om patiënten te informeren over cofactoren en hoe om te gaan hun voedselallergie met het oog op een mogelijke rol van cofactoren.

Het dieetadvies naar aanleiding van een voedselprovocatie wordt regelmatig niet goed opgevolgd

In **hoofdstuk 6 en 7** gaat het over de opvolging van het dieetadvies na een positieve, respectievelijk negatieve voedselprovocatie. **Hoofdstuk 6** beschrijft een prospectieve studie waarbij is onderzocht of patiënten na een positieve provocatie, waarbij het bestaan van een voedselallergie is bevestigd, het advies ten aanzien van het eliminatiedieet opvolgden. Afhankelijk van de ernst van de vastgestelde voedselallergie werd één van de volgende dieetadviezen gegeven: 1) het voedingsmiddel strikt vermijden (inclusief voorverpakte producten met waarschuwingen voor (mogelijke verontreinigingen met) het allergeen), 2) het voedingsmiddel vermijden maar voorverpakte producten met waarschuwingen zijn wel toegestaan of 3) bepaalde (kleine) hoeveelheden toegestaan. In de studie werd aangetoond dat na 69% van de positieve voedselprovocaties, patiënten het dieetadvies niet opvolgden: 17% volgde een strikter dieet en 52% een minder strikt dieet dan geadviseerd. Na voedselprovocaties waarna een strikt eliminatie-dieet (optie 1) was geadviseerd, volgde zelfs 82% van de patiënten een minder strikt dieet dan geadviseerd, wat een verhoogd risico geeft op (ernstige) allergische reacties. Er kwamen drie factoren naar voren die samenhangen met het niet opvolgen van het dieetadvies: 1) het niet onthouden hebben van het dieetadvies, 2) het moeten aanpassen van het dieet na diagnostiek en 3) de emotionele impact en daardoor een verminderde kwaliteit van leven. Er werd geconcludeerd dat het dieetadvies na een positieve voedselprovocatie regelmatig niet goed wordt opgevolgd, wat aangeeft dat meer begeleiding nodig is ten aanzien van dieetopvolging, afgestemd op de individuele patiënt.

Anderzijds gaat het opvolgen van het dieetadvies ook regelmatig niet goed na een negatieve provocatie waarbij een voedselallergie is uitgesloten. **Hoofdstuk 7** beschrijft een prospectieve studie over herinstructie van een voedingsmiddel nadat een allergie voor

een (specifiek) voedingsmiddel is uitgesloten. Deze patiënten kregen gestandaardiseerde nazorg na de voedselprovocatie, waarbij een stapsgewijs herinroductieschema werd meegegeven gevolgd door telefonische consulten met een verpleegkundig specialist voor de begeleiding. Uit deze studie bleek dat op korte termijn (2 weken na de provocatie) 20% van de patiënten er niet in slaagde het voedingsmiddel te herinroducteren. De meest voorkomende redenen hiervoor waren klachten gedurende de herinroductie en geen behoefte hebben aan herinroductie van het voedingsmiddel. Op lange termijn (5-12 maanden na de provocatie(s)) was het aantal patiënten dat het voedingsmiddel niet gebruikte toegenomen tot zelfs 40%. De meest genoemde redenen hiervoor waren atypische klachten na eten van het voedingsmiddel en angst voor allergische reacties. We concludeerden dat ondanks een gestandaardiseerde nazorgtraject, het mislukken van herinroductie van het voedingsmiddel frequent voorkomt en toeneemt op langere termijn. Het meer afstemmen van de begeleiding op de individuele behoeften van patiënten, zowel voor als na een voedselprovocatie, lijkt van belang.

Conclusies en toekomstperspectief

In **hoofdstuk 8** worden de belangrijkste bevindingen van dit proefschrift in de context van de bestaande literatuur besproken. Figuur 1 toont een overzicht van de verschillende onderzochte facetten van onverwachte voedselallergische reacties. Uit dit proefschrift blijkt dat onverwachte allergische reacties regelmatig voorkomen in het dagelijks leven van volwassenen met voedselallergie, waarbij geregeld sprake is van ernstige klachten. Ze hebben significante invloed op directe en indirecte kosten.

Gezien de regelmaat waarin onverwachte allergisch reacties optreden, lijkt de huidige gestandaardiseerde zorg niet te voldoen. Verschillende factoren spelen een rol bij onverwachte allergische reacties, waarbij belangrijk is dat niet elke factor geldt voor elke patiënt. Geconcludeerd kan worden dat zorg voor patiënten met een voedselallergie (nog) meer moet worden afgestemd op het individu. Het effect hiervan zal moeten worden geëvalueerd in toekomstige studies.

Een belangrijke factor is de afwezigheid van duidelijke regelgeving ten aanzien van etikettering van voedselallergenen die mogelijk aanwezig zijn door verontreiniging gedurende het productieproces. Verbetering van de regelgeving op dit vlak lijkt een noodzakelijke stap. Er zijn door The Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) aanbevelingen beschreven voor het verbeteren hiervan, bestaande uit duidelijke normen voor wanneer wel en niet gewaarschuwd moet worden voor een mogelijke aanwezigheid van allergenen, alsmede richtlijnen voor hoe deze in de praktijk toegepast moeten worden. De volgende stap is om dit te implementeren, bij voorkeur ondersteund door een wettelijk kader.

Figuur 1. Overzicht van de verschillende onderzochte facetten van onverwachte allergische reacties zoals beschreven in de samenvatting



*HRQL = Health-related quality of life





CHAPTER 10

LIST OF ABBREVIATIONS

CONTRIBUTING AUTHORS

DANKWOORD (ACKNOWLEDGEMENTS)

LIST OF PUBLICATIONS

ABOUT THE AUTHOR

List of abbreviations

ACEIs	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
CI	Confidence interval
EU	European Union
FA	Food allergy
FA-ECOQ	Food Allergy Socio-Economic Questionnaire
FAIM	Food Allergy Independent Measure
FAQLQ-AF	Food Allergy Quality of Life Questionnaire-Adult Form
FC	Food challenge
FDEIA	Food-dependent exercise induced anaphylaxis
HRQL	Health-related quality of life
IgE	Immunoglobulin E
LTP	Lipid transfer protein
MCID	Minimal clinically important difference
N	Number
NA	Not applicable
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
PAL	Precautionary allergen labelling
SD	Standard deviation
SPT	Skin prick test
STAI	State-Trait Anxiety Inventory
TCA	Tricyclic antidepressants
WDEAI	Wheat-dependent exercise-induced anaphylaxis

Contributing authors

Joseph L. Baumert

Department of Food Science & Technology, University of Nebraska-Lincoln, Lincoln, Nebraska, United States of America

Mark A. Blankestijn

Department of Dermatology and Allergology, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands | Center for Translational Immunology, University Medical Centre Utrecht, University Utrecht, Utrecht, The Netherlands

W. Marty Blom

TNO, Netherlands Organization for Applied Scientific Research, Utrecht, The Netherlands

Jacqueline J. M. Castenmiller

Netherlands Food and Consumer Product Safety Authority, Utrecht, The Netherlands

Francine C. van Erp

Department of Dermatology and Allergology, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands | Center for Translational Immunology, University Medical Centre Utrecht, University Utrecht, Utrecht, The Netherlands
Current affiliation: Department of Dermatology, Tergooi Hospital, Hilversum, The Netherlands

Geert F. Houben

TNO, Netherlands Organization for Applied Scientific Research, Utrecht, The Netherlands | Center for Translational Immunology, University Medical Centre Utrecht, University Utrecht, Utrecht, The Netherlands

André C. Knulst

Department of Dermatology and Allergology, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands | Center for Translational Immunology, University Medical Centre Utrecht, University Utrecht, Utrecht, The Netherlands

Astrid G. Kruizinga

TNO, Netherlands Organization for Applied Scientific Research, Utrecht, The Netherlands

Thuy-My Le

Department of Dermatology and Allergology, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands | Center for Translational Immunology, University Medical Centre Utrecht, University Utrecht, Utrecht, The Netherlands

Yolanda Meijer

Department of Pediatric Pulmonology and Allergology, University Medical Centre Utrecht, Utrecht, The Netherlands

Current affiliation: Department of Pediatric Allergology, Amsterdam University Medical Center, Amsterdam, The Netherlands

Anouska D. Michelsen- Huisman

Department of Dermatology and Allergology, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands

Current affiliation: Department of dietetics, St. Jansdal Hospital, Harderwijk, The Netherlands

Hubert P. J. M. Noteborn

Netherlands Food and Consumer Product Safety Authority, Utrecht, The Netherlands

Harmieke van Os-Medendorp

Department of Dermatology and Allergology, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands

Current affiliation: School of Health, Saxion University of Applied Sciences, Deventer, The Netherlands

Dankwoord (acknowledgements)

Mijn boekje is klaar! Met dankbaarheid en waardering kijk ik terug op de afgelopen jaren. Wat was het mooi om patiëntenzorg te kunnen combineren met onderzoek en om hier uiteindelijk een proefschrift van te kunnen maken.

Allereerst alle patiënten die hebben meegedaan aan het onderzoek. Bedankt dat jullie bereid waren om deze onmisbare bijdrage te leveren.

André, we werken alweer heel wat jaren samen. Al vanaf het begin stond je klaar om met me mee te denken, heb je mij vertrouwen gegeven en mij gesteund om onderzoek te combineren met de praktijk. Dit was onmisbaar om mijn promotietraject te doorlopen. Het is inspirerend om te zien hoeveel passie je hebt voor onderzoek binnen de voedselallergie en hoe je altijd ideeën hebt om hiermee aan de slag te gaan. Ik heb veel van jou geleerd. Heel erg bedankt voor alles!

Geert, de laatste jaren ben je erbij gekomen in mijn promotieteam. Jouw fijne begeleiding, heldere feedback en kennis over voedsletikettering hebben mijn onderzoek beter gemaakt. De bevoegenheid die je hebt voor het vakgebied is mooi en inspirerend om te zien. Bedankt voor alle input, het vertrouwen en support!

Harmieke, je bent mijn voorbeeld van een verpleegkundige die zich heeft ontwikkeld binnen het verpleegkundig onderzoek. Wat fijn hoe je mij stimuleerde en hebt geholpen om onderzoek te doen. Je hebt mij altijd gesteund ook nadat je het UMCU hebt verruild voor Saxion. Jouw adviezen over onder andere methodologie, analyses en de verpleegkundige insteek van mijn onderzoeken waren altijd waardevol. Bedankt voor al deze jaren begeleiding!

Thuy-My, de laatste jaren van mijn promotie ben je steeds meer betrokken geraakt en uiteindelijk ook mijn copromotor geworden. Jouw prettige manier van samenwerken, kennis over voedselallergie, kritische blik, suggesties voor verbeteringen van artikelen en ideeën voor grafische weergaves hebben mijn onderzoek op een hoger niveau gebracht. Heel erg bedankt!

Leden van de beoordeling- en leescommissie: Prof. dr. Lisette Schoonhoven, Prof. dr. Kors van der Ent, Prof. dr. Suzanne Pasmans, Prof. dr. Tiny Jaarsma en Prof. dr. Johan Garssen. Bedankt voor jullie bereidheid om het proefschrift te beoordelen.

Alle coauteurs wil ik bedanken voor hun waardevolle bijdragen aan dit proefschrift.

Verpleegkundigen van de dagbehandeling Allergologie, bedankt voor de fijne samenwerking! Nienke, Lizzie en Bea, wat kijk ik met veel plezier terug op alle jaren dat we al naaste collega's zijn. Jullie staan altijd voor mij klaar om te helpen. Ook bij mijn onderzoekswerkzaamheden, zoals het verzamelen van alle vragenlijsten.

Petra, Jan, Judy en Carien, wat fijn om jullie als mijn leidinggevenden te hebben (gehad). Ik kon altijd rekenen op jullie steun. Dit heeft geholpen om mijn promotietraject mogelijk te maken.

Collega's van de afdeling Dermatologie/Allergologie, wat fijn om onderdeel uit te mogen maken van dit team. Bedankt voor alle hulp en ondersteuning. Anouska, wat heb jij veel kennis over voedselallergie. Bedankt voor je vele nuttige inzichten en het meedenken. Sawita, jij stond altijd klaar voor de secretariële ondersteuning die nodig was voor mijn onderzoek en er was altijd ruimte voor een gezellig praatje. Mark en Marieke, jullie hielpen mij onder andere met de dataverzameling voor mijn project als ik afwezig was door bijvoorbeeld één van mijn reizen of zwangerschapsverloven. Veel dank daarvoor. Anne, bedankt voor je interesse en bijdrage aan mijn onderzoek. Kees, bedankt voor de hulp met het extraheren van data uit grote databases.

Medepromovendi, bedankt voor al het meedenken over mijn onderzoek en alle gezelligheid tijdens de overleggen en congressen.

Ans, Edward, Heike, Henny, Kitty en Stans, wat we hebben met elkaar een hoop 'acute ontstekings' overlegmomenten meegemaakt. Bedankt voor de vele waardevolle inzichten.

Studenten, Digna, Bregje, Grace en Anne, wat een fijne samenwerking. Bedankt voor jullie inzet!

Andrew, veel dank voor alle Engelse correcties. Dit was onmisbaar.

Lieve (ex)kameroten van D2 West, Florine, Jeanet, Lucy, Maartje, Marty, Nienke, Petra en Sanne. Ik denk met veel plezier terug aan de tijd dat ik nog op de kamer D2 West zat. Ik heb genoten van de gezelligheid en de vele mooie momenten samen. Ook was er altijd ruimte om met elkaar te sparren. Gelukkig zie ik de meesten van jullie nog steeds regelmatig tijdens de lunch of een overleg.

Lieve paranimfen, Myrthe en Jette. Wat fijn om jullie naast mij te hebben staan. Bedankt voor al jullie steun!

Al mijn vrienden, jullie zorgden altijd weer voor gezelligheid. Ook in drukke tijden. Wat fijn dat jullie er voor mij zijn!

Lieve mam en pap, jullie zijn er altijd voor mij en hebben mij altijd steunen. Bedankt voor jullie liefde, vertrouwen en steun. Dit heeft ervoor gezorgd dat ik heb kunnen bereiken waar ik nu sta. Dennis, wat fijn om jou als broer te hebben. Doordat je ook een promotietraject hebt doorlopen wist je wat hier allemaal bij komt kijken. Bedankt voor je support.

Mijn lieve meiden Sophie en Lotte, wat geweldig dat jullie er zijn. Wat heerlijk om bij jullie thuis te zijn. En wat bijzonder dat jullie beiden mijn promotiewerkzaamheden ook van heel dichtbij hebben meegemaakt toen jullie nog geborgen in mijn buik zaten.

Allerliefste Stefan, je bent mijn steun en toeverlaat. Je hebt mij altijd vertrouwen en support gegeven om mijn proefschrift te kunnen voltooien. Al onze gezellige en mooie momenten, reizen of gewoon fijn samen thuis zijn zorgden voor de nodige afleiding. Dit gaf mij altijd weer energie om aan de slag te gaan.

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About the author

Astrid Versluis was born April, 23rd, 1986 in Gorinchem, The Netherlands. She attended secondary school at the Lyceum Oudehoven in Gorinchem, from which she graduated in 2003. From 2003 to 2007, she pursued a bachelor's degree in nursing (HBO-V) at the Hogeschool Utrecht. After graduation, she worked for three years as a nurse at the Pulmonology Department at the St. Antonius Hospital in Nieuwegein. During this time, she also completed the pulmonary nurse course at the St. Antonius Academy. In 2010, Astrid first entered the field of allergies when she started working as a senior nurse at the Dermatology/Allergology Department of



the University Medical Centre Utrecht. From 2010 to 2012, apart from her obligations as a nurse, she earned a master's degree in Nursing Science by completing the Clinical Health Sciences program at the University of Utrecht. In 2014, she also obtained a master's degree in Advances Nursing Practice at the Hogeschool Utrecht, and was promoted to the role of clinical nurse specialist in Allergology. Since she started working at the Dermatology/Allergology department in 2010, she has combined her duties in patient care with research work on food allergy. Her research work resulted in a PhD trajectory under the supervision of Prof. dr. André Knulst, Prof. dr. Geert Houben, dr. Harmieke van Os- Medendorp and dr. Thuy-My Le. The results of her PhD research projects have been described in this thesis. For the foreseeable future, Astrid intends to continue combining patient care with research activity in the field of allergy. Astrid lives with her partner Stefan and their two daughters, Sophie (2017) and Lotte (2019), in Hoef en Haag, The Netherlands.

