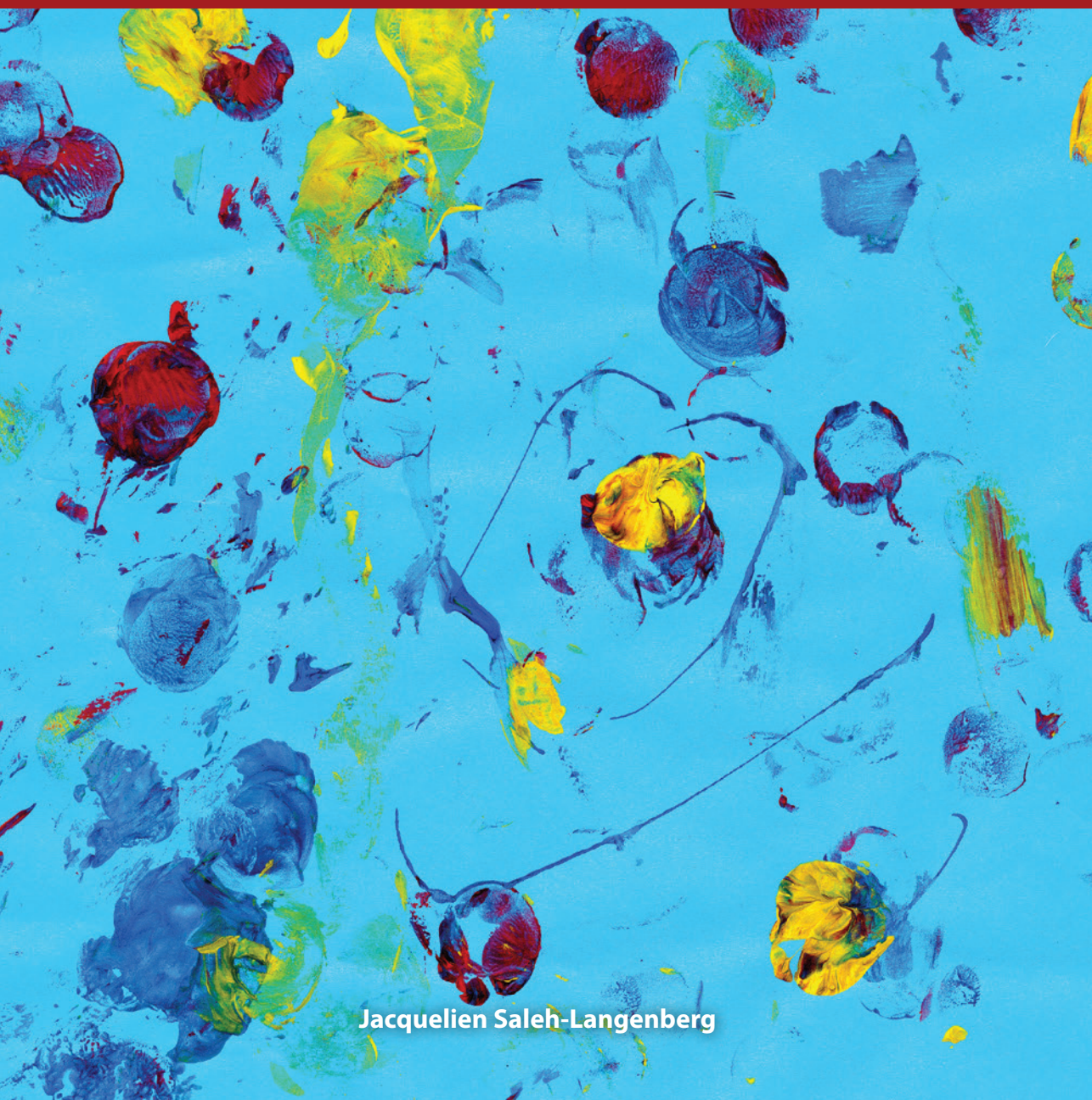
EPINEPHRINE AUTO-INJECTOR for ANAPHYLAXIS in FOOD ALLERGIC PATIENTS



Jacquelien Saleh-Langenberg

EPINEPHRINE AUTO-INJECTOR for ANAPHYLAXIS in FOOD ALLERGIC PATIENTS

J. Saleh-Langenberg

Epinephrine auto-injector for anaphylaxis in food-allergic patients

ISBN: 978-90-367-9233-2 (hard copy)
ISBN: 978-90-367-9232-5 (e-book)

Financial support
The studies described in this thesis were funded by EU through Europrevall project, ALK Abelló BV, Bausch&Lomb and MEDA Pharma.

Financial support printing thesis
Printing of this thesis was financially supported by the University of Groningen (RuG), the Graduate School for Drug Exploration (GUIDE), the University Medical Center Groningen (UMCG), ALK Abelló BV and MEDA Pharma.

Cover design: Brian Saleh, Groningen, the Netherlands
Lay-out: Jardine Media, Rotterdam, the Netherlands
Printed by: Ridderprint B.V., Ridderkerk, the Netherlands

university of groningen

EPINEPHRINE AUTO-INJECTOR for ANAPHYLAXIS in FOOD ALLERGIC PATIENTS

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. E. Sterken
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Monday 12 December 2016 at 11.00 hours

by

Jacquelien Langenberg

born on 23 May 1981
in Noordoostpolder

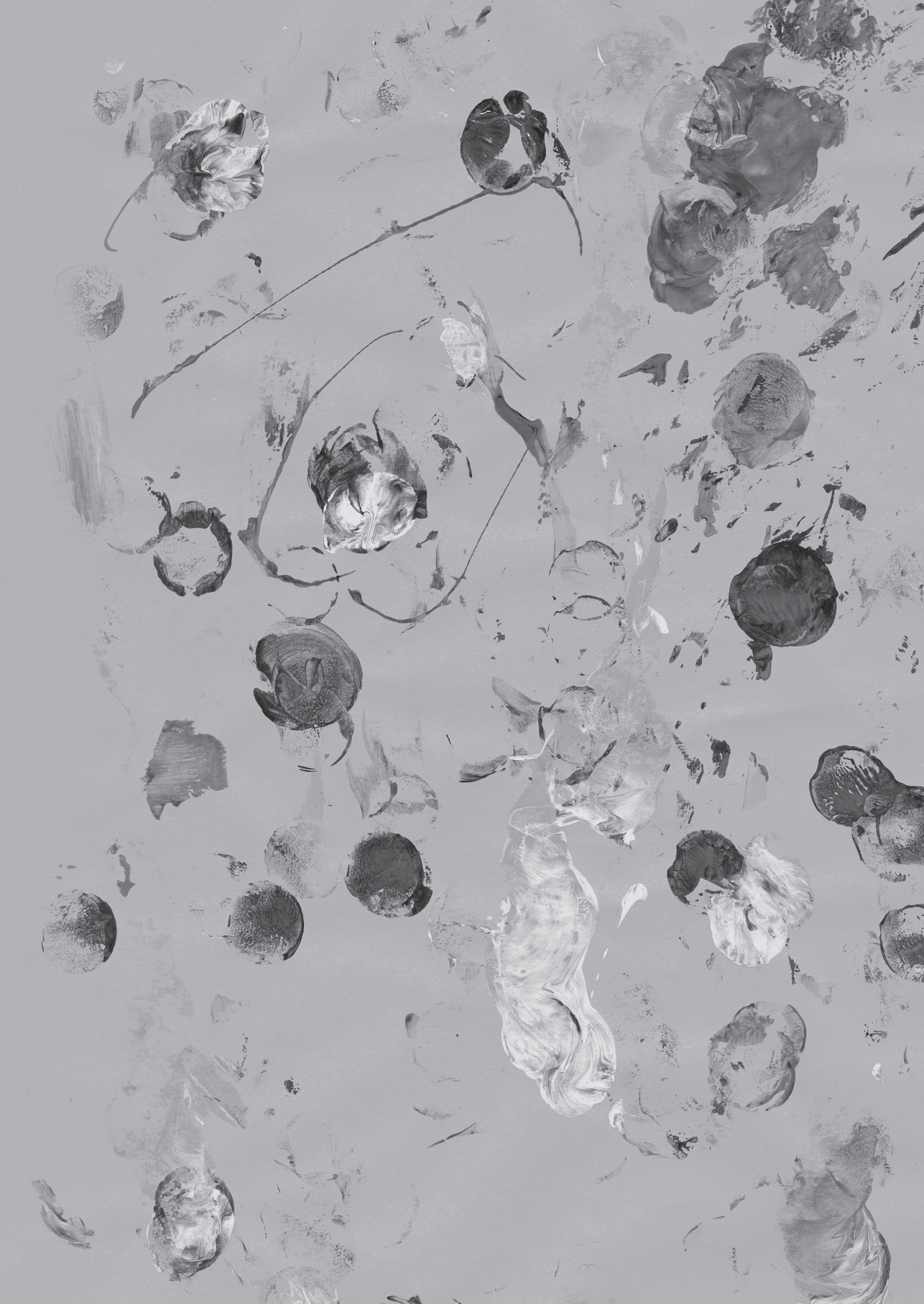
Supervisor
Prof. A.E.J. Dubois

Co-supervisor
Dr. B.M.J. Flokstra-de Blok

Assessment Committee
Prof. R. Gerth van Wijk
Prof. G.H. Koppelman
Prof. J. O'B Hourihane

Paranymfs
Ping He
Dr. N.J. Goossens

TABLE OF CONTENTS



Chapter 1

General introduction and outline of the thesis

Jacquelien Saleh-Langenberg

INTRODUCTION

Hey, would you like to have some?" your friend asks as she offers you a mouthwatering homemade brownie. You are tempted by the delicious dessert, but then you see the crushed nuts on top. Darn! You are allergic to nuts. Mmm, maybe just one little tiny bite? …….Nope!

Imagine what life would be like if you had to constantly check out the ingredients in your foods to make sure your life was not in danger after eating even a tiny bit. For children and adolescents with food allergies, that is their way of life.

FOOD ALLERGY: DEFNITION, CLINICAL MANIFESTATION, PREVALALENCE AND DIAGNOSIS

Definition and clinical manifestations

A food is defined as *any substance—whether processed, semi-processed, or raw—that is intended for human consumption, and includes drinks, chewing gum, food additives, and dietary supplements*.[1] Although any food may cause a reaction, relatively few foods are responsible for the majority of food allergic reactions: cow's milk, hen's egg, peanut, tree nuts, (shell) fish, soy, celery, sesame seeds and wheat.[1] Allergies for cow's milk, hen's egg, and peanut are the most common in children.[1]

Food allergy is defined as an *adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food*.[1] The term food allergy refers to a reaction to food that is initiated by immunological mechanisms and is most commonly IgE-mediated.

IgE-mediated food allergies cause a wide spectrum of clinical signs and symptoms. Food allergic reactions can cause oral allergy syndrome (e.g. local itching and/or mild swelling of lips, tongue, palate, throat, ears), rhino conjunctivitis (e.g. sneezing, blocked or running nose, itching and watering eyes) , skin symptoms (e.g. worsening eczema, exanthema, pruritis, angioedema, urticaria), gastrointestinal symptoms (e.g. nausea, vomiting, abdominal pain, diarrhea), respiratory symptoms (e.g. asthmatic symptoms or laryngeal edema) or cardiovascular symptoms (e.g. dizziness, loss of consciousness, palpitations).[2]

Prevalence of food allergy

Food allergy is a growing health issue in countries with a Western lifestyle. Food allergy affects about six to eight percent of children in the first year of life.[3] Most children outgrow their sensitivity to certain foods, and approximately two to three per cent of the adult population still have food allergies.[3]

It has been suggested that the prevalence of food allergy appears to be have increased over the last decade. However, reliable population-based data are limited.[4,5] Most studies have based their estimates only on patient perceptions of reactions to foods within the general population, showing prevalences of self-reported food allergy varying from three per cent to as high as thirty-five percent.[5-8] A few studies have included double-blind, placebo-controlled food challenges (DBPCFCs), the gold standard to diagnose food allergy.[6,8-12] These studies showed prevalences of approximately three per cent for all foods together. The prevalence of self-reported food allergy is higher than the prevalence of food allergy confirmed by DBPCFCs. This might be due to problems with determining the prevalence of food allergy, such as misclassification, biased participation, lack of simple diagnostic tests, rapid evolution of disease, large numbers of potential triggers, varied clinical phenotypes, or differences between populations. The prevalence of food allergy is also thought to be dependent on geographical differences (e.g. differences in dietary intake and eating habits) and demographic differences (e.g. age, sex, and ethnicity).[13-15] With the prevalence increasing it is therefore important to improve food allergy awareness, to identify food allergic patients at high risk for anaphylaxis and to diagnose and to manage food allergy and anaphylaxis adequately.

Diagnosis of food allergy

The diagnosis of food allergy is primarily based on a detailed patient's clinical history and can be supported by physical examination and diagnostic tests. Several diagnostic tests may be useful for the diagnosis of food allergy, including the skin prick test, intracutaneous or intradermal test, or determination of allergen-specific IgE (sIgE) test in serum. These tests detect sIgE to suspected food(s) and may assist in the identification of foods that may be the cause in specific cases of IgE-mediated food allergic reactions.[1] However, although these tests can be used easily, are safe, quick and inexpensive,[2,16] they cannot by themselves be considered to be diagnostic.[1]

Another important diagnostic test is the oral food challenge. An oral food challenge can ascertain whether a clinical allergy is the result of ingesting a specific food. There are three different kinds of oral food challenges: (1) an open oral challenge (2) a single-blind oral challenge or (3) a double-blind, placebo-controlled challenge (DBPCFC). The gold standard to diagnose food allergy is a DBPCFC.[1,2,17,18] An oral food challenge is always performed in a hospital setting under physician surveillance, with the possibility to administer emergency treatment. Although a DBPCFC is the gold standard, it is expensive, labor-intensive and can be time consuming for patients. However, it is an accurate and safe diagnostic test for food allergy, and, most importantly, undergoing a DBPCFC improves health-related quality of life (HRQL) of food allergic patients irrespective of the outcome of the test.[19]

ANAPHYLAXIS: DEFNITION, CLINICAL MANIFESTATION, PREVALENCE AND DIAGNOSIS

Anaphylaxis

Fatal allergic reactions have been recognized for over 4000 years.[20] Hieroglyphics suggest an anaphylactic death caused by a Hymenoptera sting.[20] However, it was not until the last century that the syndrome of anaphylaxis was fully characterized. Anaphylaxis was first described in 1902 by Portier and Richet.[21] In their classic studies they described the rapid death of several dogs that they were attempting to immunize against the toxic sting of the sea anemone. Since this reaction represented the opposite of their intended 'prophylaxis', they coined the term 'anaphylaxis', or 'without or against protection'. From these studies, they concluded that anaphylaxis required a latent period for sensitization and re-exposure to the sensitizing material. Three years later, in 1905, Schlosser reported a patient who developed acute shock after the ingestion of cow's milk.[22] In 1969 Golbert et al. described ten cases of anaphylaxis following the ingestion of various foods.[23] Thereafter, the reports by Yunginger et al., Sampson et al. and Bock et al. further characterized the natural course of near-fatal and fatal food-induced anaphylaxis.[24-27]

Definition and clinical manifestations

Anaphylaxis is defined as '*a serious allergic reaction that is rapid in onset and may cause death*'.[28] Food is the most common elicitor of anaphylaxis in children and the second most common in adults.[29,30] The proposed clinical diagnostic criteria for anaphylaxis are presented in Table 1.[28] In brief, anaphylaxis is a probable diagnosis in the presence of symptoms from two or more organ systems after exposure to a likely allergenic food, or hypotension alone after exposure to a known allergenic food for that patient.

An anaphylactic reaction may be immediate and uniphasic, or may be delayed in onset, biphasic, or protracted. Biphasic anaphylaxis is defined as '*a recurrence of symptoms that develops following the apparent resolution of the initial anaphylactic event not due to the given treatment*'.[31,32] Biphasic reactions have been reported to develop in 20% of food related anaphylactic reactions. These reactions typically occur within one to four hours following the resolution of the initial symptoms, although some cases have been reported up to 72 hours later.[31] Protracted anaphylaxis is defined as '*an anaphylactic reaction that lasts for hours or in extreme cases, for days*'.[31,33] These reactions may persist up to 32 hours after treatment.

Table 1. Clinical Criteria for Diagnosing Anaphylaxis[28]

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus, or flushing, swollen lips–tongue–uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse), syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin–mucosal tissue (e.g., generalized hives, itch-flush, swollen lips–tongue–uvula)
b. Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
c. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse), syncope, incontinence)
d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic blood pressure* (age-specific) or greater than 30% decrease in systolic blood pressure
b. Adults: systolic blood pressure 90 mm Hg or greater than 30% decrease from that patient's baseline

* Low systolic blood pressure for children: 1 month–1 year <70 mm Hg; <1–10 years [70 mm Hg + (2 × age)]; <11–17 years 90 mm Hg.

Symptoms and signs of anaphylaxis can occur within minutes to hours after ingesting the culprit food. In a large case series of fatal anaphylaxis, the median time from the onset of symptoms to cardiac arrest was reported as 30 minutes for food allergy.[34] Although nearly every organ system can be affected by an anaphylactic reaction, most effects involve the cutaneous, respiratory, cardiovascular, and gastrointestinal systems.[2] Respiratory and cardiovascular symptoms or signs are potentially the most life-threatening features of anaphylaxis.[2,34] Nausea and vomiting may also be associated with anaphylaxis.[34]

Diagnosis of anaphylaxis

Anaphylaxis is a clinical diagnosis that is based on the criteria shown in Table 1. To date, there are no reliable tests to diagnose anaphylaxis. Retrospectively, the diagnosis may be supported if serum tryptase is elevated within a few hours after the reaction. This elevated serum tryptase level needs to be compared with the patient's baseline levels. It is important to know that serum tryptase levels are often normal, especially in food-triggered reactions in children.[35] A severity score can be helpful in the diagnosis and ensuring the timely administration of epinephrine (Table 2).[36,37]

Table 2. Grading severity of anaphylaxis*

Grade	Skin	GI tract	Respiratory	Cardiovascular	Neurological
1. Mild	Sudden itching of eyes and nose, generalized pruritus, flushing, urticaria, angioedema,	Oral pruritus, oral tingling, mild lip swelling, nausea or emesis, mild abdominal pain	Nasal congestion and/ or sneezing, rhinorrhoea, throat pruritis, throat tightness, mild wheezing	Tachycardia (increase >15 beats/min)	Change in activity level plus anxiety
2. Moderate	Any of the above	Any of the above, crampy abdominal pain, diarrhoea, recurrent vomiting	Any of above, **hoarseness, barky cough, difficulty swallowing, stridor, dyspnoea, moderate wheezing**	As above	Light headedness feeling of impending doom
3. Severe	Any of the above	Any of the above loss of bowel control	Any of the above, **cyanosis** or Saturation <92%, **respiratory arrest**	**Hypotension** and/or collapse, dysrhythmia, severe bradycardia and/or cardiac arrest**	Confusion, loss of consciousness

*The severity score should be based on the organ system most affected. **Bold face** symptoms and signs are mandatory indication for the use of adrenaline (epinephrine).[36]

** Hypotension defined as low systolic blood pressure (age-specific): 1 month–1 year <70 mm Hg; <1–10 years [70 mm Hg + (2 × age)]; <11–17 years 90 mm Hg or greater than 30% decrease in systolic blood after exposure to known allergen for that patient. Modified from Sampson.[36]

Risk and co-factors of anaphylaxis

Risk factors for anaphylaxis include individual patient related aspects and circumstances, and the severity of the reaction depends on a complex interplay between various factors.[37-43]

Epidemiological risk factors for a food-induced anaphylactic reaction are defined as (a) a previously severe anaphylactic reaction to a food requiring emergency treatment or hospitalization as a result, (b) asthma or asthmatic reactions to food, (c) adolescent or young adult age, (d) systemic reaction to traces of the food allergen, and (e) having a peanut or nut allergy.[44] When the first factor is present or when at least two of the other risk factors are present in the context of suspected or proven food allergy, food allergic patients are considered high-risk patients, and candidates for an epinephrine auto-injector (EAI).[2]

Co-factors, also called augmenting factors, increase the risk of an allergic reaction occurring or its severity.[2] Co-factors are life style factors (alcohol and physical exercise); medication (NSAIDs, ACE inhibitors, ß-blockers); patient specific factors (adolescence, infections, hormonal status, psychogenic stress); and pre-existing conditions (asthma and other IgE dependent diseases, cardiovascular diseases, mastocytosis and/or increased basal tryptase). Other factors that are known risk factors for fatal food-induced anaphylaxis are not recognizing an allergic reaction, delayed or no administration of epinephrine or inadequate use of an epinephrine auto-injector.[34,45]

The prevalence of anaphylaxis

Estimates of the actual prevalence of anaphylaxis are uncertain. For ethical reasons, it is not possible to conduct randomized, placebo-controlled trials in anaphylaxis. With anaphylaxis being a syndrome with variable symptoms, signs and time course, none of the definitions are ideal and impede accurate epidemiological study.[46] Comparisons of epidemiologic data are often complicated due to differences in anaphylaxis definitions, methodologies, and characteristics of the study population.[47] It has been reported that the life-time prevalence of anaphylaxis in Europe is 0.3% (95% CI 0.1-0.5).[47] Fatalities due to food-induced anaphylaxis are rare. Overall, the case fatality ratio from anaphylaxis is estimated at under 0.0001%.[47]

Acute management and long-term management of food allergy and anaphylaxis

The care for patients with food allergies and anaphylaxis may be subdivided into acute, or emergency and long-term management. It is very difficult to predict the severity of an allergic reaction and, in fatal reactions, death may occur within minutes of onset. Therefore effective, acute management is important. However, long-term management is also important which provides the best quality of life for the food allergic patients.

Acute management

The first step in the acute management of food-induced anaphylaxis is the intramuscular injection of epinephrine.[41,48-50] The initial treatment should include a rapid assessment to determine the extent and severity of the allergic reaction, the adequacy of oxygenation, cardiac output and tissue perfusion, any potential confounding medications, co-existing diseases and the suspected cause of the reaction.[48-50] The patient should be placed in the supine position with the legs elevated, if tolerated, to help maintain adequate perfusion and blood pressure. Initial therapy should be directed at the maintenance of an effective airway and circulatory system.[48-50]

Epinephrine and epinephrine auto-injectors

Epinephrine is the medication of choice in the emergency treatment of anaphylaxis in the community.[49,51] Epinephrine is a natural body constituent, comprising approximately 80% of the catecholamines in the human adrenal medulla.[48] During sudden frightening or life-threatening situations, endogenous epinephrine is released from this site and exerts its action via sympathomimetically innervated structures all over the body.[48] Heart rate accelerates and the force of cardiac contractions increases. Blood pressure rises. Blood flow is redistributed from the skin and subcutaneous tissue to the skeletal muscles, splanchnic circulation, and brain.[48] The bronchi and pupils dilate.[48] Oxygenation increases, blood glucose rises, and the body is prepared for 'fight or flight'.[48]

For food allergic patients at high risk of anaphylaxis in the community, epinephrine should be prescribed in the form of an auto-injector.[52] Intramuscular epinephrine should be given at a dose of 0.01 mg/kg of body weight to a maximum total dose of 0.5 mg for a large adult and 0.3 mg for most adults and older children.[48] This is based on tradition and clinical consensus rather than on randomized controlled trials.[48] After using an EAI the patient should be transported to a hospital as soon as possible for further anaphylaxis treatment. The time during which children are observed following an (severe) allergic reaction varies in clinical practice. Recommendations vary from between two to twenty-four hours.[28,32,53-56]

Bronchodilators such as albuterol (salbutamol) and other medications, including antihistamines, or oral corticosteroids, although useful adjuncts in the treatment of anaphylaxis, but are not a substitute for epinephrine.[41,49] On the basis of clinical consensus, the epinephrine dose can be repeated every five to fifteen minutes, as needed.[41,48,49]

Available epinephrine auto-injectors

EAIs are not in every country available to food allergic patients.[57] An EAI is a single use, disposable, prefilled automatic injection device (auto-injector) with a fixed dose of epinephrine. There are several auto-injectors: EpiPen®, Jext®, Emerade®, Anapen®, Intellijject®, Twinject®, Adrenaclick®, and Auvi-Q®. This thesis will focus on EAIs available in the Netherlands: EpiPen®, Jext®, and Emerade®. Anapen® was previously available in the Netherlands, but not after June 2012.[58] Intellijject®, Twinject®, Adrenaclick®, and Auvi-Q® are not available in the Netherlands. EAIs differ significantly with regard to size, ease of carrying, ease of use, needle protection, and robustness.[39] They are not inter-changeable.[59] Descriptive characteristics of available EAIs in the Netherlands are shown in Table 3.

In the Netherlands there are different fixed epinephrine doses available (0.15 mg, 0.30 mg and 0.50 mg). Food allergic children between 7.5 kg and 25 kg of weight should be prescribed an EAI containing 0.15 mg epinephrine.[41] Food allergic children and adolescents over 25 kg of weight should be prescribed an EAI containing 0.30 mg of

Table 3. Characteristics of epinephrine auto-injectors available in the Netherlands

EAIs	EpiPen®	Jext®	Emerade®
Doses (mg)	0.15; 0.30	0.15;0.30	0.15;0.30;0.50
Excipients			
Sodium chloride	1.8mg; 1.8mg	Present; mg n/a*	Present; mg n/a*
Sodium metabisulfite (E223)	0.5mg; 0.5mg	Persent; mg n/a*	Present; mg n/a*
Other	Hydrochloric acid, water	Hydrochloric acid, water	Disodium edetate, hydrochloric acid
Exposed needle length (mm)	12.7; 15.02	13; 15	16; 23; 23
Needle gauge (G)	22	22	n/a
Needle protection	yes	yes	yes
Length (cm)	±15.6	±19.5	±22.0
Shelf-life (months)	18	18	30
No. of doses per auto-injector	1	1	1
Manufacturer/Distributor	Meda-Pharma	ALK-Abelló	Bausch&Lomb

*n/a: information not available

epinephrine.[41,48,60] There is no fixed epinephrine dose available for food allergic infants and children <7.5 kg. Currently, health care providers must choose between two alternatives for these children at risk for anaphylaxis: prescribing a user-friendly EAI (0.15 mg) and potentially overdosing the food allergic infants and children of <7.5 kg, or prescribing an epinephrine ampule along with a sterile syringe/needle and instructions.[52] Although for the first-aid treatment of anaphylaxis in food allergic infants and children of <7.5 kg, the goals of precise epinephrine dosing of 0.01 mg/kg is preferable, Simons et al.[52] demonstrated that many of the parents felt uncomfortable using an epinephrine ampule along with a sterile syringe/needle. Prescribing an EAI (0.15 mg) for use in food allergic infants and children of <7.5 kg —though it is certainly not ideal, because it delivers a threefold epinephrine overdose to those weighing approximately 5 kg and a twofold epinephrine overdose to those weighing approximately 7.5 kg— appears to be a preferable alternative to the epinephrine ampule/syringe/needle technique.[52] An EAI for this age group or additional premeasured or pharmacy preset sterile epinephrine doses of 0.05 mg and 0.1 mg in user-friendly formulations are urgently needed.[52] All devices are also produced as training devices. These are needleless replicas of the actual devices that patients can use to practice using the device with a trainer.

The design of currently available EAIs has not changed significantly in the last decade. A previous study showed that treatment failures and unintentional needle-stick injuries have been reported which may be attributed to EAI design.[61] However, unintentional needle-stick injuries may decrease as EAIs with improved design, including a needle protection feature, are being introduced.[49,62,63] Several new devices and alternative delivery systems have been developed.[62-65] The new devices of EpiPen®, Jext® and Emerade® available in the

Netherlands have needle guards following use to protect against needle stick injury.[66-68] Patients not carrying their EAI at all times may also be due to its design and/or inadequate training. Patients reported that an EAI is difficult to carry and impractical because of its size.[64,69] To date no studies seem to have been undertaken to evaluate EAIs together with patients.

When to use an EAI: mild, moderate and/or severe allergic symptoms

Food allergic patients are instructed to use their epinephrine auto-injectors if they have signs of an allergic reaction. However to recognize the start of an allergic reaction and to distinguish between mild, moderate or severe allergic symptoms can be quite difficult for a patient or their parent(s)/caregiver(s). There are different recommendations given by health-care professionals and manufacturers of EAIs as to when an EAI should be administered. Administering an EAI after a patient has ingested the culprit food but is not yet experiencing allergic symptoms is unlikely to be necessary.[70] In our center we advise food allergic patients to administer their EAI for any (reasonably definite) allergic symptoms in the context of being reasonably sure of possibly having accidentally ingested the culprit food, and we stress to call the emergency number immediately after such administration. It has been proposed that the use of an EAI for initial, mild allergic symptoms may lead to overtreatment of an allergic reaction, and possible subsequent unavailability of a second dose for the event that symptoms worsen.[70] However, the progress after the onset of an allergic reaction is uncertain. Previous studies on fatalities caused by anaphylactic reactions to food suggest that there is only a brief window of time during which the first dose of epinephrine is effective.[27,34,71,72] Early administration of an EAI may therefore be justified.

Possible side-effects of epinephrine and EAI use

There are no absolute contra-indications to treatment with epinephrine in a patient experiencing anaphylaxis.[41] Side-effects of epinephrine in general are associated with the α- and β-receptor activity of epinephrine.[41] Transient pharmacologic effects of epinephrine, such as pallor, tremor, anxiety, palpitations, headache, and dizziness, that occur within five to ten minutes after injection are usually mild and confirm that a therapeutic epinephrine dose has been given.[41,48-50] Serious adverse effects are rare with intramuscular use.[48-50] The majority of serious adverse effects occur when epinephrine is given intravenously or incorrectly dosed, which is unlikely to happen when using an auto-injector with a single fixed dose of epinephrine. When epinephrine is given intravenously, this should be done by experienced health-care professionals, and should be monitored with continuous cardiac monitoring, pulse oximetry and frequent non-invasive blood pressures.[41,49] EAIs contain sodium metabisulphite, which may rarely cause severe hypersensitivity reactions.[73,74] There is also the risk of accidentally injecting epinephrine into a digit.

Figure 2. Pictures of available epinephrine auto-injectors in the Netherlands

1. Epipen®

2. Jext®

3. Emerade ®

(Under)prescription of EAIs

All food allergic patients at high risk for anaphylaxis should carry an EAI at all times. However, previous studies have shown that many high-risk food allergic patients do not have an epinephrine auto-injector (EAI). A previous study by Flokstra-de Blok et al. showed that there is an alarming under-prescription of EAIs in high-risk food allergic adolescents (11-20 years) in Dutch high schools.[75] Less than 1 in 30 of these adolescents had actually been prescribed an EAI.[75] This study highlights the shortcoming to effective management of anaphylaxis in adolescents in the Netherlands. Fatality studies also show that some patients dying from anaphylaxis had unfortunately not been prescribed an EAI.[34,45] It might be possible that these patients did not visit a health-care professional.

To identify patients who are at high risk for anaphylaxis and to assess the need for an EAI is important. A risk factor assessment based on the guidelines of the *European Academy of Allergy and Clinical Immunology* (EAACI) can be used for any patient who experienced allergic symptoms due to food.[2]

In the Netherlands general practitioners (GPs) play an important role in diagnosing, treating food allergic patients and prescribing EAIs. However, primary care guidelines in the Netherlands, the NHG (*Nederlandse Huisartsen Genootschap*) guidelines,[76] recommend that an EAI should only be prescribed to patients after a previous anaphylaxis. Significantly, risk factors for a life-threatening food-induced anaphylactic reaction are mentioned, but are not put forward as a reason to prescribe an EAI in the absence of a previous anaphylactic reaction.

Previous studies also show that GPs are not always knowledgeable about food allergic patients at high risk for anaphylaxis.[77-80] These studies show that there is a lack of allergy knowledge in primary care, especially the recognition and treatment of anaphylaxis are problematic and that national guidelines are often not followed. Therefore, the prescription of EAIs is an important issue and there is a need for improvement of the quality of care for high-risk food allergic patients in primary care. The incomplete data might be due to under-reporting of patients (or their parents), under-documentation of clinical information by GPs or lack of knowledge and/or practice behavior gaps experienced by GPs.

How many EAIs to prescribe?

There is no consensus among experts about how many EAIs to prescribe for each food allergic patient. There is data about absolute indications for a prescription of an EAI, however there is no high quality data to help decide how many EAIs should be available to individual patients.[41,51] Previous studies showed that the percentage of patients who required a second dose of epinephrine after having used an EAI to treat allergic symptoms varied between zero to 32%.[81-85] A decision to prescribe one, two or more devices is influenced by a number of factors.[41] Some authorities advise that patients should have

one EAI at each site that they regularly attend (e.g. kindergarten, school, work). Others advise there should be two EAIs at each location, in case one is defective or misfires, or a second injection is needed before emergency help arrives. This would be particularly important if the patient is going to a remote location where prompt medical attention is unavailable. There may be practical, psychological or policy considerations as to why an individual patient needs more than one EAI.[37] However, prescribing more than one EAI may negatively influence compliance and burden of treatment.

It is important is to identify the patients who need to have access to more than one EAI. The EAACI has suggested indications for prescription of a second EAIs,[41] namely (1) co-existing unstable or moderate to severe, persistent asthma and a food allergy, (2) co-existing mast cell diseases and/or elevated baseline tryptase concentration, (3) lack of rapid access to medical assistance to manage an episode of anaphylaxis due to geographical or language barriers, (4) previous requirement for more than one dose of epinephrine prior to reaching hospital, (5) previous near fatal anaphylaxis, (6) if available EAI dose is much too low for body weight.

Compliance and burden of treatment of EAIs

A number of studies show that food allergic patients, adolescents in particular, are often poorly compliant and do not always carry their EAI.[86,87] The reluctance to carry an EAI may be the result of the perception of patients that such treatment is burdensome. It has been previously shown that the burden of treatment (BoT) of an EAI in vespid allergic patients is high.[88] Additionally, regularly replacing devices, the need to educate about how and when to use an EAI, the potential stigma associated with requiring an EAI as well as the cost of devices might contribute to being poorly compliant and the burden of treatment.

Non-use of EAIs

EAIs are underused by patients for a variety of reasons. In some countries, EAIs are not available or not prescribed when indicated, or they are not affordable.[57] Another reason is that many patients do not have their EAI(s) with them at the time of accidental ingestion of the allergic food. In adolescents, this may be caused by problems occurring at the time of the transfer of responsibility for managing their food allergy from parents to themselves. Other reasons of non-use may be that patients do not think that their allergic reaction is severe enough to use an EAI, anxiety, use of other medication, peer pressure, feeling ashamed, or practical problems.[64,69,86,89-96]

How to use an EAI?

Several studies showed that a significant proportion of patients and their parents (or other caregivers), and even health-care professionals, do not know how to correctly use an EAI.[82,97-100] Anaphylaxis usually occurs in the community, and therefore, all food allergic patients at risk for anaphylactic reactions as well as their parents (and other caregivers) should be provided with educational resources. Training should cover avoidance strategies, recognition of symptoms, and when and how to administer an EAI. Health-care professionals prescribing and/or dispensing an EAI should provide such training, although it has been shown that failure to provide this is commonplace.[51]

Long-term management

The only way to avoid an allergic reaction is to avoid the food(s) that cause the allergic reaction. However, accidental ingestion is common and can cause a severe allergic reaction, and because of the life-threatening nature of anaphylaxis the cornerstone of therapy is prevention. Consequently, an accurate diagnosis is very important in order to identify which foods should be avoided, and it is also important to identify risk- and co-factors for the individual patient. It is also of importance to provide food allergic patients and their families with comprehensive information on food allergen avoidance, and prompt recognition and management of allergic reactions in order to manage his or her food allergy.

Quality of life in food allergy and anaphylaxis

Impact of food allergy and having to carry an EAI on quality of life

Food allergy and anaphylaxis carries with it the additional psychological burden of daily dietary restriction in a variety of settings (e.g. home, restaurants, schools, social gatherings) and having to carry an EAI at all times. Usually, food allergic children do not have objective allergic symptoms until exposed to the allergenic food, and this may cause confusion and misunderstanding in people in the child's environment about the severity or occasionally even the existence of the child's allergy.

Also, food allergic children, especially adolescents, have the desire to be 'normal' and are afraid of the embarrassment encountered in certain social situations when having an allergic reaction. The burden of avoidance and fear of an accidental exposure, and having to carry an EAI at all times are all associated with poorer quality of life (QoL).[44,90,91,101-107]

QoL is a broad concept and the term is used to denote the general well-being of individuals. QoL means different things to different people in different cultures, and many definitions of this concept have been proposed. The World Health Organization (WHO) has defined quality of life as '*the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations,*

standards and concerns'.[108] The component of overall quality of life that pertains to an individual's health is called health-related quality of life (HRQL) and is defined by the WHO as '*a state of complete physical, mental, and social well-being and not merely the absence of disease and infirmity*'.[108]

Food allergy health-related quality of life measures

QoL can be measured with generic or disease-specific questionnaires. Generic QoL questionnaires are useful for evaluating and comparing different diseases, and they are also sensitive to co-morbidities.[109] The limitations of generic QoL questionnaires are that they are less sensitive and responsive to change than disease-specific instruments. Hence potentially important differences or changes may be missed.[109] This is particularly relevant in the context of food allergy, where, unless individuals are exposed to the allergenic food, they may have no symptoms or problems other than the direct and indirect psychological effects resulting from the need for the constant vigilance of continued avoidance.[110] Disease-specific questionnaires have been developed for this purpose, and are therefore significantly more sensitive and are able to detect small but potentially (clinically) important differences. The previously mentioned disease-specific questionnaires are significantly more sensitive in measuring the response to interventions or future treatments as well as estimating the general burden of food allergy.[19,111]

The development and validation of disease-specific HRQL measures applicable to all age groups and parents and/or caregivers has provided important means of assessing the global impact of food allergy on patients and families' lives. There are several *Food Allergy Quality of Life Questionnaires* (FAQLQs) currently validated and used for research and clinical evaluation (Table 4).[110,112-114]

Table 4. Food Allergy Quality of Life Questionnaires (FAQLQs)

Questionnaire	Target population	Respondent	Developed in
FAQLQ-*adult form* (AF)	adults (≥18 years)	patient	The Netherlands
FAQLQ-*teenager form* (TF)	adolescents (13-17 years)	patient	The Netherlands
FAQLQ-*child form* (CF)	children (8-12 years)	patient	The Netherlands
FAQLQ-parent form (PF)	children (0-12 years)	parent/caregiver	Ireland
FAQLQ-parent form teenager (PFT)	adolescents (13-17 years)	parent/caregiver	United Kingdom

These instruments were developed as part of the Europrevall project, a multi-center research study on food allergy. One of the aims of the Europrevall was to investigate the impact of food allergy on HRQL of patients throughout Europe. The FAQLQs were originally developed and validated in the Netherlands, Ireland and United Kingdom. The translation of FAQLQs was performed using established methods.[115] The FAQLQs are now available in multiple languages.[116] Other disease-specific instruments have been developed and validated in the United Kingdom for children and adolescents: *You and Your Food Allergy*[117] and *Paediatric Food Allergy Quality of Life Questionnaire* (PFA-QL).[118]

Aims of the thesis

The three major aims of this thesis are to investigate the reasons for the under-prescription of auto-injectors in food allergic patients at high risk for anaphylaxis, and the reasons for non-compliance and non-use of epinephrine auto-injectors by this group of patients. The first part of this thesis describes the prevalence of food allergy and under-prescription of epinephrine auto-injectors. The second part of this thesis describes the reasons for non-compliance, the burden of treatment with having to carry an EAI at all times and the impact of food allergy, anaphylaxis and carrying an EAI at all times on the health-related quality of life in food allergic patients. The third part of this thesis describes the reasons for non-use of an EAI in case of (severe) allergic reactions. This part also describes late reactions after double-blind, placebo-controlled food challenges.

Outline of the thesis

Part I. Prevalence of food allergy and under-prescription epinephrine auto-injectors

Chapter 2 estimates the prevalence of probable and self-perceived food allergy, EAI need and ownership in adolescents aged 11-20 in Dutch high schools. The results of this study are compared with the findings by Flokstra-de Blok et al. in 2009.[75]

Chapter 3 describes and evaluates the practice in EAI prescriptions by general practitioners to food allergic patients in the Netherlands.

Part II. Non-compliance, burden of treatment and HRQL

Chapter 4 determines the burden of treatment (BoT) of an EAI and examines the relationship between this burden and compliance. It also analyzes which factors contribute to the BoT of the EAI as perceived by food allergic adolescents and their parents.

Chapter 5 investigates which factors predict health-related quality of life in food allergic patients. The influence of participant characteristics, experiencing anaphylaxis and being prescribed an EAI were investigated in this context.

Part III. Non-use

Chapter 6 investigates the knowledge, attitudes, and beliefs regarding food allergy and anaphylaxis among pharmacists in the Netherlands. It also investigates how accurately pharmacists demonstrate how and when to use an EAI to patients.

Chapter 7 determines the prevalence, severity and clinical characteristics of late reactions in food allergic children and adolescents after DBPCFC, and ascertains which factors are associated with and may predict late reactions.

Finally, *Chapter 8* is a general discussion of the findings presented in this thesis and some future perspectives concerning food allergy, anaphylaxis and epinephrine auto-injectors.

In *Chapter 9* the findings are summarized in English, Dutch, and Mandarin-Chinese.

REFERENCES

(1) Boyce JA, Assa'a A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. Nutrition 2011 Feb;27(2):253-267.

(2) Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy 2014 Aug;69(8):1008-1025.

(3) Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol 2010 Feb;125(2 Suppl 2):S116-25.

(4) Sicherer SH. Epidemiology of food allergy. J Allergy Clin Immunol 2011 Mar;127(3):594-602.

(5) Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy 2014 Jan;69(1):62-75.

(6) Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy 2014 Aug;69(8):992-1007.

(7) Koplin JJ, Mills EN, Allen KJ. Epidemiology of food allergy and food-induced anaphylaxis: is there really a Western world epidemic? Curr Opin Allergy Clin Immunol 2015 Oct;15(5):409-416.

(8) Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. J Allergy Clin Immunol 2007 Sep;120(3):638-646.

(9) Zuidmeer L, Goldhahn K, Rona RJ, Gislason D, Madsen C, Summers C, et al. The prevalence of plant food allergies: a systematic review. J Allergy Clin Immunol 2008 May;121(5):1210-1218. e4.

(10) Venter C, Pereira B, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. Pediatr Allergy Immunol 2006 Aug;17(5):356-363.

(11) Zuberbier T, Edenharter G, Worm M, Ehlers I, Reimann S, Hantke T, et al. Prevalence of adverse reactions to food in Germany - a population study. Allergy 2004 Mar;59(3):338-345.

(12) Roehr CC, Edenharter G, Reimann S, Ehlers I, Worm M, Zuberbier T, et al. Food allergy and non-allergic food hypersensitivity in children and adolescents. Clin Exp Allergy 2004 Oct;34(10):1534-1541.

(13) Steinke M, Fiocchi A, Kirchlechner V, Ballmer-Weber B, Brockow K, Hischenhuber C, et al. Perceived food allergy in children in 10 European nations. A randomised telephone survey. Int Arch Allergy Immunol 2007;143(4):290-295.

(14) Beyer K, Morrow E, Li XM, Bardina L, Bannon GA, Burks AW, et al. Effects of cooking methods on peanut allergenicity. J Allergy Clin Immunol 2001 Jun;107(6):1077-1081.

(15) TM Le, I. Kummeling, E. van Hoffen, TM Lindner, AFM Lebens, EJC Van Ameijden, et al. Epidemiology, diagnosis and management of food allergy. Chapter 3. Prevalence of adverse food reactions and doctordiagnosed food allergy in different ethnic, age and sex groups; 2013.

(16) Asero R, Ballmer-Weber BK, Beyer K, Conti A, Dubakiene R, Fernandez-Rivas M, et al. IgE-mediated food allergy diagnosis: Current status and new perspectives. Mol Nutr Food Res 2007 Jan;51(1):135-147.

(17) Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, et al. Standardization of food challenges in patients with immediate reactions to foods--position paper from the European Academy of Allergology and Clinical Immunology. Allergy 2004 Jul;59(7):690-697.

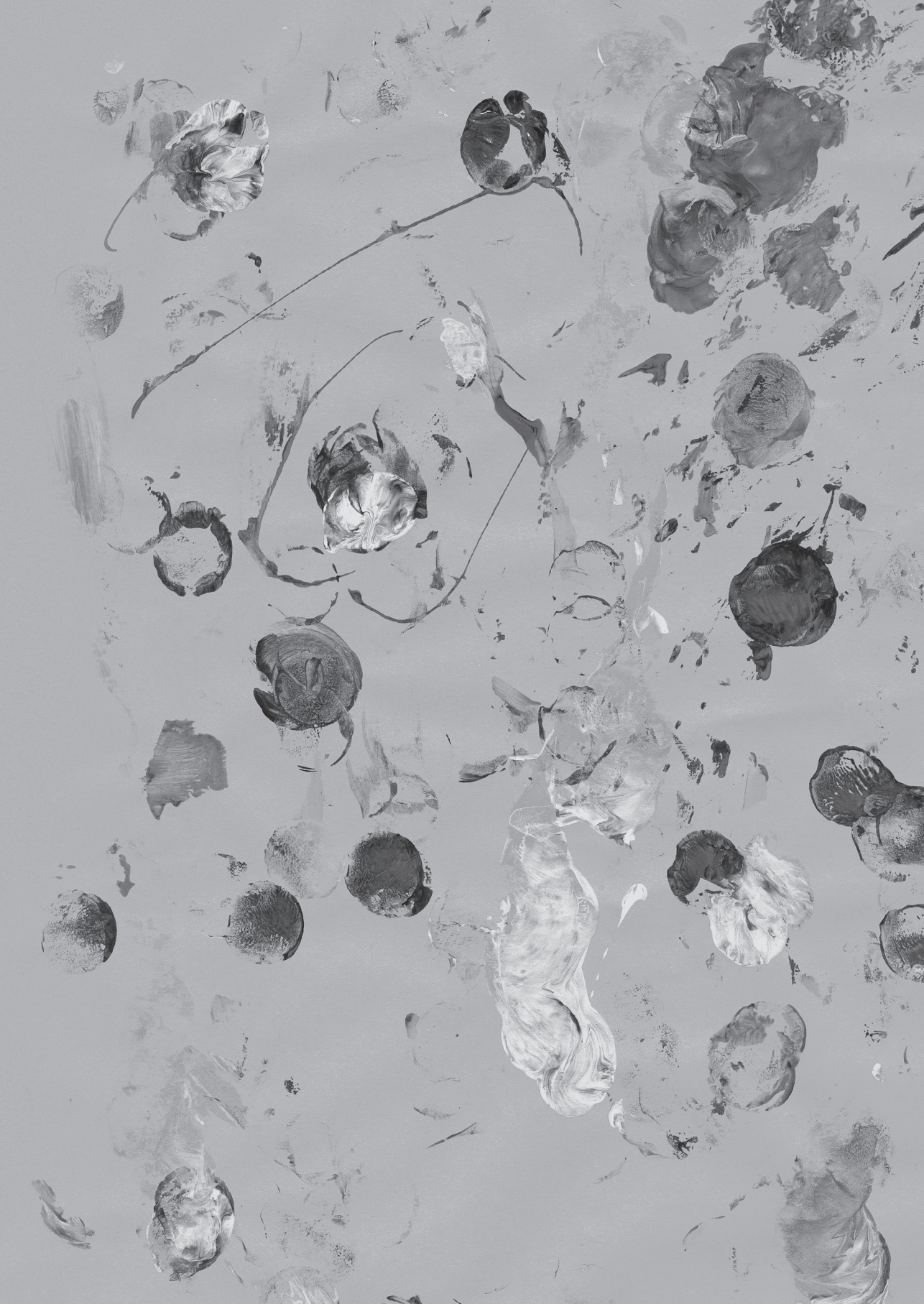
(18) Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol 2012 Dec;130(6):1260-1274.
(19) van der Velde JL, Flokstra-de Blok BM, de Groot H, Oude-Elberink JN, Kerkhof M, Duiverman EJ, et al. Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents, and children. J Allergy Clin Immunol 2012 Nov;130(5):1136-1143.e2.
(20) Sheffer AL. Anaphylaxis. J Allergy Clin Immunol 1985 Feb;75(2):227-233.
(21) Portier P, Richet C. De l'action anaphylactique de certains venins. C R Soc Biol (Paris) 1902;54:170-172.
(22) Anderson J, Sogn D. Adverse Reactions to Foods. no 8402442 ed. Bethesda, Maryland: National Institute of Allergy & Infectious Disease, NIH Publication; 1984.
(23) Golbert TM, Patterson R, Pruzansky JJ. Systemic allergic reactions to ingested antigens. J Allergy 1969 Aug;44(2):96-107.
(24) Yunginger JW, Sweeney KG, Sturner WQ, Giannandrea LA, Teigland JD, Bray M, et al. Fatal food-induced anaphylaxis. JAMA 1988 Sep 9;260(10):1450-1452.
(25) Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med 1992 Aug 6;327(6):380-384.
(26) Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 2001 Jan;107(1):191-193.
(27) Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol 2007 Apr;119(4):1016-1018.
(28) Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF,Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006 Feb;117(2):391-397.
(29) Beyer K, Eckermann O, Hompes S, Grabenhenrich L, Worm M. Anaphylaxis in an emergency setting - elicitors, therapy and incidence of severe allergic reactions. Allergy 2012 Nov;67(11):1451-1456.
(30) Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. J Allergy Clin Immunol 2015 Apr;135(4):956-63.e1.
(31) Lieberman P. Biphasic anaphylactic reactions. Annals of allergy, asthma, & immunology 2005;95(3):217-26.
(32) Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. Pediatrics 2000 Oct;106(4):762-766.
(33) Sampson HA, Munoz-Furlong A, Bock SA, Schmitt C, Bass R, Chowdhury BA, et al. Symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol 2005 Mar;115(3):584-591.
(34) Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000 Aug;30(8):1144-1150.
(35) Sala-Cunill A, Cardona V, Labrador-Horrillo M, Luengo O, Esteso O, Garriga T, et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. Int Arch Allergy Immunol 2013;160(2):192-199.
(36) Sampson HA. Anaphylaxis and emergency treatment. Pediatrics 2003 Jun;111(6 Pt 3):1601-1608.
(37) Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004 Aug;114(2):371-376.

(38) Worm M, Edenharter G, Rueff F, Scherer K, Pfohler C, Mahler V, et al. Symptom profile and risk factors of anaphylaxis in Central Europe. Allergy 2012 May;67(5):691-698.
(39) Simons FE, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J 2015 Oct 28;8(1):32-015-0080-1. eCollection 2015.
(40) Park HJ, Kim SH. Factors associated with shock in anaphylaxis. Am J Emerg Med 2012 Nov;30(9):1674-1678.
(41) Muraro A, Roberts G, Worm M, Bilo MB, Brockow K, Fernandez Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014 Aug;69(8):1026-1045.
(42) Stoloff SW. Optimizing the clinical identification and management of patients at risk for anaphylaxis. J Fam Pract 2010 Aug;59(8 Suppl Optimizing):S1-8.
(43) Munoz-Furlong A, Weiss CC. Characteristics of food allergic patients placing them at risk for a fatal anaphylactic episode. Curr Allergy Asthma Rep 2009 Jan;9(1):57-63.
(44) Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy 2007 Aug;62(8):857-871.
(45) Pumphrey RS. Fatal anaphylaxis in the UK, 1992-2001. Novartis Found Symp 2004;257:116-28; discussion 128-32, 157-60, 276-85.
(46) Lieberman P, Camargo CA,Jr, Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. Ann Allergy Asthma Immunol 2006 Nov;97(5):596-602.
(47) Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, et al. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy 2013 Nov;68(11):1353-1361.
(48) Simons KJ, Simons FE. Epinephrine and its use in anaphylaxis: current issues. Curr Opin Allergy Clin Immunol 2010 Aug;10(4):354-361.
(49) Simons FE. Anaphylaxis. J Allergy Clin Immunol 2010 Feb;125(2 Suppl 2):S161-81.
(50) Simons FE. Emergency treatment of anaphylaxis. BMJ 2008 May 24;336(7654):1141-1142.
(51) Muraro A, Agache I, Clark A, Sheikh A, Roberts G, Akdis CA, et al. EAACI food allergy and anaphylaxis guidelines: managing patients with food allergy in the community. Allergy 2014 Aug;69(8):1046-1057.
(52) Simons FE, Chan ES, Gu X, Simons KJ. Epinephrine for the out-of-hospital (first-aid) treatment of anaphylaxis in infants: is the ampule/syringe/needle method practical? J Allergy Clin Immunol 2001 Dec;108(6):1040-1044.
(53) Grunau BE. Incidence of clinically important biphasic reactions in emergency department patients with allergic reactions or anaphylaxis. Ann Emerg Med 2014-6;63(6):736-44.
(54) Mehr S, Liew WK, Tey D, Tang ML. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. Clin Exp Allergy 2009 Sep;39(9):1390-1396.
(55) Jarvinen KM, Amalanayagam S, Shreffler WG, Noone S, Sicherer SH, Sampson HA, et al. Epinephrine treatment is infrequent and biphasic reactions are rare in food-induced reactions during oral food challenges in children. J Allergy Clin Immunol 2009 Dec;124(6):1267-1272.
(56) Lee S, Bellolio MF, Hess EP, Erwin P, Murad MH, Campbell RL. Time of Onset and Predictors of Biphasic Anaphylactic Reactions: A Systematic Review and Meta-analysis. J Allergy Clin Immunol Pract 2015 May-Jun;3(3):408-16.e1-2.
(57) Simons FE. Lack of worldwide availability of epinephrine autoinjectors for outpatients at risk of anaphylaxis. Ann Allergy Asthma Immunol 2005 May;94(5):534-538.
(58) Lincoln Medical Ltd.. Mogelijk kwaliteitsdefect bij Anapen® auto-injectoren. Available at: http://www.igz.nl/Images/Final%20Anapen%20letter%20to%20prescribers-pharmacies_tcm294-330556.pdf. Accessed 06/13, 2016.

(59) Umasunthar T, Procktor A, Hodes M, Smith JG, Gore C, Cox HE, et al. Patients' ability to treat anaphylaxis using adrenaline autoinjectors: a randomized controlled trial. Allergy 2015 Jul;70(7):855-863.
(60) Simons FE, Gu X, Silver NA, Simons KJ. EpiPen Jr versus EpiPen in young children weighing 15 to 30 kg at risk for anaphylaxis. J Allergy Clin Immunol 2002 Jan;109(1):171-175.
(61) Simons FE, Lieberman PL, Read EJ,Jr, Edwards ES. Hazards of unintentional injection of epinephrine from autoinjectors: a systematic review. Ann Allergy Asthma Immunol 2009 Apr;102(4):282-287.
(62) Guerlain S, Wang L, Hugine A. Intellijject's novel epinephrine autoinjector: sharps injury prevention validation and comparable analysis with EpiPen and Twinject. Ann Allergy Asthma Immunol 2010 Dec;105(6):480-484.
(63) Camargo CA,Jr, Guana A, Wang S, Simons FE. Auvi-Q versus EpiPen: preferences of adults, caregivers, and children. J Allergy Clin Immunol Pract 2013 May-Jun;1(3):266-72.e1-3.
(64) Frew AJ. What are the 'ideal' features of an adrenaline (epinephrine) auto-injector in the treatment of anaphylaxis? Allergy 2011 Jan;66(1):15-24.
(65) Guerlain S, Hugine A, Wang L. A comparison of 4 epinephrine autoinjector delivery systems: usability and patient preference. Ann Allergy Asthma Immunol 2010 Feb;104(2):172-177.
(66) EpiPen®. Available at: https://www.epipen.com/. Accessed 06/28, 2016.
(67) Jext. Available at: http://www.jext.com. Accessed 06/28, 2016.
(68) Emerade. Available at: http://www.emerade.com/. Accessed 06/28, 2016.
(69) Monks H, Gowland MH, MacKenzie H, Erlewyn-Lajeunesse M, King R, Lucas JS, et al. How do teenagers manage their food allergies? Clin Exp Allergy 2010 Oct;40(10):1533-1540.
(70) Turner PJ, DunnGalvin A, Hourihane JO. The Emperor Has No Symptoms: The Risks of a Blanket Approach to Using Epinephrine Autoinjectors for All Allergic Reactions. J Allergy Clin Immunol Pract 2016 Jun 7.
(71) Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. J Allergy Clin Immunol 2007 Apr;119(4):1018-1019.
(72) Greenberger PA, Rotskoff BD, Lifschultz B. Fatal anaphylaxis: postmortem findings and associated comorbid diseases. Ann Allergy Asthma Immunol 2007 Mar;98(3):252-257.
(73) Farmacotherapeutisch Kompas. Adrenaline. Available at: https://www.farmacotherapeutischkompas.nl/bladeren-volgens-boek/preparaatteksten/a/adrenaline. Accessed 06/13, 2016.
(74) EMC. Jext 300 micrograms Solution for Injection in pre-filled pen. Available at: https://www.medicines.org.uk/emc/medicine/23894. Accessed 06/13, 2016.
(75) Flokstra-de Blok BM, Doriene van Ginkel C, Roerdink EM, Kroeze MA, Stel AA, van der Meulen GN, et al. Extremely low prevalence of epinephrine autoinjectors in high risk food allergic adolescents in Dutch high schools. Pediatr Allergy Immunol 2011 Jun;22(4):374-377.
(76) Lucassen P, Albeda F, Van Reisen M, Silvius A, Wensing C, Luning-Koster M. NHG guideline Food Hypersensitivity. 2010(53):537-553.
(77) Agache I, Ryan D, Rodriguez MR, Yusuf O, Angier E, Jutel M. Allergy management in primary care across European countries -- actual status. Allergy 2013 Jul;68(7):836-843.
(78) Jutel M, Angier L, Palkonen S, Ryan D, Sheikh A, Smith H, et al. Improving allergy management in the primary care network--a holistic approach. Allergy 2013 Nov;68(11):1362-1369.
(79) Gupta RS, Springston EE, Kim JS, Smith B, Pongracic JA, Wang X, et al. Food allergy knowledge, attitudes, and beliefs of primary care physicians. Pediatrics 2010 Jan;125(1):126-132.
(80) Waserman S, Chad Z, Francoeur MJ, Small P, Stark D, Vander Leek TK, et al. Management of anaphylaxis in primary care: Canadian expert consensus recommendations. Allergy 2010 Sep;65(9):1082-1092.
(81) Simons FE, Clark S, Camargo CA,Jr. Anaphylaxis in the community: learning from the survivors. J Allergy Clin Immunol 2009 Aug;124(2):301-306.

(82) Noimark L, Wales J, Du Toit G, Pastacaldi C, Haddad D, Gardner J, et al. The use of adrenaline autoinjectors by children and teenagers. Clin Exp Allergy 2012 Feb;42(2):284-292.
(83) Uguz A, Lack G, Pumphrey R, Ewan P, Warner J, Dick J, et al. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. Clin Exp Allergy 2005 Jun;35(6):746-750.
(84) Jarvinen KM, Sicherer SH, Sampson HA, Nowak-Wegrzyn A. Use of multiple doses of epinephrine in food-induced anaphylaxis in children. J Allergy Clin Immunol 2008 Jul;122(1):133-138.
(85) Clark AT, Ewan PW. Good prognosis, clinical features, and circumstances of peanut and tree nut reactions in children treated by a specialist allergy center. J Allergy Clin Immunol 2008 Aug;122(2):286-289.
(86) Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Epinephrine auto-injector use in adolescents at risk of anaphylaxis: a qualitative study in Scotland, UK. Clin Exp Allergy 2011 Jun;41(6):869-877.
(87) Macadam C, Barnett J, Roberts G, Stiefel G, King R, Erlewyn-Lajeunesse M, et al. What factors affect the carriage of epinephrine auto-injectors by teenagers? Clin Transl Allergy 2012 Feb 2;2(1):3.
(88) Oude Elberink JN, van der Heide S, Guyatt GH, Dubois AE. Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis. J Allergy Clin Immunol 2006 Sep;118(3):699-704.
(89) Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Strategies for living with the risk of anaphylaxis in adolescence: qualitative study of young people and their parents. Prim Care Respir J 2012 Dec;21(4):392-397.
(90) Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. Allergy 2010 Aug;65(8):933-945.
(91) Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JS. Management of nut allergy influences quality of life and anxiety in children and their mothers. Pediatr Allergy Immunol 2010 Jun;21(4 Pt 1):586-594.
(92) MacKenzie H, Roberts G, van Laar D, Dean T. Teenagers' experiences of living with food hypersensitivity: a qualitative study. Pediatr Allergy Immunol 2010 Jun;21(4 Pt 1):595-602.
(93) Marrs T, Lack G. Why do few food allergic adolescents treat anaphylaxis with adrenaline?--Reviewing a pressing issue. Pediatr Allergy Immunol 2013 May;24(3):222-229.
(94) Rodham K, Brewer H, Mistral W, Stallard P. Adolescents' perception of risk and challenge: a qualitative study. J Adolesc 2006 Apr;29(2):261-272.
(95) Rolison MR, Scherman A. Factors influencing adolescents' decisions to engage in risk-taking behavior. Adolescence 2002 Fall;37(147):585-596.
(96) Sampson MA, Munoz-Furlong A, Sicherer SH. Risk-taking and coping strategies of adolescents and young adults with food allergy. J Allergy Clin Immunol 2006 Jun;117(6):1440-1445.
(97) Kastner, M Harada,L Waserman, S. Gaps in anaphylaxis management at the level of physicians, patients, and the community: a systematic review of the literature. Allergy 2010;65(4):435-444.
(98) Pouessel G, Deschildre A, Castelain C, Sardet A, Sagot-Bevenot S, de Sauve-Boeuf A, et al. Parental knowledge and use of epinephrine auto-injector for children with food allergy. Pediatr Allergy Immunol 2006 May;17(3):221-226.
(99) Grouhi M, Alshehri M, Hummel D, Roifman CM. Anaphylaxis and epinephrine auto-injector training: who will teach the teachers? J Allergy Clin Immunol 1999 Jul;104(1):190-193.
(100) Gosbee LL. Nuts! I can't figure out how to use my life-saving epinephrine auto-injector! Jt Comm J Qual Saf 2004 Apr;30(4):220-223.
(101) MacKenzie H, Dean T. Quality of life in children and teenagers with food hypersensitivity. Expert Rev Pharmacoecon Outcomes Res 2010 Aug;10(4):397-406.

(102) Allen CW, Bidarkar MS, vanNunen SA, Campbell DE. Factors impacting parental burden in food allergic children. J Paediatr Child Health 2015 Jan 15.
(103) Lieberman JA, Sicherer SH. Quality of life in food allergy. Curr Opin Allergy Clin Immunol 2011 Jun;11(3):236-242.
(104) van der Velde JL, Flokstra-de Blok BM, Dunngalvin A, Hourihane JO, Duiverman EJ, Dubois AE. Parents report better health-related quality of life for their food allergic children than children themselves. Clin Exp Allergy 2011 May 16.
(105) Marklund B, Ahlstedt S, Nordstrom G. Food hypersensitivity and quality of life. Curr Opin Allergy Clin Immunol 2007 Jun;7(3):279-287.
(106) Akeson N, Worth A, Sheikh A. The psychosocial impact of anaphylaxis on young people and their parents. Clin Exp Allergy 2007 Aug;37(8):1213-1220.
(107) Lyons AC, Forde EM. Food allergy in young adults: perceptions and psychological effects. J Health Psychol 2004 Jul;9(4):497-504.
(108) World Health Organization. Handbook of basic documents. Constitution of the World Health Organisation Geneva; 1948. p. 3-20.
(109) Salvilla SA, Dubois AE, Flokstra-de Blok BM, Panesar SS, Worth A, Patel S, et al. Disease-specific health-related quality of life instruments for IgE-mediated food allergy. Allergy 2014 Jul;69(7):834-844.
(110) Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy 2009 Jan;39(1):127-137.
(111) van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Oude Elberink JN, Schouten JP, Dunngalvin A, et al. Test-retest reliability of the Food Allergy Quality of Life Questionnaires (FAQLQ) for children, adolescents and adults. Qual Life Res 2009 Mar;18(2):245-251.
(112) Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, et al. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. J Allergy Clin Immunol 2008 Jul;122(1):139-44, 144.e1-2.
(113) Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, et al. Development and validation of the Food Allergy Quality of Life Questionnaire - Adult Form. Allergy 2009 Aug;64(8):1209-1217.
(114) DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0-12 years: content, construct, and cross-cultural validity. Clin Exp Allergy 2008 Jun;38(6):977-986.
(115) World Health Organization. Process of translation and adaptation of instruments. Available at: http://www.who.int/substance_abuse/research_tools/translation/en/. July 2010.
(116) Food Allergy Quality of Life Questionnaire. Available at: http://faqlq.com/. Accessed 04/18, 2016.
(117) Mackenzie H, Roberts G, Van Laar D, Dean T. A new quality of life scale for teenagers with food hypersensitivity. Pediatr Allergy Immunol 2012 Aug;23(5):404-411.
(118) Knibb RC, Ibrahim NF, Petley R, Cummings AJ, King RM, Roberts G, et al. Validation of the Paediatric Food Allergy Quality of Life Questionnaire (PFA-QL). Pediatr Allergy Immunol 2013 May;24(3):288-292.

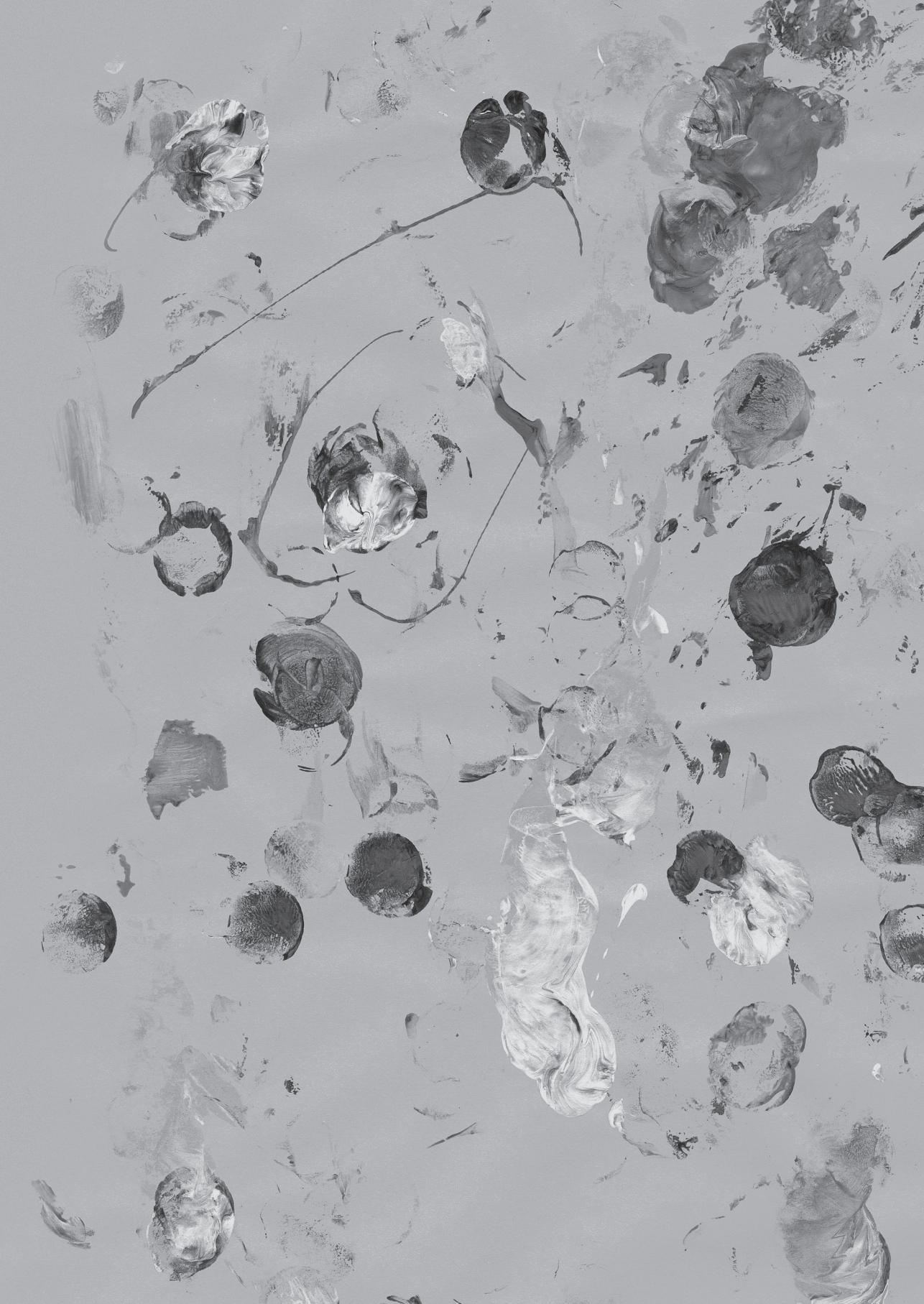


Part I

Prevalence of food allergy and under-prescription of epinephrine auto-injectors

Chapter 2
The prevalence of food allergy and epinephrine auto-injectors in Dutch food-allergic adolescents

Chapter 3
Epinephrine auto-injector prescriptions to food-allergic patients in primary care in the Netherlands



Chapter 2

The prevalence of food allergy and epinephrine auto-injectors in Dutch food-allergic adolescents

J. Saleh-Langenberg
G.M. Bootsma
C.D. van Ginkel
B.J. Kollen
B.M.J. Flokstra-de Blok
A.E.J. Dubois

Pediatr Allergy Immunol. 2016 Jul 5

ABSTRACT

Background: A previous study showed an alarming under-prescription of epinephrine auto-injectors (EAIs) in high-risk food-allergic adolescents (11-20 years) in Dutch high schools. Several subsequent studies have shown that the prevalence of food allergies and anaphylaxis is increasing, and it was therefore of interest to re-investigate if the situation in the Netherlands using the same procedures and instruments used previously. The aim of this study was therefore to estimate the prevalence of probable and self-perceived food allergy, EAI need and ownership in adolescents aged 11-20 in Dutch high schools and to compare this data with the findings of 2009.

Methods: Participants were asked to complete a screening questionnaire and were interviewed by telephone. Participants were classified as probably or unlikely to be food allergic and the need for an EAI and ownership was assessed.

Results: In total, 2632 adolescents were screened, of which 592 indicated to have problems with food and 112 were interviewed by telephone. In total 25 adolescents were classified as probably food allergic. Ten of them were considered candidates for an EAI, and two of these adolescents had been prescribed an EAI.

Conclusions: No increase in the prevalence of (high risk) food allergy in Dutch adolescents in the last six years could be found. Even though EAI ownership has improved marginally, there is still a substantial under-prescription of EAIs in high-risk food-allergic adolescents in the Netherlands.

Food-induced anaphylaxis continues to be increasing across all ages, and the risk of fatal food-induced anaphylaxis is disproportionately high in adolescents.[1,2] Effective management of food-induced anaphylaxis must include both prompt acute, emergency treatment and long-term care. When a severe food-allergic reaction occurs, prompt administration of epinephrine may be life-saving. Therefore, all food-allergic patients at high-risk of anaphylaxis should carry an epinephrine auto-injector (EAI) at all times. However, a previous study in 2009 showed that there was an alarming underprescription of EAIs to high-risk food-allergic adolescents (11-20 years) in Dutch high schools.[3] Less than 1 in 30 of these adolescents had actually been prescribed an EAI. Recent guidelines for food allergy and anaphylaxis by the European Academy of Allergy and Clinical Immunology (EAACI)[4] gave recommendations about risk assessment and management of patients who are at high-risk of experiencing anaphylaxis to improve the care for food-allergic patients. With the prevalence of food allergies and anaphylaxis increasing, it is therefore of interest to investigate if the situation in the Netherlands has changed over the years.

Therefore, the aim of this study was to estimate the prevalence of probable and self-perceived food allergy, EAI need and ownership in adolescents aged 11-20 in Dutch high schools and to compare this data with the findings of 2009.

The study population were adolescents aged 11–20 from four high schools in four different provinces of the Netherlands. The same study design was used as in 2009.[3] High schools who participated in 2009 were contacted again to participate in this study.[3] Participants were asked to complete a (digital) screening questionnaire (Figure 1).[3]

Figure 1. Screening questionnaire questions

Screening questions	**Yes**	**No**
1. Do you have a food allergy or do you think you have a food allergy?		
2. Do you get symptoms from certain foods?		
3. Do you avoid certain foods to prevent symptoms?		
4. Do you have an EpiPen®, Jext® or Anapen® (or ever had one?)*		
Other questions	**Yes**	**No**
What is your age?		
Can we contact you for further questions? If yes, please write down your phonenumber below		

*pictures of Anapen®, EpiPen® and Jext ® were shown

Adolescents, who answered 'yes' to one or more of the screening questions and agreed to be contacted, were interviewed using a telephone questionnaire. The telephone questionnaire included questions concerning the suspected food(s), allergic symptoms, the person responsible for the food allergy diagnosis, and the need for an EAI.[3]

Only allergic reactions to foods that occurred in the last 2 years were recorded. Adolescents were classified as probably food-allergic when they reported allergic symptoms after eating known allergenic foods (occurring within maximally 1 hour and to a daily serving or less.

The need for an EAI was assessed using a risk factor based protocol.[3,4] This protocol considers an EAI to be indicated if a patient has had (a) a previous severe anaphylactic reaction to a food, or (b) food allergy is suspected or confirmed and the patient has two or more of the following risk factors: (1) adolescent to young adult age, (2) asthma, (3) previous reaction to trace amounts of a food, and (4) (possible) allergy to peanuts or tree nuts.

For calculation of the questionnaire-based prevalence, it was assumed that the prevalence of food allergy in the group of adolescents that refused or could not be contacted was the same as in the group of adolescents that could be contacted.[3] Prevalence was calculated based on extrapolation of the data from the adolescents that were contacted and are shown as percentage of the total number of screened adolescents.[3] In addition, the minimal prevalence was calculated without extrapolation.[3] The diagnostic accuracy and sources of 'correct' and 'incorrect' diagnoses were investigated by calculating percentages.[3] Adolescents who thought that they were food-allergic and who were subsequently classified as probably food-allergic were referred to in this study as '*correctly diagnosed*'.[3] Adolescents who thought that they were food-allergic and who were subsequently classified as unlikely to be food-allergic were referred to in this study as '*incorrectly diagnosed*'.[3]

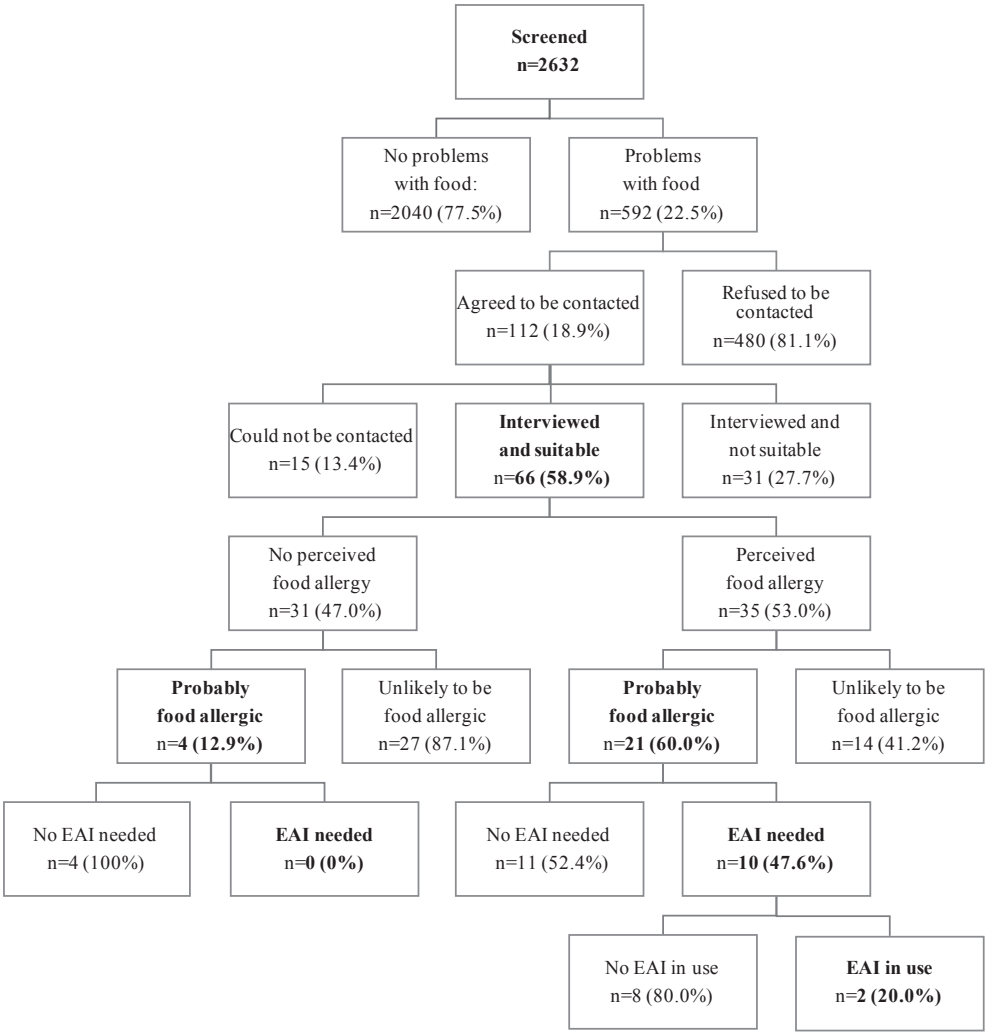
The calculated questionnaire-based prevalence of probable food allergy of present study was compared to the calculated questionnaire-based prevalence of 2009 to calculate either an increase or decrease in prevalence. Fisher exact test was used to investigate differences in prevalence of food allergy and EAI ownership between 2009 and 2016. Data entry and statistical analyses were conducted using SPSS version 23.0 (SPSS Inc. Chicago, IL, USA).

Two high schools who participated in 2009 refused to participate again in this study and were replaced for high schools with similar characteristics and located in the same province.

In total, 2632 adolescents were screened between November 2015 and February 2016, of which 592 answered 'yes' to one or more of the screening questions (Figure 2). Of these, 112 agreed to be contacted by phone. In total 15 adolescents could not be

contacted and 31 were not suitable for analysis due to incorrect information. Therefore, 66 adolescents were suitable to be evaluated further. Of these 66 adolescents, 35 thought that they were food-allergic and 31 thought that they were not food-allergic. In total 25 adolescents were classified as probably food-allergic. Most adolescents in the *probably food-allergic* group reported symptoms from fruits (28%), milk (10%), and nuts (9%). The most frequently reported symptoms of this group were skin symptoms (37%).

Figure 2. Flow chart of study



*Percentages represent those of the previous step in the chart

Of the 25 adolescents classified as probably food-allergic, ten were considered candidates for an EAI. Two of these ten adolescents had actually been prescribed an EAI. These two prescriptions were considered appropriate as both had more than two risk factors for anaphylaxis. Of the eight adolescents who had not been prescribed an EAI all of them had two or more risk factors and were considered high-risk patients.

Out of the 35 adolescents who had a food allergy in their own perception, twenty-one adolescents were classified as *probably food-allergic* (correct diagnosis) and fourteen adolescents were classified as *unlikely to be food-allergic* (incorrect diagnosis). Out of the 31 adolescents who did not have a food allergy in their own perception, four adolescents were classified as *probably food-allergic* (missed diagnosis). Most adolescents were not physician-diagnosed and adolescents with an incorrect diagnosis diagnosed themselves. Table 1 shows the diagnostic accuracy of adolescents and health care providers and sources of correct and incorrect diagnosis.

Table 1. Diagnostic accuracy of adolescents and health care providers (columns) and sources of 'correct' and 'incorrect' diagnoses (rows)

Diagnosis	*Adolescents or parent*	*General practitioner*	*Specialist**	*Alternative medical practitioner*	***Total***
Correct§	11 (48% C, 52% R)	4 (80% C, 19% R)	5 (100% C, 24% R)	1 (50% C, 5% R)	**21**
Incorrect¶	12 (52% C, 86% R)	1 (20% C, 7% R)	0 (0% C, 0% R)	1 (50% C, 7%)	**14**
Total	**23**	**5**	**5**	**2**	**35**

Percentages shown as % C, percentage column and % R, percentage row. *allergist, dermatologist, paediatrician, dietician. §adolescent thought themselves to be food allergic and classified in this study as probably food allergic. ¶Adolescent thought themselves to be food allergic but classified in this study as unlikely to be food allergic.

The calculated questionnaire-based prevalence of probable food allergy in 2016 was 6.2%. In 2009 the calculated questionnaire-based prevalence of probable food allergy was 6.2%. The minimal prevalence of probable food allergy in 2016 was at least 0.95%. In 2009 the minimal prevalence of probable food allergy was at least 2.1%. There were no differences in characteristics between the group of adolescents that refused or could not be contacted and the group of adolescents that could be contacted. The difference of prevalence of probable food allergy between 2009 and 2016 was not significant (p=0.755).

The calculated questionnaire-based prevalence for perceived food allergy classified as unlikely to be food-allergic in 2016 was 4.4%. In 2009 the calculated questionnaire-based prevalence for perceived food allergy classified as unlikely to be food-allergic was 4.0%.

The prevalence of food allergy requiring an EAI in 2016 was 2.5% and 0.5% had been prescribed an EAI. In 2009 the prevalence of food allergy requiring an EAI was 3.0% and 0.3% had been prescribed an EAI. The minimal prevalence of food allergy requiring an EAI

in 2016 was at least 0.08%. In 2009 the minimal prevalence of food allergy requiring an EAI was at least 0.09%. The differences of food allergy requiring an EAI between 2009 and 2016 was not significant (p=0.378).

This study shows that the prevalence of (high-risk) food allergy in Dutch adolescents has not increased in the last six years. Even though EAI ownership has improved marginally, there is still a substantial under-prescription of EAIs in high-risk food-allergic adolescents in the Netherlands.

The calculated questionnaire-based prevalence of probable food allergy did not change in comparison to 2009, in both years the prevalence was 6.2%. This in not in keeping with other studies which report that the prevalence of food allergy is increasing.[1,5] These studies also report a higher self-reported food allergy prevalence than our study varying from an increase of 1.7% to 4.2% for a time interval of about 6 years.

EAI ownership has improved marginally in comparison to 2009. Even though this improvement was not significant and may therefore not be generalizable, there is ultimately still a substantial under-prescription of EAIs in food-allergic adolescents in Dutch high schools at high-risk for anaphylaxis. The reason for this under-prescription may be that adolescents with problems with food are not visiting their general practitioner, and are consequently ignorant of the fact that they are at high-risk for food-induced anaphylaxis. Also the high rate of inaccurate diagnoses of food allergy by adolescents themselves and alternative medical practitioners may contribute to the under-prescription. Another reason may also be that general practitioners and other specialists are not prescribing EAIs to adolescents for whom it would be appropriate to do so even though their diagnosis is accurate.[6,7]

The under-prescription of EAIs in high-risk food-allergic adolescents and the number of self-reported probable food-allergic adolescents found in this study show that awareness about food allergy, anaphylaxis and its management still need to be increased. In recent years the Dutch government has made an effort to increase public awareness of several health-related topics through the use of government-sponsored campaigns. However, no specific campaigns to improve the management and treatment of food allergies and anaphylaxis have been undertaken. In June 2012 the European Academy of Allergy and Clinical Immunology (EAACI) launched its *Stop Anaphylaxis!* Food Allergy Campaign.[8] This campaign aimed at educating the European public in the recognition of the symptoms and triggers of anaphylaxis as well as measures to be implemented in emergency situations. Now, three years on and despite these efforts, little seems to have changed and opportunities still exist for improving awareness about food allergy, anaphylaxis and its management in the Netherlands.

Most food-allergic accidents happen outside the home. Twenty percent of food allergy reactions occur in schools. It is therefore important that schools are prepared for the management of food-allergic children. Previous studies show that in reality many schools are poorly prepared: preventive measures of food allergen exposure are missing, teachers have little knowledge of food allergy and anaphylaxis, and EAIs.[9,10] The preparedness of Dutch high schools have not yet been investigated, it would be of interest to investigate how prepared they are.

A limitation of this study may be that adolescents classified as probably food-allergic were not referred for further testing for an objective diagnosis of food allergy. However, if all probably food-allergic adolescents underwent the gold standard double blind, placebo-controlled food challenge, our experience is that approximately half of those adolescents would have a positive test outcome. Ultimately, adolescents reporting having experienced a (severe) allergic reaction would still require an EAI until challenge tests could be done, and overestimation of the need for EAIs would thus only be apparent after such tests had been completed. Our findings may thus eventually be an overestimation of the problem of under-prescription of EAIs to high-risk food-allergic patients to some degree.

Another limitation of this study may be selection bias, in that a large number of the adolescents with problems with foods did not agree to be contacted by telephone for the follow-up questionnaire. However, of those who agreed to be contacted we reached 86% of them. Adolescence is a period of developmental transition between childhood and adulthood, involving multiple physical, intellectual, personality, and social developmental changes. Therefore, there may be a variety of reasons why adolescents with problems with food did not agree to be contacted. Our reported calculated questionnaire-based prevalence may be an underestimation.

A further limitation of this study may be recall bias, to which retrospective self-reported data are prone. We limited patient reporting to the last two years in order to limit recall bias. Moreover, we used the exact same methods as were used in the study by Flokstra-de Blok et al. in 2009.[3]

In summary, the calculated questionnaire-based prevalence of probable food allergy is still the same as in 2009 (6.2%) and the EAI ownership has marginally improved. However, there is still an under-prescription of EAIs in high-risk food-allergic adolescents in Dutch high schools. There are still opportunities to raise food allergy awareness in communities, especially in schools, and also among health-care providers to improve the care for food-allergic adolescents at high-risk for anaphylaxis.

ACKNOWLEDGEMENTS

We would like to thank the high schools and the adolescents who participated in this study. We also would like to thank P. Davids (webdirector at University Medical Centre Groningen, the Netherlands) for digitalizing the questionnaire.

REFERENCES

(1) Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy 2014 Jan;69(1):62-75.

(2) Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy 2014 Aug;69(8):992-1007.

(3) Flokstra-de Blok BM, Doriene van Ginkel C, Roerdink EM, Kroeze MA, Stel AA, van der Meulen GN, et al. Extremely low prevalence of epinephrine autoinjectors in high-risk food-allergic adolescents in Dutch high schools. Pediatr Allergy Immunol 2011 Jun;22(4):374-377.

(4) Muraro A, Roberts G, Worm M, Bilo MB, Brockow K, Fernandez Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014 Aug;69(8):1026-1045.

(5) Koplin JJ, Mills EN, Allen KJ. Epidemiology of food allergy and food-induced anaphylaxis: is there really a Western world epidemic? Curr Opin Allergy Clin Immunol 2015 Oct;15(5):409-416.

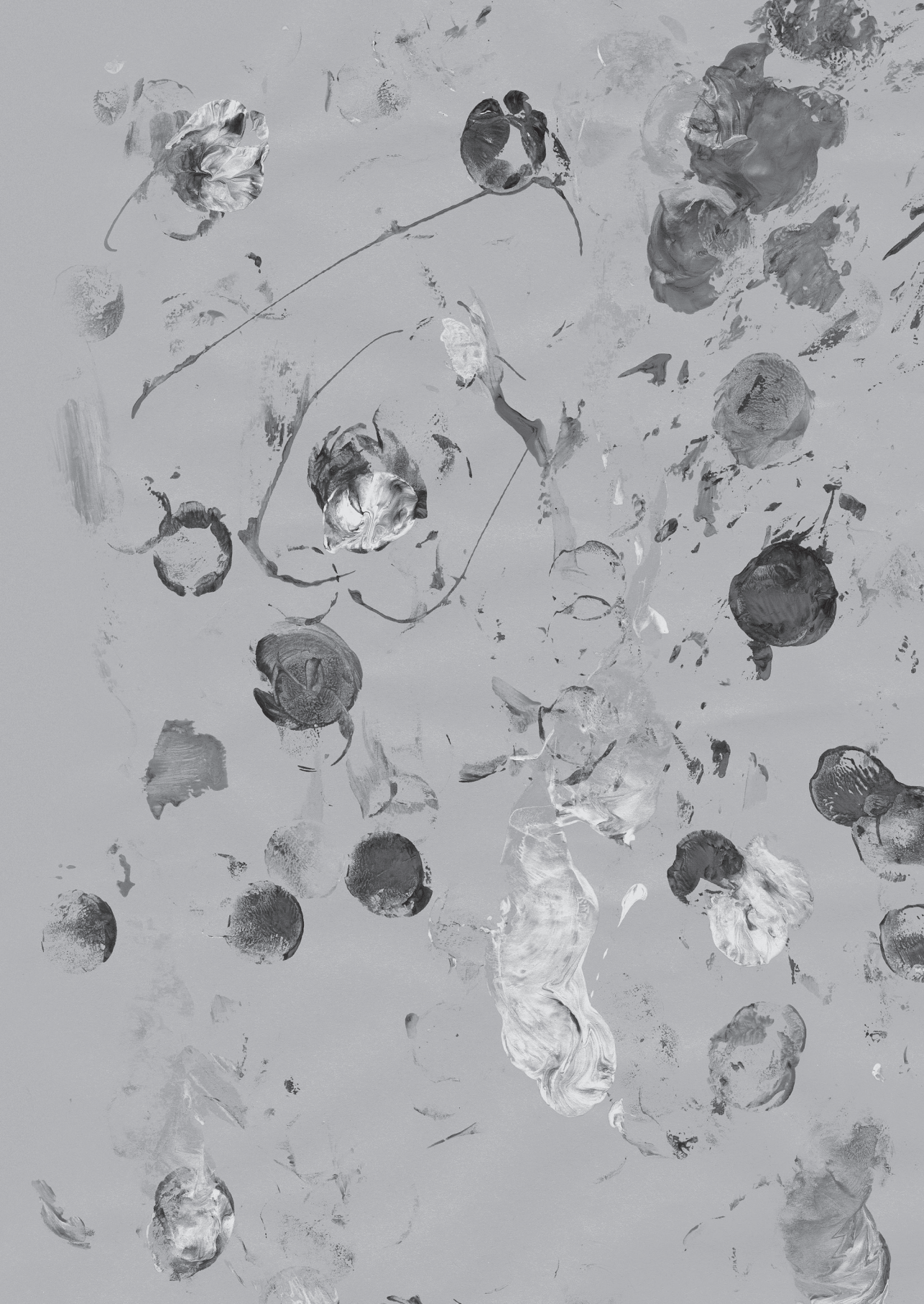
(6) Saleh-Langenberg J, Dubois AE, Groenhof F, Kocks JW, van der Molen T, Flokstra-de Blok BM. Epinephrine auto-injector prescriptions to food-allergic patients in primary care in The Netherlands. Allergy Asthma Clin Immunol 2015 Oct 15;11:28-015-0094-9. eCollection 2015.

(7) Agache I, Ryan D, Rodriguez MR, Yusuf O, Angier E, Jutel M. Allergy management in primary care across European countries -- actual status. Allergy 2013 Jul;68(7):836-843.

(8) European Academy of Allergy and Clinical Immunology (EAACI). Food Allergy & Anaphylaxis Public Declaration. 2012; Available at: http://www.eaaci.org/attachments/FoodAllergy&AnaphylaxisPublicDeclarationCombined.pdf. Accessed 13/04, 2016.

(9) Muraro A, Clark A, Beyer K, Borrego LM, Borres M, Lodrup Carlsen KC, et al. The management of the allergic child at school: EAACI/GA2LEN Task Force on the allergic child at school. Allergy 2010 Jun 1;65(6):681-689.

(10) Muraro A, Agache I, Clark A, Sheikh A, Roberts G, Akdis CA, et al. EAACI food allergy and anaphylaxis guidelines: managing patients with food allergy in the community. Allergy 2014 Aug;69(8):1046-1057.



Chapter 3

Epinephrine auto-injector prescriptions to food allergic patients in primary care in the Netherlands

J. Saleh-Langenberg
A.E.J. Dubois
F. Groenhof
J.W.H. Kocks
T. van der Molen
B.M.J. Flokstra-de Blok

Allergy Asthma Clin Immunol. 2015 Oct 15;11:28

ABSTRACT

Background: The knowledge of GPs regarding food allergy and anaphylaxis and practices in the prescription of EAIs among GPs has previously only been studied using questionnaires and hypothetical cases. Therefore, there are currently no data as to whether or not GPs prescribe EAIs to high risk food-allergic patients presenting to primary care practices. The aim of this study was therefore to describe and evaluate practice in EAI prescription by GPs to food-allergic patients in the Netherlands.

Methods: Patients aged 12-23 years who consulted their GP for allergic symptoms were identified in a primary care database. Patients were classified as probably or unlikely to be food-allergic. A risk factor assessment was done to identify probably food-allergic patients at high risk for anaphylaxis to assess the need for an EAI.

Results: One hundred forty-eight out of 1015 patients consulted their GP for allergic symptoms due to food. Eighty patients were excluded from analysis because of incomplete records. Thirty-four patients were classified as probably food-allergic. Twenty-seven of them were considered high risk patients and candidates for an EAI. Importantly, only 10 of them had actually been prescribed an EAI by their GP.

Conclusions: This study shows that high risk food-allergic patients that visit their GPs are often not prescribed an EAI. Thus, previously identified low rates of EAI ownership may be partly due to GPs not prescribing this medication to patients for whom it would be appropriate to do so. These data suggest that there is a need for improvement of the quality of care for high risk food-allergic patients in primary care.

BACKGROUND

General practitioners (GPs) play an important role in diagnosing and treating food-allergic patients. In the Netherlands, the GP is the gatekeeper of the Dutch health-care system controlling access to specialized medical care.

Previous studies have shown that many high risk food-allergic patients do not have an epinephrine auto-injector (EAI) and that GPs are not always knowledgeable about these patients.[1-10] These studies show that there is a lack of allergy knowledge in primary care, especially the recognition and treatment of anaphylaxis were problematic and that national guidelines were often not followed.

Adolescents are the age-group with the highest risk for food allergy fatalities.[11] The fact that they often engage in risk-taking behaviors[12-14] resulting in reduced vigilance about food consumption or reluctance to carry their EAI may contribute to this outcome.[13-16]

The knowledge of GPs regarding food allergy and anaphylaxis, and practices in the prescription of EAIs among GPs, has previously only been studied using questionnaires and hypothetical cases. Therefore, there are currently no data as to whether GPs actually do prescribe EAIs to high risk food-allergic patients presenting to primary care practices. The aim of this study was therefore to describe and evaluate practice in EAI prescriptions by GPs to food-allergic patients in the Netherlands.

METHODS

Study design

A retrospective analysis was performed on data from the electronic database of Registration Network Groningen (RNG). This general practice-based research network was established in 1989 and consists of patient registrations of three group practices based in the Northern part of the Netherlands. The RNG includes a dynamic population with an average annual population of approximately 30,000 patients.

Participating general practitioners use a structured medical record, in which all patient contacts are registered. This includes reason for encounter, medical diagnosis (according to the International Classification of Primary Care (ICPC), applied treatment including prescriptions, using the Anatomical Therapeutic Chemical (ATC) codes, and referrals.

From the RNG database, of the target study population (patients between 12-23 years old), a dataset was extracted with information about patients' consultations for symptoms related to allergy and prescriptions of EAIs by GPs from 2001-2012. In this study, patients with allergic symptoms were identified using the ICPC-codes A12 (allergy), T04 (feeding problem of infant/child), and T05 (feeding problem of adult). The EAI prescription was defined as the ATC-group C01CA24 (epinephrine). The database included the following additional information: date of birth, date of entry in the general practice database, GP code, type and number of patient contacts (ICPC codes), prescriptions (ATC codes) and ICPC codes associated with these medications, and (hospital) referrals.

Study population

The study population consisted of patients aged 12-23 years who consulted their GP for allergic symptoms due to food from 2001-2012. Access to the patient's medical history was a prerequisite. Patients were excluded from analyses if they did not have allergic symptoms to food or if no allergic symptoms were reported in medical record.

Classification

Food allergy

Patients' medical records were evaluated to identify patients who experienced allergic symptoms solely to food.

Patient age and gender, suspected food(s), allergic symptoms at time of allergic reaction (37 specific symptoms of the mouth, nose, eyes, skin, gastrointestinal tract, respiratory tract, cardiovascular tract), time of onset and duration of allergic symptoms, atopic co-morbidities (asthma, atopic dermatitis, rhinitis), possession of an EAI, and information about other diagnostic tests, and (hospital) referral(s) were determined.

Patients were classified as probably food-allergic when the patient's medical record indicated that the patient reported allergic symptoms after eating one of the following foods: peanut, tree nuts, milk, egg, wheat, soy, sesame seed, fish, shell fish, and celery. The foods chosen as allergenic food were based on the EU directive on labelling of pre-packaged products (EU Directive 2003/89/EC amending Directive 2000/13/EC) relevant in the Netherlands, i.e. peanut, nuts, milk, egg, wheat, soy, sesame seed, fish, shell fish, and celery. In addition, in patients also reporting reactions to fruits and vegetables, these reactions were documented.

Symptoms of the mouth, nose, eyes, skin, gastrointestinal tract, respiratory tract, or cardiovascular tract were considered allergic symptoms. The presence of only subjective gastrointestinal symptoms without other symptoms was not classified as food allergy.

Risk factor assessment and EAI indications

To identify patients who are at high risk for anaphylaxis and to assess the need for an EAI a risk factor assessment based on the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) was carried out for each patient who experienced allergic symptoms due to food. [17]

Risk factors for an anaphylactic reaction were defined as a previously severe anaphylactic reaction to a food requiring emergency treatment or hospitalization as a result, asthma or asthmatic reactions to food, adolescent or young adult age, systemic reaction to traces of the food allergen, and having a peanut or nut allergy.[18] When the first factor was present or when at least two of the other risk factors were present in the context of suspected or proven food allergy, food-allergic patients were considered high risk patients, and candidates for an EAI. Allergy only to fruits or vegetables with these risk factors did not constitute an indication for an EAI. All doubtful cases concerning food allergy and the need for an EAI were discussed with an allergist (AEJD).

Referrals

Indications for referral of a patient to a specialist with specific expertise on allergology were defined as patients who experienced allergic symptoms in association with food exposure and who need further testing for the objective diagnosis of food allergy, patients who experienced a severe allergic reaction, and patients being prescribed an EAI.[17,19,20]

Statistics

Data entry and analyses were conducted using SPSS version 20.0 (SPSS Inc. Chicago, IL, USA). For the statistical analysis descriptive methods were used.

Ethical approval

We received ethical permission to access the Registration Network Groningen from the Medical Ethical Review Board, University Medical Center Groningen (UMCG) (METc 2012/366).

RESULTS

Classification

Food allergy

In total there were 11,514 patients aged 12-23 years identified in the RNG database. Of these 11,514 patients, 1314 patients (11.4%) consulted their GP for allergic symptoms from 2001-2012 (Figure 1). In total 299 patients' medical records were not accessible because they could not be digitally restored from the archives. Therefore, a total of 1015 patients were eligible for analysis.

In total 148 patients (14.6%) out of 1015 patients consulted their GP for allergic symptoms due to food. Of these 148 patients, 80 patients were classified as 'patients with incomplete data' because no allergic symptoms were recorded by GP in the patient's medical records. Of the remaining 68 patients, half (n=34) were classified as probably food-allergic, and the other half as unlikely to be food-allergic.

Most patients classified as probably food-allergic reported symptoms from tree nuts (44.1%), milk (32.4%) and peanuts (23.5%). Most patients classified as unlikely food-allergic reported symptoms from milk (26.5%). Descriptive characteristics are shown in Table 1.

Risk factor assessment and EAI indications

Thirty-four patients (3.3%) out of 1015 patients who consulted their GP for allergic symptoms between 2001 and 2012 were prescribed an EAI. Twenty EAIs were prescribed to patients who consulted their GP for allergic symptoms due to food. The other 14 EAIs were prescribed to five patients who consulted their GP for allergic symptoms due to insect stings, to one patient on recommendation by a pediatrician, and to eight patients of whom the reason of prescription was not clearly recorded in the patient's medical records.

High risk patients and EAIs

Twenty-seven (79.4%) out of the 34 patients classified as probably food-allergic were considered high risk patients, and therefore candidates for an EAI. Ten (37%) of them had actually been prescribed an EAI.

Five out of the 27 high risk patients experienced a previous anaphylactic reaction to food. All of these patients were aged 12-17 years, had a peanut and/or tree nut allergy and had asthma. Two (40%) of them had been prescribed an EAI. One patient's medical record showed that instructions/demonstrations had been given about when and how to use an EAI.

Low risk patients and EAIs

Seven (20.6%) out of the 34 patients classified as probably food-allergic were considered low risk patients, and therefore not considered candidates for an EAI. Two (28.5%) of them were prescribed an EAI. One patient had a sesame seed allergy and the other patient a fruit allergy, and both patients reported having asthma.

Patients with incomplete data and EAIs

Eighty patients were excluded from analysis in this study because no allergic symptoms were recorded in the patients' medical records. In the records of 4 of these patients, it was remarked that they presented to the primary care practice with anaphylactic symptoms after eating food possibly containing peanuts or tree nuts. According to the risk factor assessment used for this study these patients were also considered high risk patients and candidates for an EAI. Importantly, one of them had not been prescribed an EAI. Descriptive characteristics are shown in Table 1.

The other 76 patients of which allergic symptoms were not recorded in their medical record, a risk assessment could not be made nor could the need of an EAI be assessed. In the records of five of these 76 patients, it was remarked that they had been prescribed an EAI. In total eight EAIs were prescribed to patients with incomplete data.

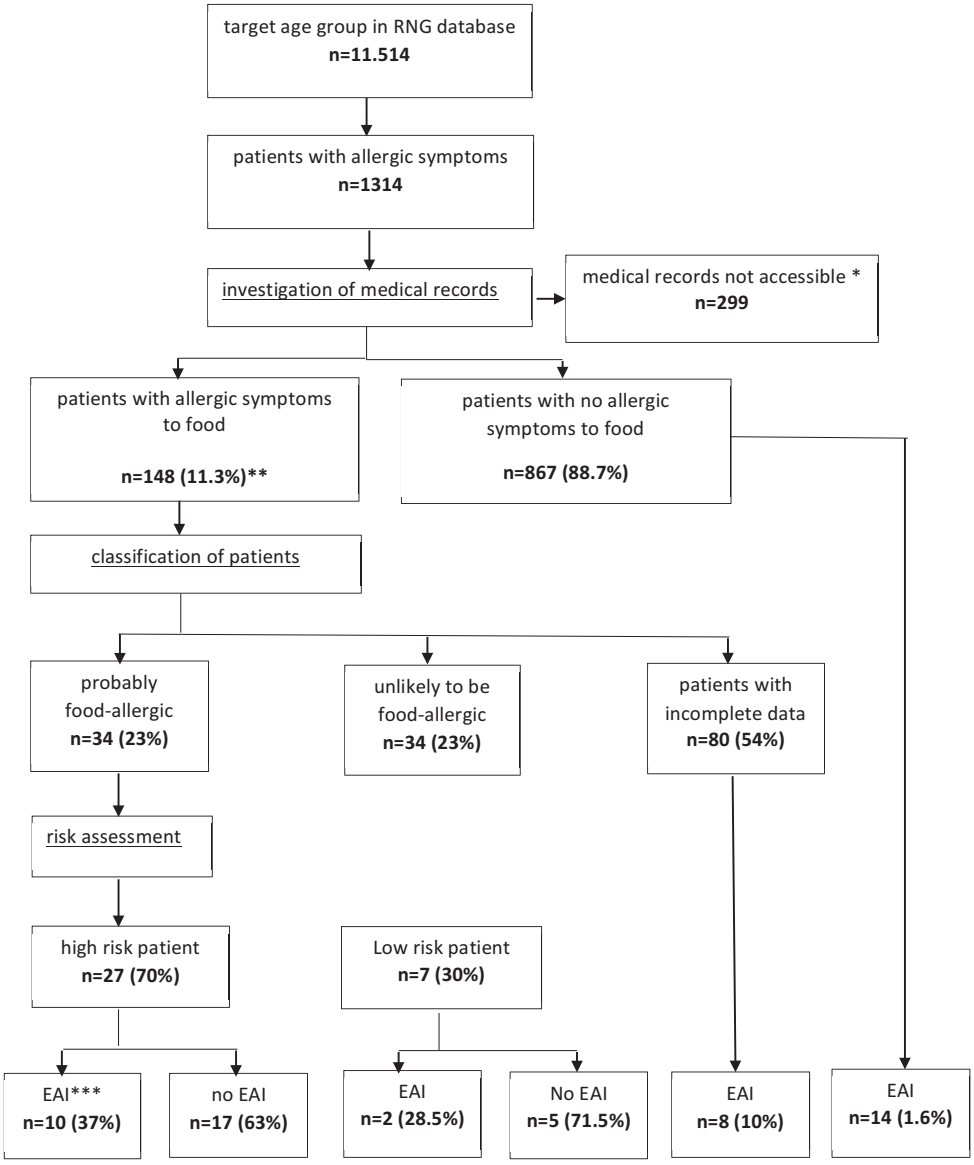
Referrals

Twelve patients (32.4%) (ten high risk and two low risk patients) classified as probably food-allergic were referred to a dietician and/ or to one or more specialist(s). Of the other 22 probably food-allergic patients who were not referred, six were prescribed an EAI and one patient experienced anaphylactic symptoms.

Seven patients (20.6%) classified as unlikely to be food-allergic were referred to a dietician and/ or to one or more specialist(s).

None of the patients with incomplete data who experienced anaphylactic symptoms were referred to a specialist.

Figure 1. Flow chart of study



*medical records were not accessible because they could not be digitally restored from the archives; **percentages represent those of the previous step in the chart; ***EAI=Epinephrine Auto-Injector

Table 1. Descriptive characteristics of study population

	Probably food-allergic	Unlikely food-allergic	Patients with incomplete data
Number participants, n (%)	34(50)	34(50)	80
Sex adolescent, boys/girls n (%)	17/17(50/50)	13/21(38/62)	43/37
Type of food allergies, n (%)			
peanut	8 (23)	4 (12)	13 (16)
tree nuts	15 (44)	4 (12)	12 (15)
cow's milk	11 (32)	9 (27)	38 (48)
egg	2 (6)	2 (6)	1 (1)
wheat	1 (6)	-	0
soy	-	-	1(1)
sesame seed	1 (3)	-	0
fish	-	2 (6)	1(1)
shell fish	-	1 (3)	1 (1)
celery	-	1 (3)	1 (1)
fruit	-	8 (24)	15 (19)
vegetables	-	2 (6)	2 (3)
other	-	7(21)	3 (4)
Tests used to diagnose food allergy, n (%)			
food-specific IgE levels (RAST)	14 (59)	14 (59)	20 (25)
open food challenge	9 (27)	7 (21)	9 (11)
skin prick test	2 (6)	-	1 (1)
Referral to, total n (%)	11 (32)	7 (21)	9 (11)
(pediatric) allergologist	2 (16)	1 (3)	-
dermatologist	-	1 (3)	1 (1)
pediatrician	2 (6)	2 (6)	1 (1)
internist	4 (12)	3 (9)	1 (1)
dietician	2 (6)	4 (12)	5 (6)
High risk patient, n(%)	27 (79)	-	4 (5)***
Experienced anaphylaxis, n(%)	5 (15)	-	4 (5)
Risk factors, n(%)			
Asthma or asthmatic reactions to food	10 (29)	3 (9)	9 (11)
Adolescent or young adult age	21 (62)	24 (71)	70 (88)
Systemic reaction to traces of the food allergen*	6 918)	1 (3)	-
Having peanut or nut allergy	23(68)	8 (24)	25 (32)
Prescribed an EAI**, yes/no n (%)			8 (10)
high risk patient	10/17 (29/71)	-	1 (1)
low risk patient	2/8 (6/24)	-	7 (9)

* not documented in all patient's medical records; **EAI=Epinephrine Auto-Injector; ***Unknown due to incomplete data, however, 4 patients had had presented to their GP with an anaphylactic reaction according to the information in the medical record. All of them had a peanut or nut allergy, and only 3 of them had been prescribed an EAI.

DISCUSSION

Although the knowledge of GPs regarding food allergy and anaphylaxis has previously been studied using questionnaires and hypothetical cases, this study is the first to examine actual epinephrine auto-injector prescription practices and the first to make use of data collected by GPs themselves.

Food-allergic patients aged 12-23 years at high risk for anaphylaxis who consult their GPs are often not prescribed an EAI by the GP. Twenty-seven (79.4%) out of the 34 patients classified as probably food-allergic were considered high risk patients, and therefore candidates for an EAI. Only ten (37%) of them had actually been prescribed an EAI. In addition, five (18.5%) out of the 27 high risk patients experienced a previous anaphylactic reaction to food. All of these patients were aged 12-17 years, had a peanut and/or tree nut allergy and had asthma, and only two of them had been prescribed an EAI. This shows that previously identified low rates of EAI ownership may be partly due to GPs not prescribing this medication to patients for whom it would be appropriate to do so.[1,8-10,21]

The clinical history is a key part of the diagnostic work-up of suspected food allergy.[17,18] Although the food allergy guidelines of the Dutch College of General Practitioners (NHG)[20,22] recommends asking the patient about the symptoms and how long these occurred after ingestion, this study shows that many patients' medical records were lacking this important information. This under-documentation might be due to the patients (or their parents) not clearly remembering or reporting their symptoms. Also, the limited time available to the GP to record the patient's symptoms during a consultation might play a role. Finally, knowledge and/or practice behavior gaps in GPs might contribute, as is suggested by other studies. [4-6,9,23]

Primary care guidelines in the Netherlands, the NHG guidelines, [20,22] recommend that an EAI should only be prescribed after a previous case of anaphylaxis. Significantly, risk factors for a life-threatening food induced anaphylactic reaction are mentioned, but are not put forward as a reason to prescribe an EAI in the absence of a previous anaphylactic reaction. Although it may therefore be argued that GPs are simply following their own guidelines, this does not seem to explain the lack of EAI prescription in 3 out of 5 high risk patients who had experienced prior anaphylaxis as well as 3 out of 4 patients presenting with anaphylaxis to their GP. The latter situation is in agreement with previous studies of anaphylaxis management in emergency rooms, where patients presenting with anaphylaxis are not always prescribed an EAI or referred to appropriate specialist care allergy. [17,18]

The need for improved EAI training has been a recurring theme in the literature on anaphylaxis.[8,11,13,24,25] Anaphylaxis usually occurs in the community, therefore, all food-allergic patients and their parents (and other caregivers) should be provided with educational resources and training should cover avoidance strategies, recognition of

symptoms, and when and how to administer an EAI. It was mentioned in one patient's medical record that EAI instructions/demonstrations had been given. The NHG guidelines recommend giving clear instructions about the use of an EAI. It may thus be possible that GPs did give clear instructions about when and how to use an EAI, but that this was not documented. The general practices did not have demonstration material and trainer EAIs on hand. We found that GPs feel that giving instructions about how to use an EAI is the responsibility of the pharmacist. Further research is needed to investigate the quality of the EAI training currently offered by GPs and pharmacists.

In this study, the majority of patients classified as probably food-allergic were not referred for further testing for an objective diagnosis of food allergy. It should be noted that there is good availability of specialist allergy care for pediatric patients in the area where this study was conducted. Infrequent or no referrals of patients to a specialist with specific expertise on allergology after an allergic reaction is in agreement with the findings in previous studies[4,5]. One might speculate that GPs do not recognize allergic reactions or underestimate their severity, and therefore do not refer patients for further diagnosis. Implementing clear referral criteria could be beneficial to assist GPs to refer patients to a specialist with specific expertise on allergology when this is needed. In the Northern part of the Netherlands our centre and other hospitals can be reached easily by car or public transportation. All patients in the Netherlands have health insurance and all costs are covered. In our centre we have a waiting list for food challenges. However, all patients are seen within 2 weeks at the out-patient clinic. When necessary they are prescribed an EAI.

In contrast to these results, inappropriate prescription or referral of patients who could conceivably be managed without an EAI in primary care seems to be numerically less of a problem. However, given the impact that overestimation of risk may have on patient well being, over-treatment should be a target for improvement of quality of care as well as under-treatment.

Strength of this study is that, to our knowledge, this is the first study to assess the epinephrine auto-injector prescription practices of general practitioners to food-allergic patients at high risk for anaphylaxis using data recorded by GPs themselves.

A limitation in this study is the number of patients excluded from analysis due to inaccessible or incomplete patient's medical records. The incomplete data might be due to under-reporting of patients (or their parents), under-documentation of clinical information by GPs or lack of knowledge and/or practice behavior gaps experienced by GPs. In this regard, it may be expected there would be more food-allergic patients at high risk for anaphylaxis not being prescribed an EAI. We did not find patients who had been prescribed an EAI who were not high risk patients. Ultimately, some of these patients would probably show no reactions when challenged with the food in question. However, such patients would still require an EAI until challenge tests could be done, and

overestimation of the need for EAIs would thus only be apparent after such tests had been completed.

Our findings may thus eventually be an overestimation of the problem of inadequate EAI prescription to high-risk food-allergic patients to some degree. More urgent, however, is the obvious extent to which high risk food allergic patients are not prescribed an EAI by their GPs.

In summary, although previous studies have shown that some high risk food-allergic patients do not seek medical care, this study shows with data recorded by GPs themselves that those that do visit their GPs are often not prescribed an EAI, even to those with a previous severe anaphylactic reaction. This shows that previously identified low rates of EAI ownership may be partly due to GPs not prescribing this medication to patients for whom it would be appropriate to do so. These data suggest that there is a need for improvement of the quality of care for high risk food-allergic patients in primary care.

CONCLUSIONS

Food-allergic patients at high risk for anaphylaxis who visit their GP are often not prescribed an epinephrine auto-injector. There is a need for improvement of the quality of care for high risk food-allergic patients in primary care.

ACKNOWLEDGEMENTS

We would like to thank Groepspraktijk Hoogezand-Sappemeer Oost, Academische Huisartsenpraktijk Groningen, and Huisartsengroepspraktijk Gezondheidscentrum 'De Weide' Hoogeveen for their assistance during the patient's medical records investigations.

REFERENCES

(1) Flokstra-de Blok BM, Doriene van Ginkel C, Roerdink EM, Kroeze MA, Stel AA, van der Meulen GN, et al. Extremely low prevalence of epinephrine autoinjectors in high-risk food-allergic adolescents in Dutch high schools. Pediatr Allergy Immunol 2011 Jun;22(4):374-377.

(2) Klemans RJB, Le TM, Sigurdsson V, Enters Weijnen CF, van Hoffen E, Bruijnzeel-Koomen CAFM, Knulst AC. Management of acute food allergic reactions by general practitioners. European annals of allergy and clinical immunology 2013;45(2):43-51.

(3) Lowe G, Kirkwood E, Harkness S. Survey of anaphylaxis management by general practitioners in Scotland. Scott Med J 2010;55(3):11-14.

(4) Kastner M, Harada L, Waserman S. Gaps in anaphylaxis management at the level of physicians, patients, and the community: a systematic review of the literature. Allergy 2010;65(4):435-444.

(5) Waserman, S, Chad Z, Francoeur MJ, Small P, Stark D, Van der Leek TK, Kaplan A, Kastner M. Management of anaphylaxis in primary care: Canadian expert consensus recommendations. Allergy 2010;65(9):1082-1092.

(6) Agache I, Ryan D, Rodriguez MR, Yusuf O, Angier E, Jutel M. Allergy management in primary care across European countries -- actual status. Allergy 2013;68(7):836-843.

(7) Jutel M, Angier L, Palkonen S, Ryan D, Sheikh A, et al. Improving allergy management in the primary care network--a holistic approach. Allergy 2013;68(11):1362-1369.

(8) Singh JA,O M. Prescription of adrenaline auto-injectors for potential anaphylaxis--a population survey. Public Health 2003;117(4):256-259.

(9) Gupta RS, Kim E, Smith J, Pongracic , Wang J, Holl XB. Food allergy knowledge, attitudes, and beliefs of primary care physicians. Pediatrics 2010;125(1):126-132 (10) (10) Pumphrey RS. Fatal anaphylaxis in the UK, 1992-2001. Novartis Found Symp 2004;257:116-28; discussion 128-32, 157-60, 276-85.

(11) Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol 2007 Apr;119(4):1016-1018.

(12) MacKenzie H, Roberts G, van Laar D, Dean T. Teenagers' experiences of living with food hypersensitivity: a qualitative study. Pediatr Allergy Immunol 2010 Jun;21(4 Pt 1):595-602.

(13) Sampson MA, Munoz-Furlong A, Sicherer SH. Risk-taking and coping strategies of adolescents and young adults with food allergy. J Allergy Clin Immunol 2006 Jun;117(6):1440-1445.

(14) Gallagher M, Worth A, Cunningham Burley S, Sheikh A. Strategies for living with the risk of anaphylaxis in adolescence: qualitative study of young people and their parents. Primary care respiratory journal 2012;21(4):392-397.

(15) Marrs TL, Gideon. Why do few food-allergic adolescents treat anaphylaxis with adrenaline?--Reviewing a pressing issue. Pediatric allergy and immunology 2013;24(3):222-229.

(16) Pinczower GD, Bertalli NA, Bussmann N, Hamidon M, Allen KJ, DunnGalvin A, et al. The effect of provision of an adrenaline autoinjector on quality of life in children with food allergy. J Allergy Clin Immunol 2013 1;131(1):238-240.e1.

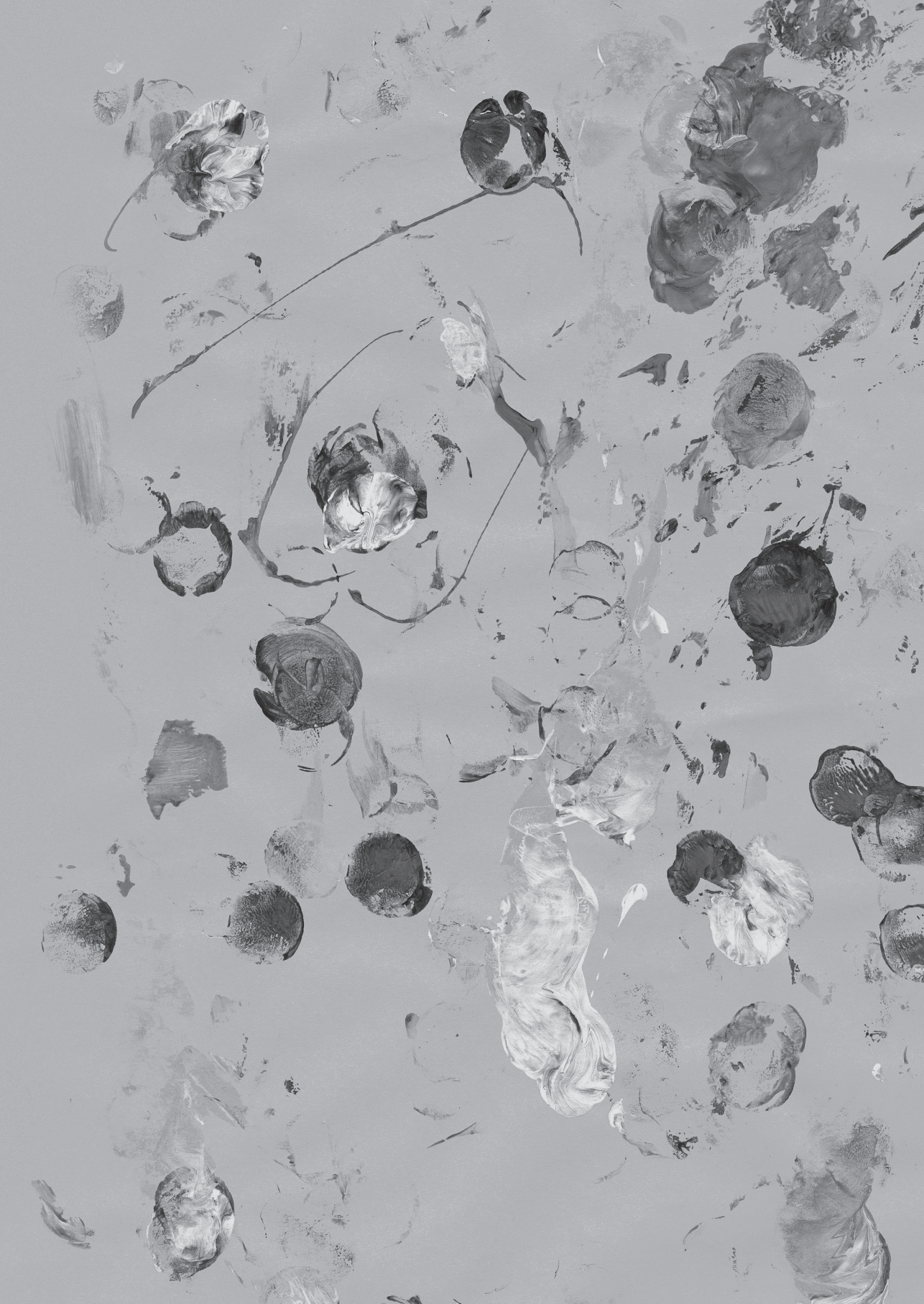
(17) Muraro, A., Werfel, T., Hoffmann-Sommergruber, K., Roberts, G., Beyer, K., Bindslev-Jensen, C., et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy 2014;69(8):1008-1025.

(18) Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy 2007 Aug;62(8):857-871.

(19) Consultation and referral guidelines citing the evidence: how the allergist-immunologist can help. J Allergy Clin Immunol 2006;117(2 Suppl Consultation):S495-S523.

(20) Lucassen P, Albeda F, Van Reisen M, Silvius A, Wensing C, Luning-Koster M. NHG guideline Food Hypersensitivity. 2010(53):537-553.

(21) Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. J Allergy Clin Immunol 2007 Apr;119(4):1018-1019.
(22) Luning Koster, Marleen Lucassen, Peter L B J Boukes, Froukje Goudswaard,A N Lex. [Summary of the Dutch College of General Practitioners' practice guideline on food hypersensitivity]. Ned Tijdschr Geneeskd 2011;155(18):A3063-A3063.
(23) Le TM, van Hoffen E, Pasmans SG, Bruijnzeel-Koomen CAFM, Knulst AC. Suboptimal management of acute food-allergic reactions by patients, emergency departments and general practitioners. Allergy 2009;64(8):1227-1228..
(24) Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Epinephrine auto-injector use in adolescents at risk of anaphylaxis: a qualitative study in Scotland, UK. Clin Exp Allergy 2011 Jun;41(6):869-877.
(25) Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 2001 Jan;107(1):191-193.

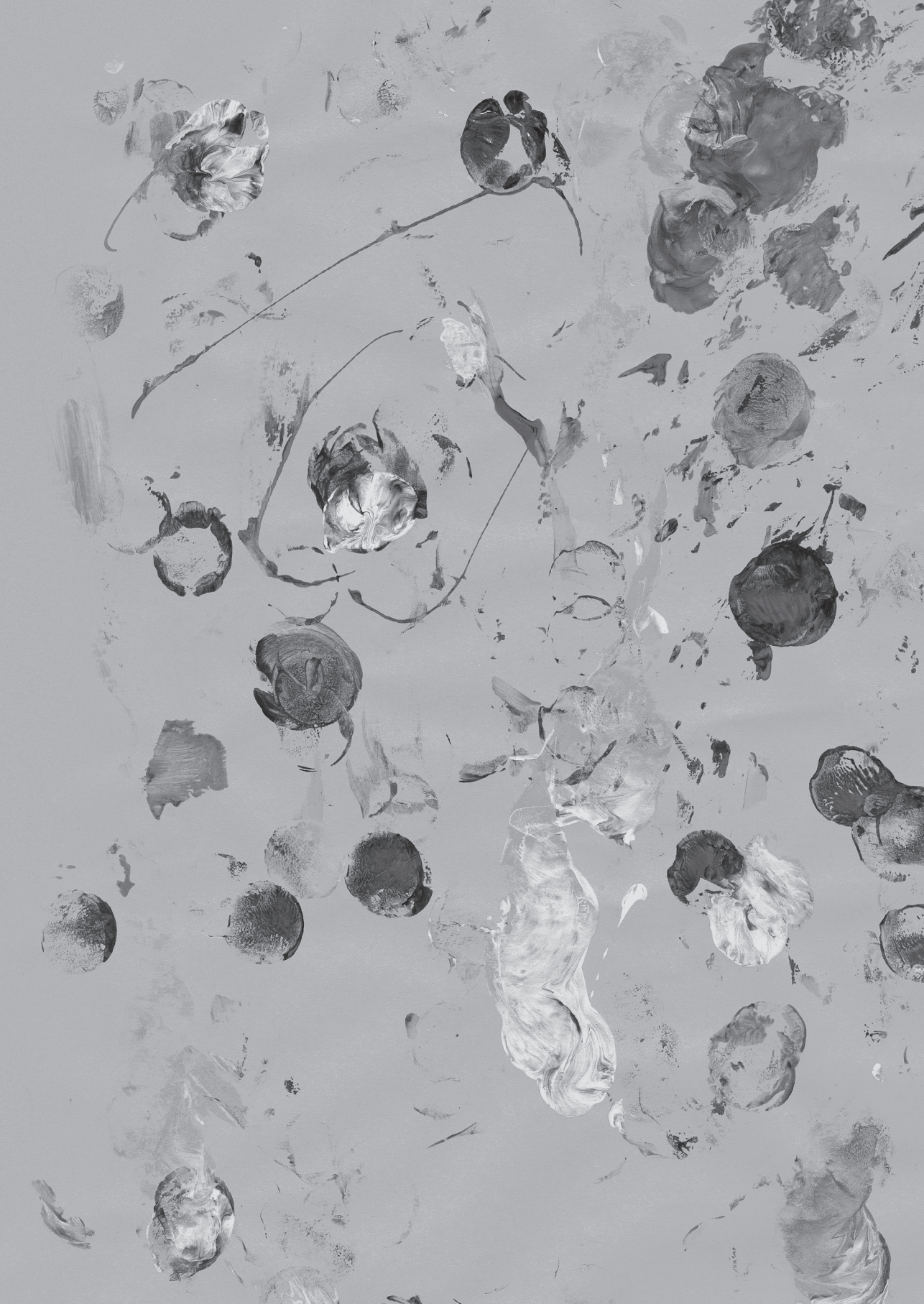


Part II

Non-compliance (compliance, burden of treatment and HRQL)

Chapter 4
The compliance and burden of treatment with the epinephrine auto-injector in food allergic adolescents

Chapter 5
Predictors of health-related quality of life of European food-allergic patients



Chapter 4

The compliance and burden of treatment with the epinephrine auto-injector in food-allergic adolescents

J. Saleh-Langenberg
B.M.J. Flokstra-de Blok
N.J. Goossens
J.C. Kemna
J.L. van der Velde
A.E.J. Dubois

Pediatr Allergy Immunol. 2016 Feb;27(1):28-34

ABSTRACT

Background: Food-allergic patients at high risk for (fatal) anaphylaxis should carry an epinephrine auto-injector (EAI) at all times. This treatment may be perceived as burdensome and this may affect compliance. The aims of the study were (1) to determine the burden of treatment (BoT) of an EAI, (2) to examine the relationship between this burden and compliance, and (3) to analyze which factors contribute to the BoT of the EAI as perceived by food-allergic adolescents and their parents.

Methods: Dutch food-allergic patients prescribed an EAI and their parents completed a questionnaire-package (n=55). Relationships between BoT and health-related quality-of-life (HRQL), illness severity and perception, and anxiety measures were investigated.

Results: Food-allergic adolescents and their parents were (extremely) positive about the EAI (54.5%;72.7% respectively)(=low BoT). The BoT-measure showed a significantly greater burden in food-allergic adolescents prescribed an EAI who reported not carrying the EAI at all times than adolescents who reported they did. The BoT-scores of both adolescents and their parents were not associated with HRQL, illness severity and perception, or trait anxiety.

Conclusions: The majority of food-allergic adolescents and their parents were positive about the EAI (=low BoT). However, the BoT was significantly associated with self-reported compliance with carrying the EAI. The BoT was higher in food-allergic adolescents prescribed an EAI who reported not carrying the EAI at all times. The BoT-measure seems to be a useful tool to study compliance with carrying an EAI. The BoT of an EAI is not associated with HRQL. The BoT measures a distinct concept related to compliance behavior.

INTRODUCTION

Currently the only treatment for food allergy is avoidance of the culprit food. Despite taking precautions, accidental food-allergic reactions may occur, and for some food-allergic patients such reactions may be fatal.[1] Therefore, food-allergic patients at high risk for anaphylaxis should always have an epinephrine auto-injector (EAI) available.[1-3]

A number of studies show that food-allergic patients, adolescents in particular, are often poorly compliant and do not always carry their EAI.[1,4,5] The reluctance to carry an EAI may be the result of the perception of patients that such treatment is burdensome. It has been previously shown that the burden of treatment (BoT) with an EAI in vespid allergic patients is high.[6] However, it is currently unknown whether food-allergic adolescents and their parents find always having to carry an EAI burdensome. Allen et al. showed that a prescription of an EAI did not increase the parental burden of food-allergic children.

A previous study using parent-proxy-reports found a more impaired health-related quality of life (HRQL) in children being prescribed an EAI compared to those who were not prescribed an EAI.[7] It is of interest whether HRQL contributes to the burden of treatment (BoT) of the EAI as perceived by food-allergic adolescents and their parents.

Adolescents are the age-group with the highest risk for food allergy fatalities.[2,8] This may be caused by problems occurring at the time of the transfer of responsibility for managing their food allergy from their parents to themselves.[4,9] The fact that they often engage in risk-taking behaviors[1,8-10] resulting in reduced vigilance about food consumption or reluctance to carry their EAI may contribute to this outcome.[9-13]

The aims of the study were (1) to determine the burden of treatment (BoT) of an EAI, (2) to examine the relationship between this burden and compliance, and (3) to analyze which factors contribute to the BoT of the EAI as perceived by food-allergic adolescents and their parents.

METHODS

Participants and procedure

Food-allergic patients (13-17 years old) and parents were recruited through our pediatric allergy clinic or Dutch food allergy support organizations between October 2010 and May 2011. Food-allergic patients and parents were analyzed separately.

The participants (adolescents and parents) were asked to complete a questionnaire-package including: BoT-measure, Food Allergy Quality of Life Questionnaire-Teenager Form (FAQLQ-TF) or Food Allergy Quality of Life Questionnaire-Parent Form Teenager (FAQLQ-PFT), Food Allergy Independent Measure (FAIM), Illness Perception Questionnaire (IPQ), State Trait Anxiety Inventory (STAI), statements about the EAI, and descriptive questions.

The participants recruited from the clinic were asked to complete the questionnaire-package while attending our clinic. The other participants were sent the questionnaire-package by mail to be completed at home.

Adolescent-parent pairs were requested not to discuss questions and responses with each other. Parents were asked to explain a question to their child when needed but to do so without telling the child which answer to give.

Adolescents with at least one physician-diagnosed food allergy and who had been prescribed an EAI were included. Adolescent-parent pairs were excluded if the BoT-measure was not completed. Participation in the study was completely voluntary. This study was assessed by the local medical ethics review committee (METc 2010/318) who deemed that formal approval from the committee was not required.

Questionnaire-package

The BoT-measure was completed by the food-allergic patients and parents of food-allergic adolescents both from their own perspective. The BoT-measure contains a single item which is scored on a scale ranging from 1 (extremely positive) to 7 (extremely negative). The BoT-measure objectifies the overall effect of the treatment from the patient's perspective and attempts to capture negative aspects of treatment with the EAI and weigh them against the positive aspects of such treatment. The BoT-measure was previously validated in venom allergic patients,[6,14] and was adapted for food allergic patients in this study.

The FAQLQ-TF was completed by the adolescent and is a self-report instrument for measuring the impact of food allergy on the adolescent's HRQL.[15]

The FAQLQ-PFT is a parent-proxy-report instrument for measuring the impact of food allergy on the adolescent's HRQL.[16,17] The FAQLQ-TF and the FAQLQ-PFT may be downloaded from www.FAQLQ.com.

The FAIM-TF was completed by the adolescent and is a self-reported measure for patients' perceived disease severity.[18] The FAIM-PFT was completed by the parent and is proxy-reported.

The brief-IPQ was completed by the adolescent and parent both from their own perspective. The brief-IPQ contains five items reflecting cognitive illness representations, two items reflecting emotional illness representations and two items reflecting coherence (illness comprehension) and causal illness representation.[19] The New Zealand brief-IPQ was previously validated in the Netherlands.[20]

The STAI was completed by the adolescent and parent both from their own perspective. The STAI measures anxiety in a specific situation (state) or anxiety as a disposition (trait). In this study only trait anxiety was measured.[21]

A total of 11 statements about the EAI were included in the questionnaire to examine possible negative and positive aspects of carrying the EAI (Table 3).[6] The statements about the EAI were completed by the adolescent and parent both from their own perspective.

Statistical analyses

Statistical analyses were conducted using SPSS version 20.0 (SPSS Inc. Chicago, IL, USA.). Spearman's correlations and Fisher's exact test were used to investigate associations between the BoT-measure and other outcome measures. The Mann-Whitney U-test was used to investigate differences in total scores for BoT, HRQL, perceived disease severity, illness perception, and anxiety between participants who reported carrying an EAI at all times and participants who reported they did not.

To investigate associations between the BoT-measure and the statements about the EAI, the BoT-score was divided into a dichotomous variable in which an (extremely) positive opinion of the EAI was the opposite of a slightly positive to slightly negative opinion. The statement scores were also divided into a dichotomous variable in which agree was the opposite of disagree. The self-reported compliance scores were also divided into a dichotomous variable in which carrying an EAI by the adolescent and/or parent was the opposite of not carrying an EAI by the adolescent and/or parent. For the characteristics of the adolescents-parent pairs descriptive methods and statistics were used.

RESULTS

Participants

In total seventy adolescent-parent pairs were asked to complete the questionnaire-package. In total 63 adolescent-parent pairs (response rate 89%) completed the questionnaire-package. Eight adolescent-parent pairs were excluded because they did not complete the BoT-measure. Therefore, a total of 55 adolescent-parent pairs were eligible for analysis. Forty-one of these adolescent-parent pairs were recruited through our clinic and fourteen recruited by Dutch food allergy support organizations. There were no significant differences in the descriptive characteristics between adolescents depending on their manner of recruitment. The allergenic foods reported most frequently were tree nuts, followed by peanut. The majority of the food-allergic adolescents (78%) had multiple food allergies. There were slightly fewer girls than boys, and significantly more mothers than fathers who filled out the questionnaire-packages. Descriptive characteristics of adolescents and parents are shown in Table 1.

EAI issues

Compliance

Most food-allergic adolescents had initially been prescribed an EAI more than 2 years before the study and replaced these since then on expiry. The majority of the food-allergic adolescents reported they carried the EAI themselves. However, despite medical advice, the EAI was not carried at all times by eighteen (33%) of these adolescents and/or parents. Whether they carried the EAI or not depended on the perceived need to do so under various circumstances.

Accidental exposure and EAI use

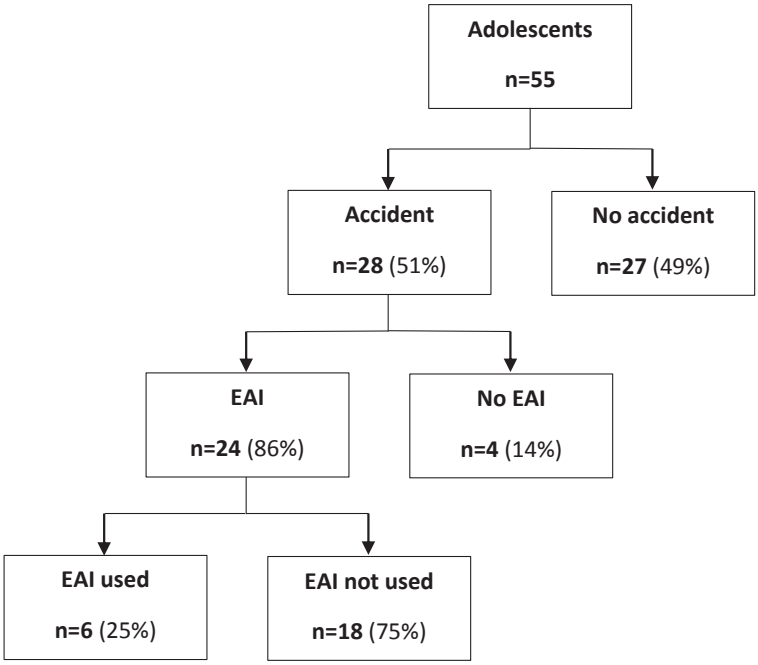
After being prescribed an EAI, twenty-eight (51%) adolescents had a food-allergic accident for which they had been instructed to use the EAI (Figure 1).The majority of these patients had reactions to tree nuts or peanuts. Four of these twenty-eight adolescents (14%) did not have the EAI available at the time of the accidental food-allergic reaction. Eighteen adolescents and/or parents (75%) who had the EAI in their possession at the time of the accidental food-allergic reaction did not use the EAI even though it was available. Six adolescents and/or parents (25%) used their EAI as instructed. None of these six adolescents received a second dose of epinephrine. Three of them were admitted to hospital.

Table 1. Descriptive characteristics adolescent-parent pairs

Number adolescent-parent pairs, n	55
Sex adolescent, boys/girls	29/26
Mean age adolescent, years (SD)	15.9 (1.29)
Sex parent, male/female	6/49
Mean age parent, years (SD)	48.3 (3.9)
Type of food allergies*, n (%)	
Tree nut	45 (81.8)
Peanut	38 (69.1)
Fruit	13 (23.6)
Soy	10 (18.2)
Milk	8 (14.5)
Vegetables	7 (12.7)
Shell fish	5 (9.1)
Sesame	5 (9.1)
Wheat	3 (5.5)
Fish	1 (1.8)
Celery	0
Number of food allergies, n (%)	
1 food	11 (20.0)
2 foods	18 (32.7)
3 foods	13 (23.6)
> 3 foods	12 (21.7)
Most severe symptoms**, n (%)	
Cardiovascular	24 (43.6)
Respiratory	40 (72.7)
Gastro-intestinal	32 (58.1)
Skin	38 (69.9)
Other***	52 (94.5)
Epinephrine auto-injector, n (%)	
Epipen®/Anapen®, yes/no	52/3 (94.5/5.5)
Always carrying EAI, yes/no	37/18 (67.3/32.7)
Person carrying EAI, n (%)	
Adolescent	34 (61.8)
Parent	3 (5.5)
Both	9 (16.4)
None	9 (16.4)
Time since prescription, n (%)	
< 6 months	1 (1.8)
6 months – 2 years	13 (23.6)
>2 years	41 (74.5)
EAI prescription by, n (%)	
general practitioner	4 (7.3)
pediatrician	12 (21.8)
allergist	31 (56.4)
other	8 (14.5)
Anaphylaxis, n (%)	
EAI carriage at time of reaction, yes/no	24/4 (86.0/14.0)
EAI used at time of reaction, yes/no	6/18 (25.0/75.0)
Last experience of anaphylaxis, years (SD)	5.2 (4.5)
Atopic co-morbidities**, n (%)	
Asthma	27 (49.1)
Allergic rhinitis	23 (41.8)
Eczema	16 (29.1)

* Some adolescents reported having more than one food allergy; ** Some adolescents reported having more than one severe symptom; *** Oral allergy symptoms, nose and eye symptoms; **** Some adolescents reported having more than one atopic co-morbidity.

Figure 1. Flowchart accidental food-allergic reaction and EAI use

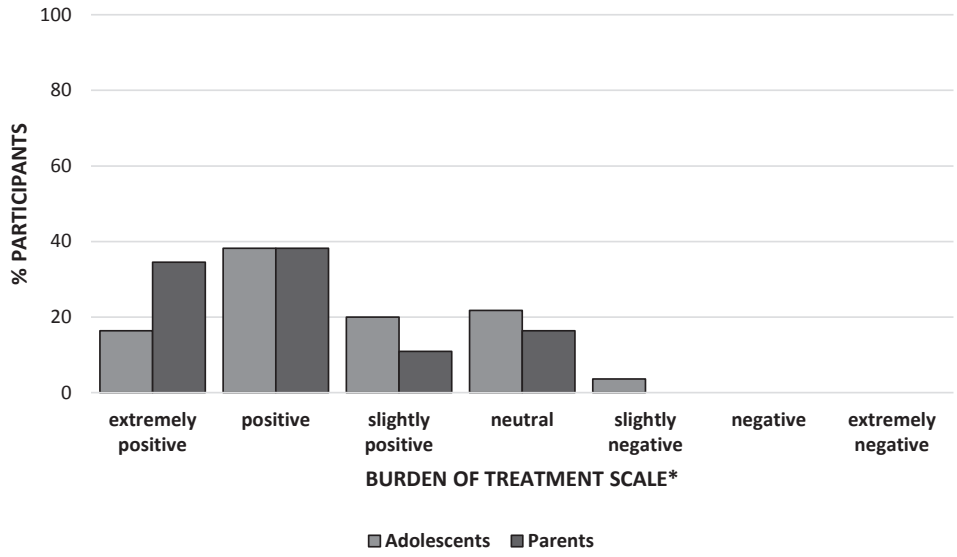


Questionnaires

Burden of Treatment

Of the 55 adolescents, 54.5% were positive to extremely positive about the EAI, and 3.6% were slightly negative (Figure 2). None of the adolescents were negative or extremely negative about the EAI. Parents were even more positive about the EAI than the adolescents: 72.7% of the parents were positive to extremely positive. Thus, parents perceived a lower burden of treatment associated with the EAI than did adolescents themselves. Adolescents who reported not to carry the EAI at all times (n=18) had a significantly higher burden than adolescents who reported they did carry the EAI at all times (n=37)(z=-3.35;p=0.001;mean rank 22.64, 37.22 respectively). This was not the case for parents.

Figure 2. The Burden of Treatment in adolescents and their parents (n=55)



n=number of participants; * The BoT-measure contains a single item which is scored on a scale ranging from 1 (extremely positive) to 7 (extremely negative); none of the adolescent and their parents were negative or extremely negative about the EAI

Adolescents who reported only carrying their EAI when going on holidays reported also a significantly higher burden of treatment (p=0.01).

There was no significant association between the burden of treatment and the number of food allergies (p=0.52), co-morbidities (asthma (p=0.12), eczema (p=0.98), hay fever (p=0.54)), time since EAI prescription (p=0.20) or the type of specialist who had prescribed the EAI (p=0.62).

FAQLQ, IPQ and STAI

There were no significant correlations between the burden of treatment and the other outcome measures: FAQLQ-TF and FAQLQ-PFT total scores; brief-IPQ total score of adolescents and parents, and STAI total score of adolescents and parents (Table 2). In addition, there were no significant differences in total scores for these outcome measures for either adolescents or parents between self-reported compliance and non-compliance with carrying an EAI at all times.

FAIM

There was no significant correlation between the BoT-measurement and FAIM-TF total score (p=0.17), nor between the BoT-measurement and FAIM-PFT total score (p=0.43) (Table 2). However, there was a significant correlation between the BoT-measurement and one individual FAIM-TF item "chance of not dealing with a reaction" (p=0.02). Those reporting a greater burden of treatment were more concerned that they would not be able to deal with a reaction successfully. There was no significant difference in the FAIM-TF total score or FAIM-PFT total score between self-reported compliance and non-compliance with carrying an EAI at all times (ρ=0.105, p=0.54; ρ=0.117, p=0.60, respectively).

Table 2. Adolescent- and parent-reports on food-allergy quality of life (FAQLQ), perceived disease severity (FAIM), illness perception (IPQ), anxiety (STAI) and correlations between BoT and these outcome measures

	Outcome adolescent-report	Outcome parent-report	Correlation between BoT and outcome measure (adolescent/parent)	
	mean (SD)	mean (SD)	Corr Coef ¶	p-value
FAQLQ score§	4.03 (1.35)	3.42 (0.97)	0.175/0.009	0.20/0.95
FAQLQ domains scores				
Allergen avoidance & Dietary Restrictions*	4.02 (1.44)		0.186	0.18
Risk of accidental exposure*	3.92 (1.46)		0.054	0.69
Emotional impact*	3.99 (1.51)		0.192	0.16
Dietary Restrictions**		3.85 (1.32)	-0.122	0.38
Food anxiety**		3.83 (1.08)	-0.033	0.81
Social Restrictions**		2.84 (1.23)	-0.012	0.17
Emotional impact**		2.82 (1.02)	0.067	0.64
FAIM score±	3.57 (0.96)	3.58 (0.81)		0.17/0.60
FAIM total score				
Chance of accidental exposure	3.51 (1.14)	3.27 (1.24)	0.200/0.179	0.14/0.19
Chance of severe reaction	4.60 (1.69)	4.36 (1.89)	0.221/-0.101	0.10/0.47
Chance of dying following exposure	2.91 (1.57)	2.87 (1.52)	-0.068/-0.105	0.62/0.46
Chance of not dealing with a reaction	3.00 (1.37)	3.09 (1.27)	0.311/0.110	0.02/0.43
Number of products to avoid	4.29 (1.32)	4.13 (1.35)	0.023/-0.166	0.87/0.23
Impact on social life	2.95 (1.42)	2.93 (1.35)	0.238/-0.004	0.08/0.98
IPQ score#	5.18 (1.25)	5.12 (1.06)	0.136/0.110	0.32/0.43
IPQ items scores				
Consequences	6.02 (2.65)	5.69 (2.38)	0.065/-0.215	0.64/0.19
Timeline	10.3 (1.41)	10.1 (1.89)	-0.160/-0.022	0.24/0.88
Personal control	8.45 (2.28)	8.75 (2.42)	-0.178/-0.290	0.19/0.03
Treatment control	6.01 (2.57)	6.49 (3.04)	-0.124/-0.242	0.37/0.08
Identity	4.86 (3.23)	4.78 (2.92)	0.076/0.187	0.58/0.18
Illness concern	4.86 (3.23)	5.19 (2.75)	0.105/-0.144	0.45/0.29
Coherence (illness comprehension)	9.41 (1.74)	9.76 (1.97)	-0.152/0.041	0.26/0.77
Emotional representations	3.62 (2.62)	4.14 (2.58)	0.214/0.174	0.12/0.21
STAI scores^	23.54 (17.50)	19.20 (12.21)	0.113/0.094	0.41/0.51

¶ Corr Coef =Correlation coefficient; * Not a domain in FAQLQ-TF; ** Not a domain score in FAQLQ-PFT.
§ FAQLQ scores: 1 (minimal impairment in HRQL) to 7 (maximal impairment in HRQL); ±FAIM score 1 (minimal perceived disease severity) to 7 (maximal perceived disease severity); #IPQ score 1 (benign view of illness) to 11 (threatening view of illness); ^STAI score 1 (no anxiety) to 80 (severe anxiety).

Statements about EAI

A low burden of treatment as reported by adolescents was associated with statements that the EAI has an agreeable shape (p=0.04) and size (p=0.007), and gives a feeling of safety (p=0.01)(Table 3). A high burden of treatment was associated with the statement that it is inconvenient to have to carry an EAI (p=0.01). These associations were not found in adolescents who reported not carrying the EAI at all times. A low burden of treatment as perceived by parents was associated with statements that the EAI has an agreeable size (p=0.009), and it reassuring to carry an EAI (p=0.019). A high burden of treatment was associated with the statement that it is inconvenient to have to carry an EAI (p=0.04).

Table 3. Statements about EAI for food-allergic adolescents

Statement	Agree n (%)	Disagree n (%)	No opinion n (%)	Correlation with BoT* p-value
1. Carrying an EAI makes you feel safe. (n=53)	37 (69.1)	4 (7.3)	12 (21.8)	0.01
2. One EAI is sufficient for the treatment of an allergic reaction. (n=54)	26 (47.3)	15 (27.3)	13 (23.6)	1.00
3. I am afraid of the side-effects of an EAI.(n=54)	6 (10.9)	39 (70.9)	9 (16.4)	0.38
4. I am concerned that a single EAI might be insufficient for the treatment of an allergic reaction. (n=53)	7 (14.5)	30 (54.4)	16 (29.1)	1.00
5. The EAI can cure your allergy. (n=55)	1 (1.8)	51 (92.7)	2 (3.6)	0.46
6. The EAI is patient-friendly because of its shape. (n=54)	24(43.6)	15 (27.3)	15 (27.3)	0.05
7. It is inconvenient to have to carry an EAI. (n=54)	28 (50.9)	22 (40.0)	4 (7.3)	0.02
8. It is reassuring having an EAI.(n=54)	35 (63.6)	5 (9.1)	14 (25.5)	0.06
9. The EAI is patient-friendly because of its size. (n=54)	22 (40.0)	23 (41.8)	9 (16.4)	0.007
10. I think I would not dare to use the EAI if this were necessary. (n=54)	9 (16.4)	40 (72.7)	5 (9.1)	0.27
11. I know how to use the EAI because of instructions given. (n=54)	43 (78.2)	6 (10.9)	(9.1)	0.01

*Associations with the BoT-measurement were measured with Fisher exact test

DISCUSSION

This is the first study examining the relationship between self-reported compliance with carrying the EAI and the burden of treatment as perceived by food-allergic adolescents and their parents. We found that the majority of food-allergic adolescents and their parents were positive about the EAI: the burden of treatment was low. Moreover, the BoT score was not associated with HRQL, perceived disease severity, illness perception, or trait anxiety. However, the BoT was significantly associated with self-reported compliance with carrying the EAI. The burden of treatment was higher in food-allergic adolescents prescribed an EAI who reported not carrying the EAI at all times. Thus, although adolescents perceive a limited burden of having to carry an EAI, this burden does seem to influence the decision many adolescents make to do so on a daily basis.

In contrast to the low burden of treatment we found in food-allergic patients, it was previously shown that patients with vespid allergy carrying an EAI reported a high burden of treatment.[14] These differences in BoT-scores are likely to be context dependent. An EAI is much more likely to be perceived as burdensome in vespid allergy, where it is a temporary measure until curative treatment makes the EAI superfluous. In food allergy it is the only meaningful measure offering protection when accidental food-allergic reactions occur. Also, vespid exposure is usually limited to certain seasons while food allergen exposure may occur throughout the year.

Food-allergic adolescents take risks pertaining to their food allergy, including not carrying their EAI at all times.[22,23] In our study considerably more food-allergic adolescents (14%) carried the EAI at the time of an accidental food-allergic accident compared to other studies, whereas 38-50% did not have the EAI available when needed.[1,24] As in previous studies,[1,25] we found that compliance is often selective, where individuals report having the EAI with them in restaurants and during holidays more often than at other times. The inconvenience, shape and size of the EAI were not associated with self-reported non-compliance with carrying the device.

Previous studies have reported that 57-78% food-allergic adolescents and adolescents prescribed an EAI reported to have had a food-allergic reaction within a 2-5 year period.[1,8,11,26] The high percentage of accidental food-allergic reactions for which an EAI was needed in our study is thus in keeping with previous reports.

Eighteen adolescents (75% of those who had an EAI available) did not use the EAI during the accidental food-allergic reaction, which is greater than in previous studies reporting 11% to 33%[1,8,27,28] of adolescents not using available epinephrine. Many of the reactions in our study often included respiratory and/or cardiovascular symptoms, and many adolescents had asthma and were reacting to accidental ingestion of peanuts or tree nuts. Reasons given for non-use of the EAI were "other medication used", "unsure if it was necessary", "didn't seem severe enough", "unsure they ingested the food" and one

patient did not dare to use the EAI. These explanations for the non-use of the EAI are similar to those found in a previous study.[29] Our data show that individuals not using available epinephrine perceived their disease as being less severe than those who did. This suggests that perceived disease severity is a motivating factor for use of the EAI during an allergic reaction to foods.

In our study there were no significant differences in the descriptive characteristics between adolescents depending on their manner of recruitment. However, it is possible that compliance in the general population is not as good as in individuals participating in studies such as ours. Conclusions in the present study should be confirmed in a "real life" setting to clarify this.

A limitation of this study may be that the parental questionnaires were mainly completed by mothers. The burden of treatment of an EAI as perceived by fathers may differ from mothers. A previous study showed that there is a sex difference in parental coping with food allergy.[30] Therefore, parental gender is important to take into account in future research. Another limitation of this study may be recall bias, to which self-reported data are prone. However, investigation using self-reported data has been accepted within the food allergy literature despite such limitations.[31]

A further possible limitation is that the size of the study may have been inadequate to find correlations between the BoT and the other outcome measures (FAQLQ, FAIM, IPQ and STAI). However, the percentage of the response variable variation (R^2) is low, and it is thus unlikely that a larger study population would have shown these correlations to be significant.

In summary, for food-allergic adolescents prescribed an EAI, a higher burden of treatment is associated with self-reported non-compliance with carrying an EAI at all times. The BoT-measure thus seems to be a useful tool to study compliance with carrying an EAI. Remarkably, the BoT-scores of both adolescents and their parents are not associated with HRQL, perceived disease severity, illness perception, or trait anxiety. Thus, the BoT-measure measures a distinct concept related to compliance behaviour. Further studies on factors influencing the BoT of food-allergic adolescents may be helpful in order to improve compliance.

ACKNOWLEDGEMENTS

This research is supported by the GUIDE Research Institute Groningen, the Netherlands. We would like to thank dr. B.J. Kollen and dr. J.G.M. Burgerhof for their help with the statistical analysis.

REFERENCES

(1) Sampson MA, Munoz-Furlong A, Sicherer SH. Risk-taking and coping strategies of adolescents and young adults with food allergy. J Allergy Clin Immunol 2006 Jun;117(6):1440-1445.

(2) Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol 2007 Apr;119(4):1016-1018.

(3) Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy 2007 Aug;62(8):857-871.

(4) Greenhawt MJ, Singer AM, Baptist AP. Food allergy and food allergy attitudes among college students. J Allergy Clin Immunol 2009 Aug;124(2):323-327.

(5) Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Strategies for living with the risk of anaphylaxis in adolescence: qualitative study of young people and their parents. Primary care respiratory journal 2012;21(4):392-397.

(6) Oude Elberink JN, van der Heide S, Guyatt GH, Dubois AE. Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis. J Allergy Clin Immunol 2006 Sep;118(3):699-704.

(7) Pinczower GD, Bertalli NA, Bussmann N, Hamidon M, Allen KJ, DunnGalvin A, et al. The effect of provision of an adrenaline autoinjector on quality of life in children with food allergy. J Allergy Clin Immunol 2013 1;131(1):238-240.e1.

(8) MacKenzie H, Roberts G, van Laar D, Dean T. Teenagers' experiences of living with food hypersensitivity: a qualitative study. Pediatr Allergy Immunol 2010 Jun;21(4 Pt 1):595-602.

(9) Marrs TL, Gideon. Why do few food-allergic adolescents treat anaphylaxis with adrenaline?--Reviewing a pressing issue. Pediatric allergy and immunology 2013;24(3):222-229.

(10) Monks H, Gowland MH, MacKenzie H, Erlewyn-Lajeunesse M, King R, Lucas JS, et al. How do teenagers manage their food allergies? Clin Exp Allergy 2010 Oct;40(10):1533-1540.

(11) Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JS. Management of nut allergy influences quality of life and anxiety in children and their mothers. Pediatr Allergy Immunol 2010 Jun;21(4 Pt 1):586-594.

(12) Akeson N, Worth A, Sheikh A. The psychosocial impact of anaphylaxis on young people and their parents. Clin Exp Allergy 2007 Aug;37(8):1213-1220.

(13) Noimark L, Wales J, Du Toit G, Pastacaldi C, Haddad D, Gardner J, et al. The use of adrenaline autoinjectors by children and teenagers. Clin Exp Allergy 2012 Feb;42(2):284-292.

(14) Oude Elberink JN, De Monchy JG, Van Der Heide S, Guyatt GH, Dubois AE. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. J Allergy Clin Immunol 2002 Jul;110(1):174-182.

(15) Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy 2009 Jan;39(1):127-137.

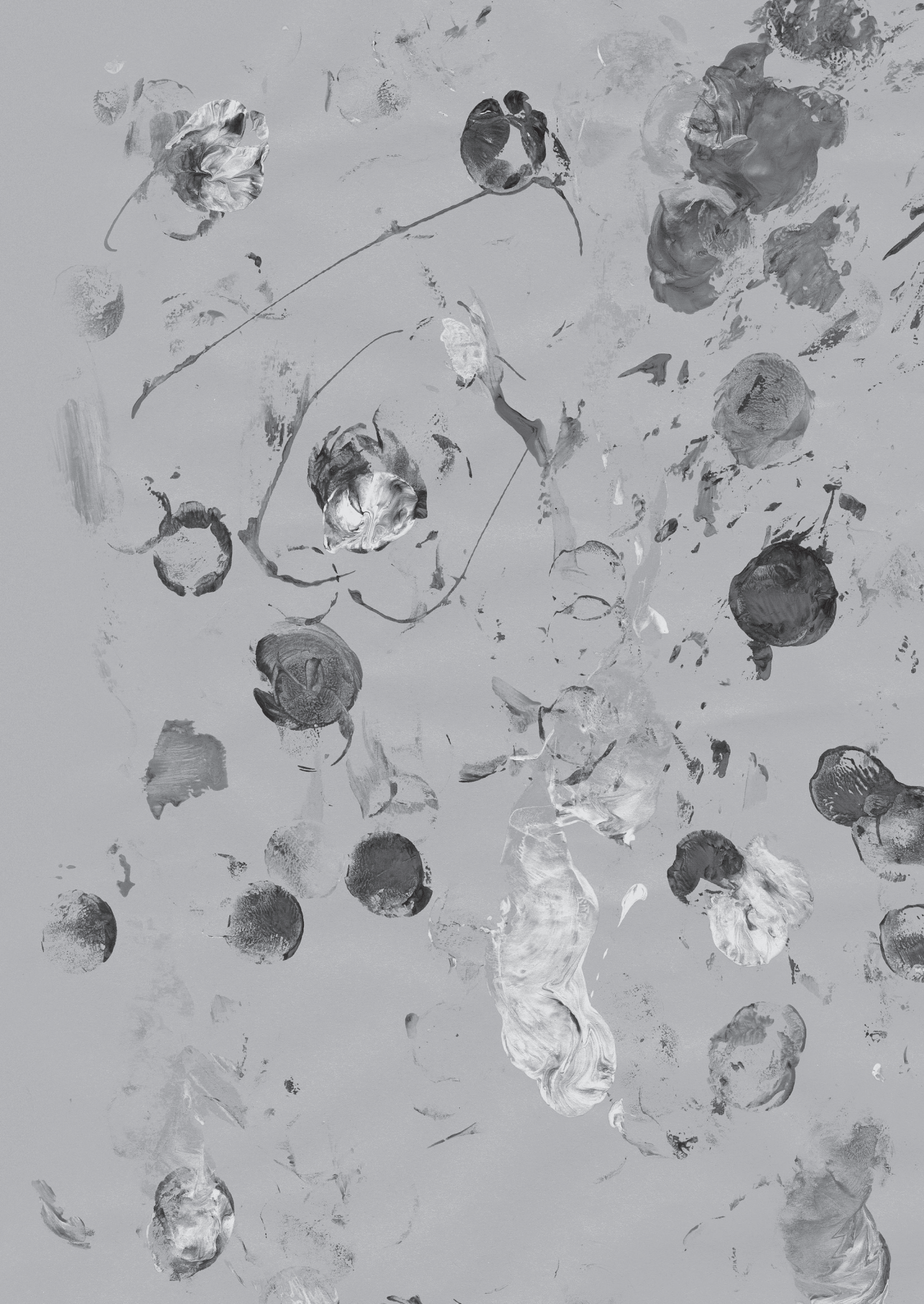
(16) Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, et al. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. J Allergy Clin Immunol 2008 Jul;122(1):139-44, 144.e1-2.

(17) Hamp A KR. Development and validation of a parent-administered food allergy quality of life questionnaire for adolescents. Submitted manuscript. 2011.

(18) van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Oude Elberink JN, DunnGalvin A, Hourihane JO, et al. Development, validity and reliability of the food allergy independent measure (FAIM). Allergy 2010 May;65(5):630-635.

(19) Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res 2006 Jun;60(6):631-637.

(20) Master thesis. Patient's illness perception: An additional part of physiotherapy assessment. Cross-cultural adaptation and measurement properties of the brief illness perception questionnaire - Dutch language version; 2007.
(21) Spielberger CD, Gorsuch RL, Lushene R, Jacobs GA, editors. Manual for the state-trait anxiety inventory (STAI). Consulting Psychologists Press 1984.
(22) Rolison MR, Scherman A. Factors influencing adolescents' decisions to engage in risk-taking behavior. Adolescence 2002 Fall;37(147):585-596.
(23) Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. J Allergy Clin Immunol 2007 Apr;119(4):1018-1019.
(24) Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med 1992 Aug 6;327(6):380-384.
(25) Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Epinephrine auto-injector use in adolescents at risk of anaphylaxis: a qualitative study in Scotland, UK. Clin Exp Allergy 2011 Jun;41(6):869-877.
(26) MacKenzie H, Dean T. Quality of life in children and teenagers with food hypersensitivity. Expert Rev Pharmacoecon Outcomes Res 2010 Aug;10(4):397-406.
(27) Sicherer SH, Forman JA, Noone SA. Use assessment of self-administered epinephrine among food-allergic children and pediatricians. Pediatrics 2000 Feb;105(2):359-362.
(28) Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000 Aug;30(8):1144-1150.
(29) Simons KJ, Simons FE. Epinephrine and its use in anaphylaxis: current issues. Curr Opin Allergy Clin Immunol 2010 Aug;10(4):354-361.
(30) Gupta RS, Springston EE, Smith B, Kim JS, Pongracic JA, Wang X, et al. Food allergy knowledge, attitudes, and beliefs of parents with food-allergic children in the United States. Pediatr Allergy Immunol 2010 Sep;21(6):927-934.
(31) Greenhawt MJ, Singer AM, Baptist AP. Food allergy and food allergy attitudes among college students. J Allergy Clin Immunol 2009 Aug;124(2):323-327.



Chapter 5

Predictors of health-related quality-of-life of European food-allergic patients

J. Saleh-Langenberg*
N.J. Goossens*
B.M.J. Flokstra-de Blok
B.J. Kollen
G.N. van der Meulen
T.M. Le
A.C. Knulst
M. Jedrzejczak-Czechowicz
M.L. Kowalski
E. Rokicka
P. Starosta
B. de la Hoz Caballer
S. Vazquez- Cortés
I. Cerecedo
L. Barreales
R. Asero
M. Clausen
A. DunnGalvin
J. O'B Hourihane
A. Purohit
N.G. Papadopoulos
M. Fernandéz-Rivas
L. Frewer
P. Burney
E.J. Duiverman
A.E.J. Dubois

** shared first authorship*

Allergy. 2015 Jun;70(6):616-24

ABSTRACT

Background: Although food allergy has universally been found to impair HRQL, studies have found significant differences in HRQL between countries, even when corrected for differences in perceived disease severity. However, little is known about factors other than disease severity which may contribute to HRQL in food-allergic patients. Therefore, the aim of this study was to identify factors which may predict HRQL of food-allergic patients and also to investigate the specific impact of having experienced anaphylaxis and being prescribed an EAI on HRQL.

Methods: A total of 648 European food-allergic patients (404 adults, 244 children) completed an age-specific questionnaire-package including descriptive questions. Multivariable regression analyses were performed to develop models for predicting HRQL of these patients.

Results: For adults, the prediction model accounted for 62% of the variance in HRQL and included perceived disease severity, type of symptoms, having a fish or milk allergy and gender. For children, the prediction model accounted for 28% of the variance in HRQL and included perceived disease severity, having a peanut or soy allergy, and country of origin. For both adults and children, neither experiencing anaphylaxis nor being prescribed an epinephrine auto-injector (EAI) contributed to impairment of HRQL.

Conclusions: In this study food allergy-related HRQL may be predicted to a greater extent in adults than in children. Allergy to certain foods may cause greater HRQL impairment than others. Country of origin may affect HRQL, at least in children. Experiencing anaphylaxis or being prescribed an EAI has no impact on HRQL in either adults or children.

INTRODUCTION

Health-related quality of life (HRQL) is increasingly being recognized as an important outcome measurement for both research and clinical practice.[1,2] Recently, Food Allergy Quality-of-Life Questionnaires (FAQLQs) have been developed, translated and validated for use in different countries.[3-6] Although food allergy has universally been found to impair HRQL, studies have found significant differences in HRQL between countries, even when corrected for differences in perceived disease severity.[6,7] It is of interest to know which factors are important in predicting HRQL in these food-allergic patients, as they may be modifiable and therefore appropriate targets for interventions.

Previous studies that have measured HRQL in patients with a food allergy all showed that HRQL is negatively affected in these patients, and identified variables that may influence the magnitude of the impact of food allergy on HRQL. The following variables have been identified: type of food allergy, severity of the allergy, the number of foods to which one is allergic, atopic co-morbidities, gender, age, EAI prescription.[8-15]

The differences in HRQL may be related to cultural differences between countries. As hypothesized in another cross-cultural comparison of HRQL in food allergic adults, the way of coping with life-events may differ between countries, and may influence the attitude towards a food allergy as well.[6] Likewise, the practice and traditions of eating may be different between European countries.[6] It is therefore of interest to know which factors are important in predicting HRQL in food-allergic patients, as they may be modifiable and therefore appropriate targets for interventions.

Despite taking precautions, accidental ingestion may occur, and for some food-allergic patients such ingestion may be fatal. Therefore, food-allergic patients at high risk for anaphylaxis should always carry their epinephrine auto-injector (EAI). Having experienced anaphylaxis and carrying an EAI at all times may be perceived as burdensome and may therefore impair HRQL.[12,16]

The aim of this study was to identify factors which may predict HRQL of food-allergic patients and also to investigate the specific impact of having experienced anaphylaxis and being prescribed an EAI on HRQL.

METHODS

Participants and procedure

Participants were recruited through the EuroPrevall project, a European multi-centre, international research project. Adults (≥18 years) were recruited in the Netherlands, Greece, Italy, France, Iceland, Spain and Poland. Children (8-12 years) and teenagers (12-17 years) were recruited in the Netherlands, Spain, Ireland and Poland.

Food-allergic patients were recruited in two ways: (i) at outpatient departments of medical centers and (ii) through a community survey. Adults, children and teenagers were invited to participate in this study when they (i) had at least one self-perceived or physician-diagnosed food allergy and (ii) had a positive screening outcome as ascertained by the self-reported screening questionnaire.

The community survey consisted of questions about the existence of a self-perceived food allergy and about the type of food(s) that were thought to cause the allergic reaction. When the first questions were answered in the affirmative and the mentioned food(s) included at least one of the 24 EuroPrevall priority foods[13,14] the screening outcome was considered as being positive for having a self-perceived allergy for an acknowledged allergenic food.

Participants completed an age-specific questionnaire-package including descriptive questions (age, sex, type and number of food allergies, type of symptoms, self-perceived or physician-diagnosed food allergy, EAI prescription), FAQLQ[4,5,17] and Food Allergy Independent Measure (FAIM).[18] Participants who completed less than 70% of the FAQLQ or less than 80% of the FAIM were excluded from analyses. Participants who experienced anaphylaxis were identified using clinical criteria for diagnosing anaphylaxis.[19]

Participation to the study was completely voluntary. This study was assessed by the local medical ethics review committee of each participating country who deemed that formal approval from the committee was not required.

Questionnaire-package

The FAQLQs used in this study were FAQLQ–Child Form (FAQLQ-CF) for children, FAQLQ-Teenager Form (FAQLQ-TF) for teenagers, and the FAQLQ–Adult Form (FAQLQ-AF) for adults. These questionnaires are self-administered instruments for measuring the impact of food allergy on the patients' HRQL.[3-5] The FAQLQs have been developed and validated for the measurement of HRQL in patient with food allergies.[7,20]

The FAQLQ-CF contains 24 items which are allocated to four different domains (Allergen Avoidance & Dietary Restrictions (AA&DR), Risk of Accidental Exposure (RAE), and Emotional Impact (EI)). The FAQLQ-TF contains 23 items which are allocated to three different domains (AA&DR, RAE, and EI).

The FAQLQ-AF is a self-administered instrument for measuring the impact of food allergy on adults' HRQL.[4] The FAQLQ-AF contains 29 items which are allocated to four domains AA&DR, RAE, EI, and Food Allergy related Health (FAH)).The total FAQLQ score is the sum of all individual item scores divided by the number of completed items (ranging from 1 (minimal impairment of HRQL) to 7 (maximal impairment of HRQL)). The FAQLQs may be downloaded from *www.FAQLQ.com*.

The FAIM is a self-reported measure for the patients' perceived disease severity.[21] The total FAIM score is the sum of all individual item scores divided by the number of completed items (ranging from 1 (minimal self-perceived disease severity) to 7 (maximal self-perceived disease severity)).

Predictors of HRQL

Prediction models were developed to find the best set of variables to predict variance in HRQL of food-allergic adults and children. Variables analysed were chosen based on previous studies and theoretical rationale: gender, age, number of food allergies, type of food allergy, type of symptoms, anaphylaxis experience, EAI prescription, country of origin and perceived disease severity.[10,12,22,23]

Anaphylaxis and EAIs

To investigate whether the previously reported impact of being prescribed an EAI on HRQL of food-allergic patients[12] is dependent on the type of patient (having experienced anaphylaxis and perceived disease severity), and whether this impact is different for the individual FAQLQ domains, subgroup analyses were performed.

For both food-allergic adults and children, those who experienced anaphylaxis were selected and allocated to two subgroups: patients who perceived their food allergy as being severe (total FAIM score >4) and patients who perceived their food allergy as being less severe (total FAIM score ≤4). These subgroups were divided into patients who had been prescribed an EAI and those who have not been prescribed an EAI. Total FAQLQ scores were compared between these groups.

In order to investigate the impact of having experienced anaphylaxis and being prescribed an EAI as precisely as possible, prediction models were made for all individual FAQLQ domains.

Statistical analysis

Data entry and statistical analyses were conducted using SPSS version 19.0 (SPSS Inc. Chicago, IL, USA). All tests were 2-tailed and the significance level was set at $\alpha \leq 0.05$.

Variables with multiple categorical responses were recoded as dummy variables. Predictors of HRQL were determined by using univariable and multivariable regression analyses. Variables that were significantly associated ($\alpha < 0.05$) with total FAQLQ scores in the univariable analyses were included in a stepwise forward manner using the enter method in a multivariate regression model, but were only retained in the model if that factor contributed to a significant change ($\alpha < 0.05$) in the R^2 of the prediction model.

Thereafter, variables were removed in a stepwise manner from this prediction model if they did not contribute significantly and independently to the prediction model. After the development of the prediction models, the assumptions for multivariable linear regression analyses were checked. The same analyses were performed for the different FAQLQ domains. Total FAQLQ-AF scores and total FAQLQ-CF scores of participants who had or who had not been prescribed an EAI were compared using the Mann-Whitney U-test. A difference in total FAQLQ scores of ≥0.5 points was considered to be a clinically relevant difference.[17]

RESULTS

Participants

Between May 2007 and September 2009, a total of 414 food-allergic adults in seven European countries and a total of 306 food-allergic children and three teenagers in four European countries completed the questionnaire-package. In total, 10 adults and 62 children and 3 teenagers were excluded because of age, incomplete information, gender or allergic symptoms not reported. Therefore, data of 404 food-allergic adults and 244 food-allergic children was available for analyses. Descriptive characteristics are shown in Table I (adults) and Table II (children).

Table I. Descriptive characteristics of food-allergic adults of participating countries

	Netherlands	Greece	Italy	France	Iceland	Spain	Poland
Participants, n	55	31	58	40	57	86	77
outpatient department	55	31	58	40	57	26	26
community survey	0	0	0	0	0	60	51
Gender, m/f	16/15	12/43	20/38	12/28	23/34	33/53	28/49
Age, mean in years (SD)	33 (13)	30 (9)	40 (13)	36 (11)	34 (13)	37 (9)	40 (11)
Food Allergy*, n (%)							
tree nuts	**37 (67)**	9 (29)	35 (60)	23 (58)	10 (18)	20 (23)	28 (36)
peanut	21 (38)	**13 (42)**	30 (52)	16 (40)	14 (25)	15 (17)	19 (25)
milk	8 (15)	2 (7)	1 (2)	2 (5)	7 (12)	15 (17)	27 (35)
egg	5 (9)	2 (7)	1 (2)	5 (13)	6 (11)	3 (4)	10 (13)
wheat	1 (2)	1 (3)	2 (3)	3 (8)	7 (12)	5 (6)	7 (9)
soy	9 (16)	0 (0)	5 (9)	7 (18)	4 (7)	3 (4)	6 (8)
sesame seed	3 (6)	2 (7)	16 (28)	9 (23)	6 (11)	1 (1)	4 (5)
fish	1 (2)	6 (19)	4 (7)	6 (15)	20 (35)	19 (22)	5 (7)
shell fish	3 (6)	6 (19)	5 (9)	4 (10)	**27 (47)**	17 (20)	7 (9)
celery	5 (9)	1 (3)	23 (40)	11 (28)	2 (4)	1 (1)	11 (14)
fruit	**37 (67)**	12 (39)	**49 (85)**	**31 (78)**	13 (23)	**42 (49)**	**41 (53)**
vegetables	12 (22)	5 (16)	27 (47)	17 (43)	7 (12)	19 (22)	24 (31)
Number of food allergies, n (%)	8 (15)	**15 (49)**	9 (16)	3 (8)	26 (46)	**38 (44)**	24 (31)
1 food allergy	15 (27)	7 (23)	9 (16)	9 (23)	5 (9)	23 (27)	13 (17)
2 food allergies	**32 (58)**	9 (28)	**41 (68)**	**28 (79)**	**26 (47)**	25 (14)	**40 (52)**
≥ 3 food allergies							
Type of most severe	17 (31)	**13 (42)**	7 (12)	11 (28)	16 (28)	21 (24)	14 (18)
symptoms, n (%)	**25 (46)**	5 (16)	**34 (59)**	**21 (53)**	**30 (53)**	**26 (30)**	**16 (21)**
cardiovascular[1]	3 (6)	4 (13)	2 (3)	1 (3)	3 (5)	16 (19)	11 (14)
respiratory tract[2]	3 (6)	6 (19)	5 (9)	5 (13)	5 (9)	15 (17)	15 (20)
gastrointestinal tract[3]	7 (11)	3 (10)	10 (17)	2 (5)	3 (5)	8 (10)	21 (27)
skin[4]							
other[5]							
Allergy was diagnosed by,	16 (29)	9 (29)	1 (2)	11 (28)	9 (16)	**51 (59)**	25 (33)
n (%)	**36 (66)**	**20 (65)**	**56 (97)**	**27 (68)**	**43 (75)**	28 (33)	**42 (55)**
patient him/herself	0 (0)	0 (0)	0 (0)	0 (0)	3 (5)	0 (0)	0 (0)
health-care professional**							
other							
Prescribed an EAI, n (%)	19 (35)	14 (45)	4 (7)	15 (38)	18 (32)	6 (7)	1 (1)
Experienced anaphylaxis, n (%)	42 (76)	16 (52)	41 (71)	30 (75)	43 (75)	43 (50)	30 (39)

BOLD values is the highest value in particular country; [1] dizziness, palpitations, loss of vision, inability to stand, light headedness, collapse, loss of consciousness; [2] tightening throat, difficulty swallowing, hoarseness, difficulty breathing, shortness of breath, wheezing, cough; [3] nausea, stomach cramps, vomiting, diarrhea; [4] itchy skin, red rash, swelling of the skin, hives, worsening eczema; [5] oral allergy, swollen tongue or lips, symptoms of the nose or eyes; * Food allergy based on patients' perception ** general practitioner, pediatrician, allergist or dermatologist.

Table II. Descriptive characteristics of food-allergic children of participating countries

	Netherlands	Spain	Ireland	Poland
Participants, n	79	35	24	106
outpatient department	47	5	24	0
community survey	32	30	0	106
Gender, n male/female	46/33	15/20	14/10	51/55
Age, mean in years (SD)	10 (1.3)	9 (1.3)	10 (1.3)	9 (1.0)
Food Allergy*, n (%)				
tree nuts	57 (72)	5 (14)	12 (50)	14 (13)
peanut	**59 (75)**	4 (11)	**18 (75)**	17 (16)
milk	21 (27)	4 (11)	3 (13)	**73 (69)**
egg	29 (37)	4 (11)	13 (54)	27 (26)
wheat	10 (13)	2 (6)	1 (4)	2 (2)
soy	12 (15)	0 (0)	2 (8)	11 (10)
sesame seed	15 (19)	0 (0)	0 (0)	2 (2)
fish	2 (3)	4 (11)	4 (17)	4 (4)
shell fish	7 (9)	3 (9)	1 (4)	2 (2)
celery	1 (1)	0 (0)	0 (0)	14 (13)
fruit	0 (0)	**21 (60)**	5 (21)	39 (37)
vegetables	0 (0)	3 (9)	0 (0)	12 (11)
Number of food allergies, n (%)				
1 food allergy	20 (25)	**24 (69)**	**12 (50)**	**47 (45)**
2 food allergies	22 (28)	7 (20)	2 (8)	30 (28)
≥ 3 food allergies	**37(47)**	4 (11)	10 (42)	29 (27)
Type of most severe symptoms, n (%)	**29 (37)**	7 (20)	6 (25)	7 (6)
cardiovascular[1]	**29 (37)**	**11 (31)**	**10 (42)**	38 (36)
respiratory tract[2]	11 (14)	4 (11)	2 (7)	17 (16)
gastrointestinal tract[3]	8 (10)	8 (23)	3 (13)	**44 (42)**
skin[4]	2 (2)	5 (15)	3 (13)	0 (0)
other[5]				
Allergy was diagnosed by, n (%)				
patient him/herself	0 (0)	9 (26)	0 (0)	16 (15)
health-care professional**	**79 (100)**	**16 (46)**	**24 (100)**	**85 (80)**
other	0 (0)	10 (28)	0 (0)	5 (5)
Prescribed an EAI, n (%)	12 (15)	3 (9)	20 (83)	0 (0)
Experienced anaphylaxis, n (%)	56 (71)	16 (46)	16 (67)	42 (40)

BOLD values is the highest value in particular country; [1] dizziness, palpitations, loss of vision, inability to stand, light headedness, collapse, loss of consciousness; [2] tightening throat, difficulty swallowing, hoarseness, difficulty breathing, shortness of breath, wheezing, cough; [3] nausea, stomach cramps, vomiting, diarrhea; [4] itchy skin, red rash, swelling of the skin, hives, worsening eczema; [5] oral allergy, swollen tongue or lips, symptoms of the nose or eyes; * Food allergy based on patients' perception **general practitioner, pediatrician, allergist or dermatologist.

Predictors of HRQL

The prediction model for food-allergic adults accounted for 62% (R^2=0.621) of the variance in HRQL (total FAQLQ-AF score)(Table III). Variables that had a significant and unique contribution to this variance were: perceived disease severity, type of symptoms, having a fish or milk allergy, and gender.

The prediction model for food-allergic children accounted for 28% (R^2=0.277) of the variance in HRQL (total FAQLQ-CF score)(Table IV). Variables that had a significant and unique contribution to this variance were: perceived disease severity, having a peanut or soy allergy, and country of origin.

Table III. The prediction model of HRQL in food-allergic adults

	n	B	95% CI for OR	p-value	R^2
Constant	404	0.950	0.592;1.308	<0.001	-
Total FAIM score	404	0.868	0.786;0.951	<0.001	0.564
Type of most severe symptoms	404				0.580
Cardiovascular (reference)[1]	99	-		-	
Respiratory[2]	157	-0.342	-0.571;-0.114	0.003	
Gastrointestinal[3]	40	-0.439	-0.788;-0.090	0.014	
Skin[4]	54	-0.230	-0.539;0.079	0.144	
Other[5]	54	-0.445	-0.783;-0.108	0.010	
Fish allergy	404				0.599
no (reference)	343	-		-	
yes	61	0.609	0.357;0.861	<0.001	
Gender	404				0.609
female (reference)	260	-		-	
male	144	-0.303	0.491;0.115	0.002	
Milk allergy	404				0.621
no (reference)	342	-		-	
yes	62	0.451	0.196;0.706	0.001	

n=number of participant. B=B coefficient. CI=Confidence Interval. R^2=R square. HRQL= Health-related quality of life. FAIM= Food Allergy Independent Measure. Only factors that significantly contribute to the model are shown. Positive B coefficients reflect higher total FAQLQ scores (more impaired HRQL), while negative B coefficients reflect lower total FAQLQ scores (less impaired HRQL), compared to the reference group. [1] dizziness, palpitations, loss of vision, inability to stand, light headedness, collapse, loss of consciousness; [2] tightening throat, difficulty swallowing, hoarseness, difficulty breathing, shortness of breath, wheezing, cough; [3] nausea, stomach cramps, vomiting, diarrhea; [4] itchy skin, red rash, swelling of the skin, hives, worsening eczema; [5] oral allergy, swollen tongue or lips, symptoms of the nose or eyes.

Table IV. The prediction model of HRQL in food-allergic children

	n	B	95% CI for B	p-value	R^2
Constant	244	2.233	1.404;3.063	<0.001	-
Peanut allergy	244				0.158
no (reference)	146	-		-	
yes	98	0.637	0.198;1.076	0.005	
Soy allergy	244				0.179
no (reference)	219	-		-	
yes	25	0.773	0.199;1.346	0.009	
Country of origin	244	0.196		0.000	0.249
the Netherlands (reference)	79	-		-	
Spain	35	-0.195	-0.851;0.460	0.558	
Ireland	24	0.700	0.068;1.331-	0.030	
Poland	106	-0.391	0.968;0.187	0.184	
Total FAIM score	244	0.249	0.086;0.413	0.003	0.277

n=number of participant. B=B coefficient. CI=Confidence Interval. R^2=R square. FAIM= Food Allergy Independent Measure. Standard error of the estimate= 1.354. Only factors that significantly contribute to the model are shown. Positive B coefficients reflect higher total FAQLQ scores (more impaired HRQL), while negative B coefficients reflect lower total FAQLQ scores (less impaired HRQL), compared to the reference group.

Anaphylaxis and EAIs

Having experienced anaphylaxis and being prescribed an EAI were not independent predictors of HRQL in food-allergic adults.

No significant difference was found when total FAQLQ-AF scores of food-allergic adults who had experienced anaphylaxis and perceived their food allergy as being severe (FAIM>4) was compared between those who had and had not been prescribed an EAI (total FAQLQ scores: 5.41 vs. 4.96;p=0.154). No difference was found for food-allergic adults who perceived their food allergy as being less severe (FAIM≤4) between those who had and had not been prescribed an EAI (total FAQLQ scores: 3.52 vs. 3.23;p=0.243).

Food-allergic adults who had been prescribed an EAI had statistically significantly and clinically relevantly higher scores (≥0.5 points) for ten individual FAQLQ items. The majority of these FAQLQ items concern two important aspects of HRQL in food allergy: eating out and the labeling of food products.

Having experienced anaphylaxis was an independent predictor of HRQL for only one domain, *Risk of Accidental Exposure,* in food-allergic children (B=0.537). Being prescribed an EAI was not an independent predictor for any domain score.

No significant differences were found when total FAQLQ-CF scores of food-allergic children who had experienced anaphylaxis and perceived their food allergy as being severe (FAIM>4) was compared between those who had and had not been prescribed an EAI (total FAQLQ scores: 3.77 vs. 3.72;p=0.988). The same was found for food-allergic children who experienced anaphylaxis and perceived their food allergy as being less severe (FAIM≤4)(total FAQLQ scores: 3.85 vs. 3.11;p=0.069).

DISCUSSION

This is the first study to identify factors, other than perceived disease severity, that predict HRQL of European food-allergic adults and children. The prediction model for adults accounted for 62% of the variance in total FAQLQ-AF scores, based on having a fish or milk allergy, type of most severe symptoms and gender (women more affected) in addition to perceived disease severity (total FAIM scores). The prediction model for children accounted for only 28% of the variance in total FAQLQ scores, based on having a peanut or soy allergy and country of origin in addition to perceived disease severity. Furthermore, this study shows that being prescribed an EAI was not predictive of HRQL in food-allergic adults and children when using instruments assessing the patient's HRQL perspective. In addition, experiencing anaphylaxis did not contribute to impairment of HRQL in either adults or children.

Food-allergic adults had a more impaired HRQL when they experienced more severe symptoms, which seem logical. However, it was not expected that participants with skin symptoms would have a more impaired HRQL than participants with respiratory or gastrointestinal symptoms. One might speculate that acute skin symptoms are readily visible signs of an allergic reaction. Patients may feel embarrassed and socially disadvantaged or even depressed as has been reported for chronic skin diseases.[24,25]

Another finding in this model is that male participants had less impaired HRQL than female participants. This is in agreement with other studies, although these have focused mainly on teenagers.[23,26]

In addition, adults with a fish or milk allergy experienced a more impaired HRQL than other food-allergic patients. This study shows that HRQL in food-allergic adults can be predicted by type of food allergy. Similar findings were found by Leung et al. in parents of young children (2-7 years) who have adverse food reactions caused by multiple foods and specifically by peanut, egg and cow´s milk.[27] It is possible that relatively many milk allergic adults have had their allergy diagnosis since early childhood and have not been diagnostically evaluated with current methods such as oral challenge. The reason for the HRQL impact of fish allergy is not apparent, but deserves further study.

Country of origin was not predictive for overall food-related HRQL of food-allergic adults. This was a surprising finding, since our previous cross-cultural studies have shown differences in HRQL of food-allergic adults between participating countries.[6,7,28] Apparently, the relationship between country of origin and HRQL was not only influenced by self-perceived disease severity (FAIM), but also by type of most severe symptoms, type of food allergy and gender, because correcting for these variables obfuscated this relationship. It is remarkable that a relationship between country of origin and two different HRQL domain scores (Emotional Impact and Food Allergy related Health) remains, even after investigating several potential predictors for these domain scores. Thus, cross-cultural

differences may exist in HRQL of food allergic adults, but are mainly related to their emotions towards and the way they experience their disease.

Country of origin and perceived severity contributed significantly to the variance in HRQL in children, which we have reported previously.[3,28] Moreover, this study shows that children with a peanut or soy allergy have a more impaired HRQL than other food-allergic children. It is understandable that peanut allergic children have a more impaired HRQL, since peanut is difficult to avoid, may cause severe reactions, and has a reputation as such. Based on the FAQLQ-CF items with the highest scores as reported by soy allergic children, these children are mainly disappointed that other people do not take their allergy into account. These differences in HRQL based on type of food allergy may be important to policy makers as a basis for prioritization of allergenic foods for control measures at a societal level.

We were surprised to find the limited impact of being prescribed an EAI on HRQL in food-allergic children, even when domain scores were studied. Pinczower et al.,[12] who used parent-proxy-reports to determine HRQL of food-allergic children, found more impaired HRQL in children being prescribed an EAI compared to those who were not prescribed an EAI. However, they did not adjust the inverse relationship between EAI prescription and HRQL for self-perceived disease severity (FAIM). Their proposed relationship between EAI prescription and HRQL may thus be confounded by this self-perceived disease severity.

An important issue is whether clinicians can use the factors identified in this study to manage their food allergic patients. In principle, knowledge of factors contributing to poor HRQL could assist clinicians to identify at risk patients and might inform preventive and/or therapeutic interventions. Currently, there is little research validating HRQL measurements for clinical use in individual patients.[20] Such research should include reproducibility, validity and acceptability of measurements in HRQL in individual patients, as well as factors which might encumber proper interpretation of the data obtained. Additionally, studies showing better HRQL outcomes in management strategies guided by HRQL measurements as compared to conventional management strategies would validate this approach. Methods to assess individual validity and patient acceptability of HRQL have been used in other diseases,[29,30] however, not in food allergy. Although the instruments used in this study to measure HRQL have characteristics suggesting they may be capable of providing valid HRQL assessments at the level of individual patients,[20] further research is required in this area.

This study shows that disease severity as perceived by patients is predictive of food allergy related quality of life. This is likely to be different form the physician's perception of the patient's disease severity. For example, physicians find prior anaphylaxis important, a view that is apparently not shared by patients to a great extent. Being aware of this disconnect is important in managing food allergic patients. In the future, measuring

perceived disease severity by means of the FAIM or other instrument(s) may prove useful as a more objective way of ascertaining the patient's experience of their condition.

Strength of this study is the number of countries which participated in the Europrevall project. We were able to investigate predictors of HRQL of food-allergic patients with a great variety of participant characteristics using self-administered instruments only.

A limitation of this study is that the clinical information collected in the questionnaires was patient-reported. No clinical test results were available to check the accuracy of the diagnoses. However, it has been shown that a self-perceived food allergy may impair HRQL at least as much as a confirmed food allergy.[31]

Another limitation of this study is the lack of teenagers. This interesting age-group has its own HRQL issues. It might therefore be worthwhile to investigate whether HRQL of this age-group can be predicted by participant characteristics as well.

Another limitation of this study is that we did not collect information about individuals who declined to participate, and therefore differences between participants and non-participants could not be assessed. Our results thus await confirmation in larger studies.

Another limitation of this study may be that as yet unidentified factors not reported in our data have not been included or identified. However, the explained variance in adults was high, suggesting that the factors discovered here are important predictors of HRQL in food allergic adults. Further study will be necessary to improve prediction in children.

A limitation is that HRQL measures are valid for group measurements, and therefore further research is needed on which HRQL measures are valid at the level of individual patients to guide clinical practice.

A final limitation is the lack of longitudinal data to investigate the effect of experiencing anaphylaxis and being prescribed an EAI on HRQL. However, both research questions are difficult to investigate prospectively or longitudinally for practical and ethical reasons. The variety of medical cultures captured in this multinational study has given us the possibility to study different sub-groups of patients including those who have experienced anaphylaxis and were not prescribed an EAI.

In conclusion, this is the first study to comprehensively study and to identify factors other than self-perceived disease severity to predict HRQL of food-allergic adults (≥ 18 years) and children (8-12 years) in Europe. For adults type of allergenic food, type of symptoms, and gender are important predictors. For children type of allergenic food and country of origin are important predictors. Surprisingly, experiencing anaphylaxis or being prescribed an EAI do not seem to be related to HRQL of either food-allergic adults or children. Awareness of some of these predictors may be helpful to guide the development of interventions such as food labeling to minimize the impact of having a food allergy on HRQL. The reasons for the differences found in HRQL between countries are an important area for future research.

ACKNOWLEDGEMENTS

This research is supported by the EU through the EuroPrevall project (Food-CT-2005-514000) and GUIDE Research Institute Groningen, the Netherlands.

REFERENCES

(1) Lieberman JS, Scott. Quality of life in food allergy. Current opinion in allergy and clinical immunology 2011;11(3):236-242.

(2) Sicherer S. Food allergy. Mt Sinai J Med 2011;78(5):683-696.

(3) Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy 2009 Jan;39(1):127-137.

(4) Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, et al. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. J Allergy Clin Immunol 2008 Jul;122(1):139-44, 144.e1-2.

(5) Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, et al. Development and validation of the Food Allergy Quality of Life Questionnaire - Adult Form. Allergy 2009 Aug;64(8):1209-1217.

(6) Goossens NJ, Flokstra-de Blok BM, van der Meulen GN, Arnlind MH, Asero R, Barreales L, et al. Health-related quality of life in food-allergic adults from eight European countries. Ann Allergy Asthma Immunol 2014 Jul;113(1):63-68.e1. (7) Goossens NJ, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Duiverman EJ, Weiss CC, Furlong TJ, et al. Online version of the food allergy quality of life questionnaire-adult form: validity, feasibility and cross-cultural comparison. Clin Exp Allergy 2011 Apr;41(4):574-581.

(8) Primeau, M N Kagan, R Joseph, L Lim, H Dufresne, C Duffy, C Prhcal,D Clarke, A. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. Clinical and experimental allergy 2000;30(8):1135-1143.

(9) Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. Ann Allergy Asthma Immunol 2001 Dec;87(6):461-464.

(10) Cohen, Benjamin Noone, Sally Muñoz Furlong,Anne Sicherer, Scott. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol 2004;114(5):1159-1163.

(11) Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life in food hypersensitive schoolchildren and their families: parents' perceptions. Health Qual Life Outcomes 2006 Aug 10;4:48.

(12) Pinczower GD, Bertalli NA, Bussmann N, Hamidon M, Allen KJ, DunnGalvin A, et al. The effect of provision of an adrenaline autoinjector on quality of life in children with food allergy. J Allergy Clin Immunol 2013 1;131(1):238-240.e1.

(13) Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. Allergy 2010 Aug;65(8):933-945.

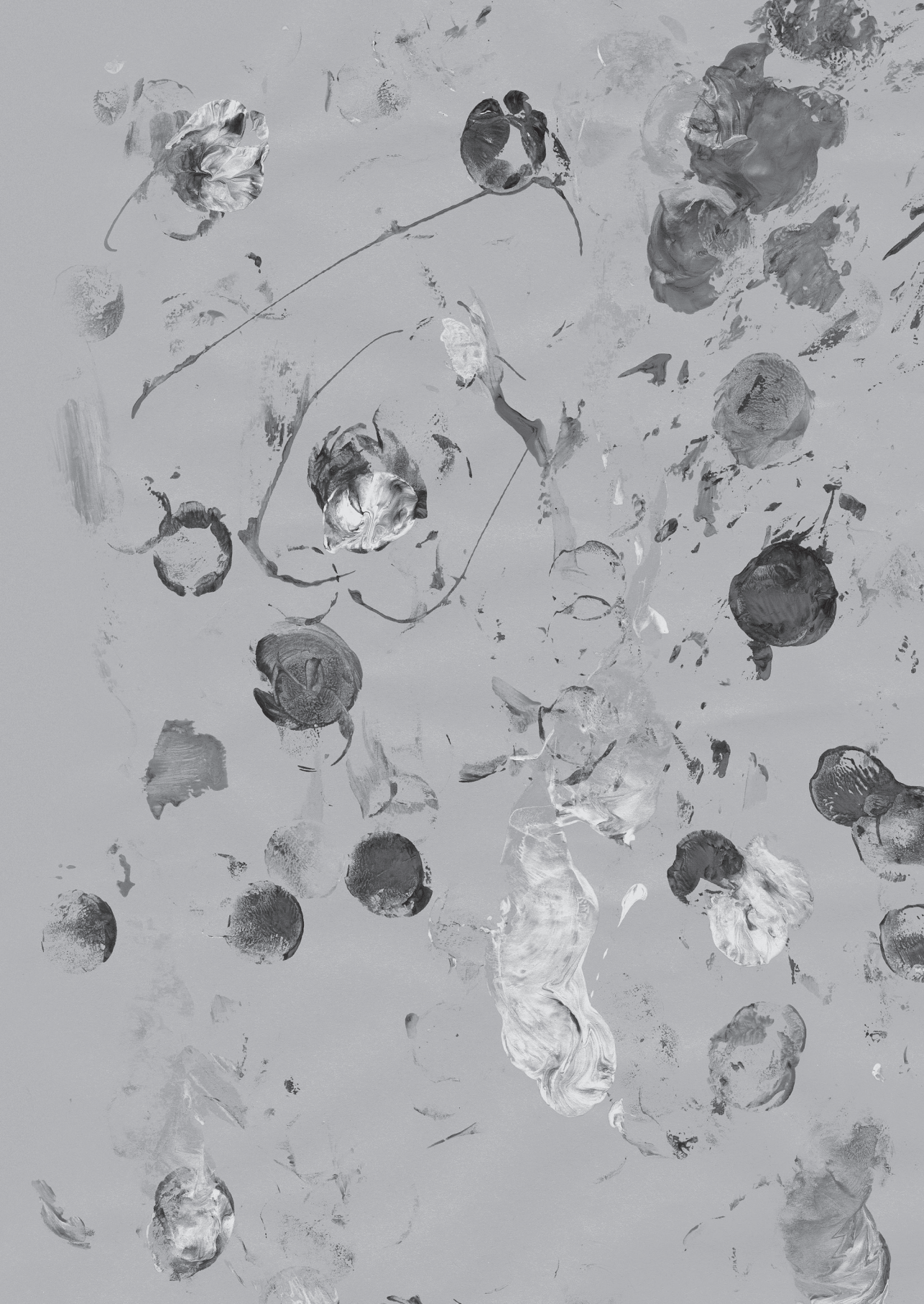
(14) Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JS. Management of nut allergy influences quality of life and anxiety in children and their mothers. Pediatr Allergy Immunol 2010 Jun;21(4 Pt 1):586-594.

(15) MacKenzie H, Dean T. Quality of life in children and teenagers with food hypersensitivity. Expert Rev Pharmacoecon Outcomes Res 2010 Aug;10(4):397-406.

(16) Oude Elberink JN, van der Heide S, Guyatt GH, Dubois AE. Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis. J Allergy Clin Immunol 2006 Sep;118(3):699-704.

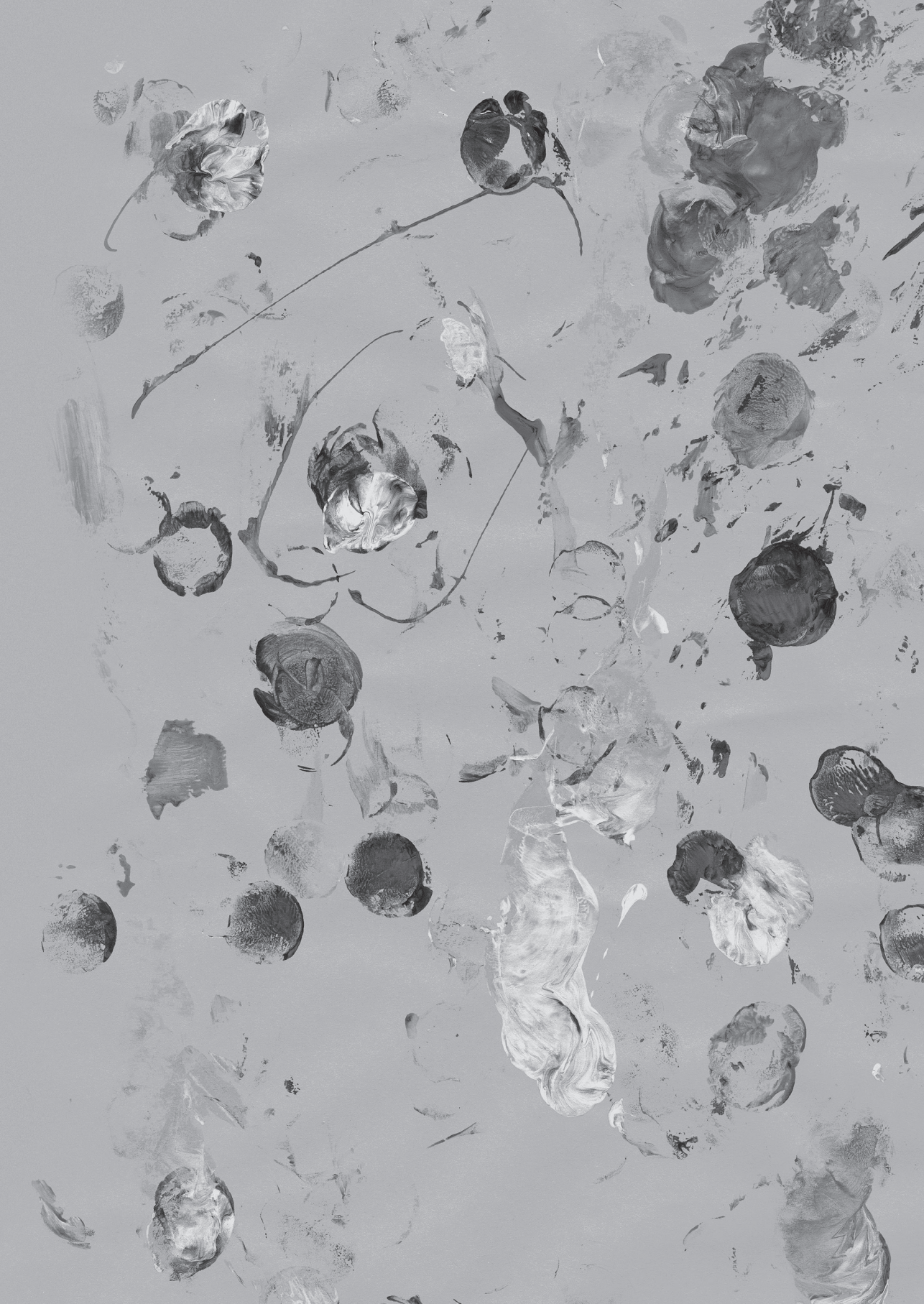
(17) Flokstra-de Blok BM, DunnGalvin A, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, Hourihane JO, et al. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy 2009 Jan;39(1):127-137.

(18) van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Oude Elberink JN, DunnGalvin A, Hourihane JO, et al. Development, validity and reliability of the food allergy independent measure (FAIM). Allergy 2010 May;65(5):630-635.
(19) Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF,Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006 Feb;117(2):391-397.
(20) Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy 2014 Aug;69(8):1008-1025.
(21) van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Oude Elberink JN, Schouten JP, Dunngalvin A, et al. Test-retest reliability of the Food Allergy Quality of Life Questionnaires (FAQLQ) for children, adolescents and adults. Qual Life Res 2009 Mar;18(2):245-251.
(22) Springston, Elizabeth Smith, Bridget Shulruff, Joshua Pongracic, Jacqueline Holl,Jane Gupta, Ruchi. Variations in quality of life among caregivers of food allergic children. Annals of allergy, asthma, & immunology 2010;105(4):287-294.
(23) Marklund, Birgitta Ahlstedt,Staffan Nordström, Gun. Health-related quality of life among adolescents with allergy-like conditions - with emphasis on food hypersensitivity. Health and quality of life outcomes 2004;2:65-65.
(24) Jowett SR, T. Skin disease and handicap: an analysis of the impact of skin conditions. Soc Sci Med 1985;20(4):425-429.
(25) Hong, Judith Koo,Bonnie Koo, John. The psychosocial and occupational impact of chronic skin disease. Dermatologic therapy 2008;21(1):54-59.
(26) DunnGalvin, A Hourihane, J O'B Frewer, L Knibb, R C Oude Elberink,J N G Klinge, I. Incorporating a gender dimension in food allergy research: a review. Allergy 2006;61(11):1336-1343.
(27) Leung TF, Yung E, Wong YS, Li CY, Wong GW. Quality-of-life assessment in Chinese families with food-allergic children. Clin Exp Allergy 2009 Jun;39(6):890-896.
(28) Goossens NJ, Flokstra-de Blok BMJ, van der Meulen G, Arnlind M, Asero R, Barrealer L. Validation and cross-cultural comparison of the 'Food Allergy Quality of Life Questionnaire - Child Form' in European Countries (submitted).
(29) Kocks JW, Kerstjens HA, Snijders SL, de Vos B, Biermann JJ, van Hengel P, et al. Health status in routine clinical practice: validity of the clinical COPD questionnaire at the individual patient level. Health Qual Life Outcomes 2010 Nov 16;8:135-7525-8-135.
(30) Moores KL, Jones GL, Radley SC. Development of an instrument to measure face validity, feasibility and utility of patient questionnaire use during health care: the QQ-10. Int J Qual Health Care 2012 Oct;24(5):517-524.
(31) van der Velde, Jantina L Flokstra-de Blok, Bertine M J de Groot, Hans Oude-Elberink, Joanne N G Kerkhof, Marjan Duiverman, Eric Dubois,Anthony E J. Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents, and children. J Allergy Clin Immunol 2012;130(5):1136-1143.e2.



Part III

Non-use



Chapter 6

Incomplete and incorrect patient epinephrine auto-injector training by pharmacists in the Netherlands

J. Saleh-Langenberg
S. de Vries
E. Bak
B.M.J. Flokstra-de Blok
B.J. Kollen
A.E.J. Dubois

Revision submitted at Pediatric Allergy and Immunology (PAI), October 2016

ABSTRACT

Background: Anaphylaxis is a severe, progressive, allergic reaction that is rapid in onset and can cause death. Successful treatment of anaphylaxis in the community relies on early and correct use of epinephrine auto-injectors (EAI). In the Netherlands pharmacists supply EAIs to patients and have a crucial role in instructing patients in how and when to use EAI. However, there are currently no data in Europe on the quality of such instruction provided by pharmacists.

Objective: The aims of this study were to investigate the knowledge, attitudes, and beliefs regarding food allergy among pharmacists in the Netherlands, and to investigate the quality of EAI instructions and demonstrations to patients by pharmacists.

Methods: Pharmacists were asked to complete an online questionnaire. Quality of instructions and demonstration accuracy were assessed in mystery guest visits to randomly selected pharmacies. Pharmacists were asked to fill a prescription for an EAI (Epipen® or Jext®) by the mystery guest. The mystery guest assessed whether or not the pharmacist gave correct instructions and adequately demonstrated the use of an EAI using a checklist. For the statistical analysis descriptive methods were used.

Results: In total 25 out of 115 questionnaires were completed (response rate 22%). Eight (32%) respondents gave wrong answers regarding the correct administration site. Only two (8%) respondents gave correct answers concerning the proper EAI demonstration. Twenty-one (84%) respondents thought that the provision of instructions was the responsibility of pharmacists. In total, ten pharmacies were included in simulated patient visits. Five of them (50%) demonstrated the EAI. None of them demonstrated the EAI use correctly.

Conclusion: Food-allergic patients at high risk for anaphylaxis who receive their EAI from a community pharmacy in the Netherlands are often not instructed on how to use an EAI or receive incorrect instructions. Pharmacists show considerable gaps in knowledge about food allergy and its management. These data suggest that opportunities exist to improve the quality of care provided by pharmacies to high risk food-allergic patients.

INTRODUCTION

The need for improved epinephrine auto-injector (EAI) training has been a recurring theme in the literature on anaphylaxis.[1-3] Anaphylaxis usually occurs in the community, and therefore, all food-allergic patients at risk for anaphylactic reactions as well as their parents (and other caregivers) should be provided with educational resources. Training should cover avoidance strategies, recognition of symptoms, and when and how to administer an EAI. Physicians prescribing an EAI should provide such EAI training, although it has been shown that failure to provide this is commonplace.[4,5] Pharmacists are obliged to give instructions when they supply medications to patients and Dutch pharmacies charge each patient a certain amount for explaining how the medicine is to be used.

A previous study showed that general practitioners (GPs) in the Netherlands feel that giving instructions about how and when to use an EAI is the responsibility of pharmacists.[6] Therefore pharmacists have a crucial role training patients in how and when to use an EAI. However, there are currently no data on the quality of instructions given by pharmacists regarding the use of the EAI. Studies in this area are limited to evaluation of EAI demonstration rates and open assessment of EAI demonstration steps.[7-12] There is, to our knowledge, no study assessing real-world EAI instructions and demonstrations by pharmacists in Europe.[13]

Our primary aim was to investigate the knowledge, attitudes, and beliefs regarding food allergy and anaphylaxis among pharmacists in the Netherlands as the quality of instructions, on which there is currently no data, may depend on such knowledge.

Secondly, we aimed to investigate how accurately community pharmacists in the Netherlands demonstrate how and when to use an EAI to patients.

METHODS

Study population

The study population consisted of pharmacists who were currently working in a pharmacy in the Northern part of the Netherlands.

Pharmacies were recruited through two associations: (1) the Frisian Pharmacists Association (*Friese Apotheken Vereniging* (FAV)) and (2) Groningen Pharmacists Association (*Groningen Apotheken Vereniging* (GAV)). These associations represent all pharmacies of the Dutch provinces Friesland, Groningen and Northern part of Drenthe. The pharmacists were asked to complete an online questionnaire and to participate in a mystery guest visit. This study was conducted between March-October 2015. Participation was voluntary.

Study procedures

Pharmacists were invited to participate in this study by a personal invitation by e-mail containing a hyperlink to the online questionnaire and were asked for their informed consent for a mystery guest visit at their pharmacy. After entering the website, the participants were asked whether they were currently practicing or not. If this question was completed affirmatively, the survey started automatically. Pharmacies were informed that the results of the mystery guest visit would be used to improve quality of care. No information about the study and purpose of the visit was revealed. A random sample of pharmacies who gave their informed consent to a mystery guest visit was selected. For the mystery guest visit a fixed scenario was used and data collection tool capturing demographic variables (type/location of pharmacy, hour of visit, total number of personnel, number of waiting patients, gender and estimated age), and self-injectable epinephrine variables (materials used for demonstration, use of references, steps used in demonstration, errors or omissions in demonstration and other advice provided). Prior to the study, the usability of the scenario was assessed. The data collection tool was evaluated for usability in a round-table discussion.

Online questionnaire

The questionnaire used for this research was previously validated in general practitioners (manuscript submitted), and was adapted for pharmacists in this study. A pre-test was performed with two pharmacists. They were asked to complete the online questionnaire and comment on the content and format of the questionnaire. After this pre-test, the online questionnaire was modified slightly based on their comments. Changes were made to the wording of some of the questions, but not to the content. All data was entered into a database. During the study, an independent auditor cross-checked data entered in the database. Data in disagreement were corrected in the database prior to analysis.

The questionnaire contained 56 questions to investigate food allergy knowledge, EAI experience, and attitudes and beliefs among the pharmacists. The questionnaire was divided into four categories: (1) participant characteristics (n=8); (2) knowledge items (n=34); (3) EAI experience items (n=11), and (4) attitudes and beliefs items (n=3).

Characteristics of participating pharmacies

Data on the characteristics of participating pharmacies were collected. Of the eight participant characteristics items there were four items regarding personal characteristics, three items regarding work related issues, and one item regarding a food-allergy related issue.

Pharmacists' knowledge

Of the 34 knowledge items, one item had multiple responses and the other items were multiple-choice questions. In addition, participants were able to answer every knowledge item with '*I don't know*'. Overall knowledge scores of participants were calculated by counting all correctly answered knowledge items. Percentages of participants who answered the individual knowledge items correctly and incorrectly were calculated.

Pharmacists' EAI experience

Of the eleven experience items, three items consisted of a multiple-choice question, two items consisted of multiple-choice scaling (yes/no/don't know/not applicable), and two items consisted of multiple-choice scaling (never/now and then/sometimes/ almost always/always). In addition, participants were able to answer every EAI experience item with '*I don't know*' or '*not applicable*'. Overall EAI experience scores of participants were calculated by counting all correctly answered EAI experience items. Percentages of participants who answered the individual EAI experience items correctly and incorrectly were calculated.

Pharmacists' attitudes and beliefs

Of the three attitudes and beliefs items, one item consisted of seven statements with multiple-choice scaling (agree/disagree/don't know), one item consisted of a multiple-choice question, and one item consisted of an open-ended question for suggestions or improvements of quality of care for food-allergic patients. Overall knowledge scores of participants were calculated by counting all correctly answered attitudes and beliefs items. Percentages of participants who answered the individual attitudes and beliefs items correctly and incorrectly were calculated.

Mystery guest visits

The scenario for the mystery guest visit was initiated by the mystery guest asking for the pharmacist to fill a prescription for an EpiPen® or Jext®. Pharmacies were randomly assigned to fill a prescription for an EpiPen® or Jext®. The mystery guest practised the role of the simulated patient, and learnt a script so that all responses to the pharmacists' questions were similar. Questions that might be asked by the pharmacist were anticipated and responses practised during a training session. If a pharmacist asked any question beyond those anticipated and for which responses had not been prepared, the mystery guest answered either "I can't remember" or "I don't know".

The mystery guest was a medical student with an allergy to peanut, tree nuts and sesame seeds, and a trained EAI user. She was accompanied by a researcher who was also a medical student, and who observed the demonstration and made an audio recording of the meeting. If the mystery guest recognised the pharmacist or pharmacy assistants on duty, the visit was abandoned and the pharmacy excluded.

The mystery guest would wait and see whether the pharmacist explained how and when to use the EAI. Accurate demonstration of EAIs was defined as one that successfully completed all ten steps (Table 1)[14,15]

Errors and omissions in demonstration were (voice) recorded, along with materials used for demonstration and any additional advice provided by the pharmacist.

Immediately after the visit the researcher completed a data collection tool and subsequently entered data into a database [SPSS version 20.0, SPSS Inc. Chicago, IL, USA].

Table I. Ten demonstrations steps for EAI

Step	Demonstration
1	Grasps the EAI firmly
2	Has thumb closest to the safety cap
3	Removes safety cap with other hand
4	Holds EAI about 10cm away from injection area or places gently the injector tip against mid-anterolateral thigh
5	Demonstrates the thigh as injection area
6	Place and press the tip of EAI firmly into mid-anterolateral thigh until a 'click' is heard confirming the injection has started
7	Holds the EAI firmly in place for 10 seconds
8	Removes EAI
9	Massages the injection area for 10 seconds
10	Gives instructions to call emergency number to ask for an ambulance and say "anaphylaxis"

Statistical analyses

Statistical analyses were primarily descriptive. Overall knowledge scores and percentages were calculated by counting all correct knowledge -, EAI experience - and attitudes and beliefs items. All analyses were performed using SPSS version 20.0, SPSS Inc. Chicago, IL, USA.

Ethical approval

This study was approved by the local medical ethics review commission who deemed that no further approval was required from the Medical Ethical Committees of the University Medical Centre Groningen. Participants were asked to participate voluntarily in the present study and were only able to enter the online questionnaire after reading the information and instructions page. Completing the online questionnaire after reading this information was taken as an informed consent. Participants were asked in writing to participate in a mystery guest visit and had to reply to give their informed consent.

RESULTS

Study population

In total, 115 pharmacies in the Northern part of the Netherlands were asked to complete an online questionnaire and to participate in a mystery guest visit: 55 through the *Frisian Pharmacists Association* and 60 through *Groningen Pharmacists Association*.

Online questionnaire

Characteristics of participating pharmacies

In total 25 pharmacists completed the online questionnaire (response rate 22%) and were eligible for analysis. The majority of the participants who completed the online questionnaire were female (n=19), and also the majority of them had a private practice. Participant characteristics are shown in Table II.

Pharmacists' knowledge

The mean overall knowledge score of participants was nineteen out of 34, which means that 55% of the knowledge items were answered correctly (Table III). The individual item with the highest score was '*Adrenaline is a natural hormone that is produced by the body*', which was answered correctly by all participants (100%) (Table III). The item with the lowest score was '*What is the highest dose of epinephrine for adults after a severe allergic reaction*', which was answered correctly by one participant (4%) (Table III).

Table II. Participant characteristics of online questionnaire (n=25)

Characteristic		n(%)
Gender	Male	5 (20.0)
	Female	19 (76.0)
	Total	24 (96.0)
	Missing data	1 (4.0)
	Total	**25 (100)**
Age (years)	25-30	4 (16.0)
	31-35	3 (12.0)
	36-40	4 (16.0)
	41-45	5 (20.0)
	46-50	4 (16.0)
	51-55	1 (4.0)
	56-60	3 (12.0)
	61-65	1 (4.0)
	Total	**25 (100)**
Function	Pharmacist	25 (100)
	Total	25 (100)
Type of pharmacy	Indepenent	14 (56.0)
	Healtcare center based	11 (44.0)
	hospital based pharmacy	0 (0.0)
	Total	**25 (100)**
Food allergic acquintance	Yes, him/herself	5 (20.0)
	Yes, spouse/partner/child	1 (4.0)
	Yes, brother/sister, caretaker	0 (0.0)
	Yes, relative/friend	5 (20.0)
	No	14 (56.0)
	Total	**25 (100)**

Table III. Knowledge

Knowledge questions	Answers							
	Correct		Incorrect		Don't know		Missing data	
	N	%	N	%	N	%	N	%
1. How often EAI is prescribed for apple allergy	13	52	12	48	/	/	0	0
2. Food component that causes food allergic reactions	24	96	1	4	0	0	0	0
3. Age group most likely to have food allergy	16	64	5	20	3	12	1	4
4. Timely administration of epinephrine prevents fatal anaphylaxis	18	72	4	16	3	12	0	0
5. Number of EAI's that are prescribed to children <12 years of age	4	16	21	84	/	/	0	0
6. Shelf-life of an EAI after production	6	24	19	76	/	/	0	0
7. Use of EAI after expiry date	16	64	8	32	/	/	1	4
8. Dose of epinephrine, child weight 27 kg	19	76	4	16	2	8	0	0
9. The highest dose of epinephrine for adults after severe allergic reaction	1	4	17	68	6	24	1	4
10. Onset of symptoms after accidental ingestion (time)	3	12	21	84	/	/	1	4
11. Type of injection (intra muscular)	17	68	8	32	/	/	0	0
12. Injection site	17	68	8	32	0	0	0	0
13. Using EAI when allergic reaction is not sure	12	48	12	48	/	/	1	4
14. Duration of holding the EAI firmly in place	16	64	8	32	/	/	1	4
15. Duration of massaging the injection area	12	48	12	48	/	/	1	4
16. Instructions to patients after using EAI	11	44	13	52	/	/	1	4
17. When to use second dose of epinephrine	17	68	6	24	/	/	2	8
18. Law for mandatory labeling of 14 allergenic ingredients on every food label	3	12	16	64	5	20	1	4

Table III. (continued)

Knowledge questions	Answers							
	Correct		Incorrect		Don't know		Missing data	
	N	%	N	%	N	%	N	%
19. Asthma is an important risk factor for severe anaphylaxis	16	64	7	28	2	8	0	0
20. Teenagers are at higher risk for fatal anaphylaxis than younger children	5	20	13	52	7	28	0	0
21. Food allergens are passed from maternal diet into breast milk	18	72	4	16	3	12	0	0
22. The number of children with food allergies in the Netherlands is increasing	22	88	1	4	2	8	0	0
23. There are no absolute contra-indications for prescribing an EAI	14	56	7	28	4	16	0	0
24. Instructions on how to use an EAI are shown on the device itself	20	80	2	8	2	8	1	4
25. A holiday destination influences how many EAIs are prescribed to a patient	14	56	7	28	4	16	0	0
26. Adrenaline is a natural hormone that is produced by the body	25	100	0	0	0	0	0	0
27. Law for administering EAI by public employees (e.g. at schools)	15	60	4	16	6	24	0	0
28. Immediate use of EAI after onset allergic symptoms	5	20	14	56	5	20	1	4
29. Daily antihistamine can prevent food allergic reaction	16	64	4	16	5	20	0	0
30. There is a cure for food allergy	20	80	1	4	4	16	0	0
31. An EAI cannot be injected through clothing	21	84	2	8	1	4	1	4
32. Adrenaline tablets can be prescribed to patients having an allergic reaction	25	100	0	0	0	0	0	0
33. Mild allergic reactions before severe life-threatening allergic reaction in 1 out of 10 patients	7	28	13	52	5	20	0	0
34. Three most common childhood food allergens	3	12	22	88	0	0	0	0

Pharmacists' EAI experience

The majority of participants (52%) filled prescriptions for children over 15 years of age. Twenty-four participants (96%) answered that of all prescriptions that they filled less than five percent was for the treatment of food allergy.

Eleven participants (44%) gave instructions most of the time on how to use an EAI to patients, six participants (24%) sometimes gave instructions and eight occasionally gave instructions. The majority of them did not use an EAI trainer to explain how to use an EAI (88%) and patients did often not get the opportunity to practice themselves with an EAI trainer at the pharmacy (92%).

Seventeen participants (71%) did not instruct patients to consult national reference materials including patients' information websites. Seven participants (29%) always gave flyers to the patient when filling a prescription of an EAI.

Pharmacists' attitudes and beliefs

The majority of the participants (42%) believed that identifying the cause of food allergy is most important to help food allergic patients.

Most participants did not agree with the following statements: *'My education adequately prepared me to care for food allergic patients'*, *'Pharmacists and pharmacy assistants are knowledgeable about food allergy and its management'* and *'General practitioners are more responsible than pharmacists for giving instructions about the EAI to food allergic patients'* (Table IV).

Most participants agreed with the following statements: *'Confident in my ability to care for patients with food allergy and an EAI'* and *'Food allergic patients know how to use their EAI'* (Table IV).

Mystery guest visits

In total, fifteen pharmacies gave their informed consent for a mystery guest visit. Ten of them were selected for a mystery guest visit. All ten of them were included for analysis. Eight pharmacies were asked to fill a prescription of EAI® and two were asked to fill a prescription of Jext®. See Table V for pharmacy and participant characteristics.

Demonstration accuracy and errors

Half of the pharmacists (50%) demonstrated how to use an EAI. Of the pharmacists who agreed to demonstrate how to use an EAI, none of them demonstrated the device (Epipen®) correctly according to the ten step scoring system (Figure 1). One pharmacist demonstrated all steps incorrectly.

Table IV. Attitudes and beliefs

Attitudes and beliefs statements	Answers					
	Agree		Disagree		Don't know	
	N	%	N	%	N	%
1. In public places an epinephrine auto-injector should be kept just like an automatic external defibrillator	6	23	11	44	8	8
2. Pharmacists and pharmacy assistants are knowledgeable about food allergy and its management	7	28	8	32	10	40
3. My education adequately prepared me to care for food allergic patients	2	8	20	80	3	12
4. Confident in my ability to care for patients with food allergy and an EAI	14	56	3	12	8	32
5. Food allergic patients know how to use their EAI	19	76	2	8	4	16
6. General practitioners are more responsible for giving instructions about the EAI to food allergic patients	3	12	21	84	1	4
7. Most people take food allergy seriously	16	64	7	38	2	8

The most frequent errors in demonstration were '*massage injection site after use*' (100%) and '*call the emergency number to ask for an ambulance and say "anaphylaxis"* ' (100%). Other common errors were failure to state to press the tip of EAI firmly into mid-anterolateral thigh until a 'click' is heard confirming the injection has started, and incorrect positioning of the thumb over the needle of the EAI.

Demonstration materials and anaphylaxis advice

Of the five pharmacists who demonstrated how to use an EAI three of them (60%) consulted reference materials including books, websites and the device itself prior to attempting to demonstrate. One pharmacist (10%) gave information about how and where to store an EAI, another pharmacist (10%) gave information about the side effects of adrenaline. Two pharmacists (20%) mentioned to regularly check the expiry date of the EAI. None of the pharmacists explained the signs of anaphylaxis, asked if the mystery guest was aware of the precipitating allergen or checked if the mystery guest had an anaphylaxis action plan.

Figure 1. Demonstration accuracy and errors (n=5)

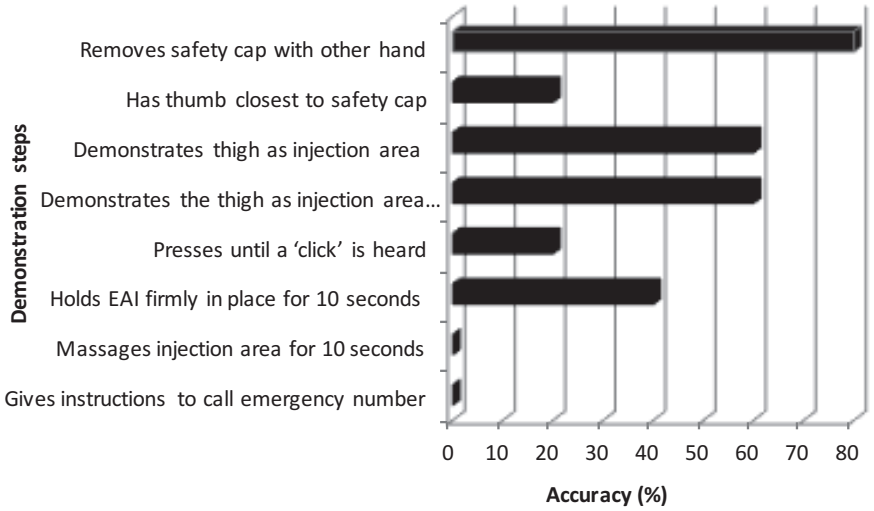


Table V. Pharmacy and participant characteristics of mystery guest visits (n=10)

Characteristic	n (%)
Pharmacy	
Type/location	
independent	6 (60)
healtcare center based pharmacy	3 (30)
hospital based pharmacy	1 (10)
Mystery guest visit	
Time of visit	
08:00am - 11:00am	6 (60)
11:00am - 02:00pm	4 (40)
02:00pm – 06:00pm	0 (0)
Number of personnel	
1-2	1 (10)
3-4	2 (20)
5-6	4 (40)
7 or more	3 (30)
Number of waiting patients	
1-2	6 (60)
3-4	2 (20)
5-6	2 (20)
Pharmacist	
Gender	
Male	0 (0)
Female	10 (100)
Estimated age (years)	
20-30	3 (30)
31-40	2 (20)
41-50	1 (10)
51-60	3 (30)
60+	1 (10)

DISCUSSION

This is the first study to investigate the knowledge, attitudes, and beliefs regarding food allergy among pharmacists in the Netherlands and the quality of EAI use instructions. However, our study showed that there are knowledge gaps about food allergy and its management among pharmacists in the Netherlands, and that they often give incorrect and incomplete demonstration of EAI use.

Anaphylaxis usually occurs in the community, and thus all food-allergic patients and their family should be provided with educational resources and training about when and how to administer an EAI. A previous study by Saleh-Langenberg et al.[6] showed that general practitioners in the Netherlands feel that giving instructions about how to use an EAI is the responsibility of the pharmacist. Therefore, it is necessary that pharmacists in the Netherlands know about food allergy and its management. Even though most pharmacists reported that they are confident that their knowledge is sufficient to care for food allergic patients, a suboptimal knowledge about food allergy of pharmacists in the Netherlands was found in this study. This is an important addition to the previously reported international lack of allergy knowledge.[6,16-18]

In addition, pharmacists need to know how to correctly demonstrate the use of an EAI. However, our study shows that of the pharmacists who agreed to demonstrate how to use an EAI, none of them demonstrated the device correctly according to the ten step scoring system. Errors made by pharmacists in this study are in keeping with other studies.[7,9,10,12,13,19,20] For example, van Dijk et al.[21] also showed that when dispensing first or repeat prescription medications at the pharmacy counter, pharmacy staff do provide medication-related information, but this information is incomplete according to the professional guidelines of the pharmacist organization.

Other frequent errors in demonstration were failure to activate the device, to hold it firmly for ten seconds after the injection and incorrect positioning of the thumb. These errors are of concern. The instructions given by the pharmacist may lead to a patient not receiving epinephrine or unintentional injection of epinephrine from these devices. Although the true rate of occurrence of unintentional injection of epinephrine from auto-injectors is unknown, it is said to be increasing.[22] These data suggest that opportunities exist to improve the EAI demonstration by pharmacists to food-allergic patients.

Pharmaceutical care in European countries are quite diverse because of legal, political and healthcare systems and because practices have developed in different ways and at different paces in different countries.[23-27] To our knowledge there are no studies investigating the knowledge, attitudes, and beliefs regarding food allergy among pharmacist elsewhere in Europe. One may speculate that opportunities to improve EAI demonstrations by pharmacists to food-allergic patients may be of international concern. In addition, it has been shown that there is a good effect of pharmaceutical

care for asthma patients in community pharmacies: it showed a significant impact on economic, clinical and humanistic outcomes.[23] Asthma seems to be a disease to which applying pharmaceutical care can be very successful.[23] One might speculate that applying pharmaceutical care to food allergy may be successful too.

Strengths and limitations

Strength of this study is the use of mystery guest visits. This technique is well described in the literature as a measuring tool.[28] By posing as a regular customer, the mystery guest can map experiences and provide practical insights for quality improvement. Another strength is that we voice recorded the demonstration between the pharmacist and the mystery guest, therefore recall bias was limited to the minimum.

A limitation in this study is the number of mystery guest visits. Although generalizability might be limited, they are no assumptions there are any form of bias how we choose our pharmacies.

In summary, pharmacists show considerable gaps in knowledge about food allergy and its management. Food-allergic patients at high risk for anaphylaxis who receive their EAI from a pharmacy in the Netherlands are often not or incorrectly instructed on how to use an EAI. Given the importance of timely and correct administration of epinephrine in case of a (severe) food allergic reaction, improvement of demonstration accuracy is promptly needed. These data suggest that opportunities exist to improve the quality of care provided by pharmacies to food-allergic patients.

ACKNOWLEDGEMENTS

We would like to thank the Frisian Pharmacists Association (Friese Apotheken Vereniging (FAV)) and the Groningen Pharmacists Association (Groningen Apotheken Vereniging (GAV)) for helping with the recruitment. We also would like to thank P. Davids (webdirector at University Medical Centre Groningen, the Netherlands) for digitalizing the questionnaire.

REFERENCES

(1) Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol 2007 Apr;119(4):1016-1018.

(2) Sampson MA, Munoz-Furlong A, Sicherer SH. Risk-taking and coping strategies of adolescents and young adults with food allergy. J Allergy Clin Immunol 2006 Jun;117(6):1440-1445.

(3) Wahl, Ann Stephens, Hilary Ruffo,Mark Jones, Amanda. The Evaluation of a Food Allergy and Epinephrine Autoinjector Training Program for Personnel Who Care for Children in Schools and Community Settings. Journal of school nursing 2014.

(4) Kastner, M Harada,L Waserman, S. Gaps in anaphylaxis management at the level of physicians, patients, and the community: a systematic review of the literature. Allergy 2010;65(4):435-444.

(5) Waserman, S Chad, Z Francoeur, M J Small, P Stark, D Vander Leek, T K Kaplan,A Kastner, M. Management of anaphylaxis in primary care: Canadian expert consensus recommendations. Allergy 2010;65(9):1082-1092.

(6) Saleh-Langenberg Jacquelien J. Epinephrine auto-injector prescriptions to food-allergic patients in primary care in The Netherlands. Allergy, Asthma and Clinical Immunology 2015;11.

(7) Grouhi M, Alshehri M, Hummel D, Roifman CM. Anaphylaxis and epinephrine auto-injector training: who will teach the teachers? J Allergy Clin Immunol 1999 Jul;104(1):190-193.

(8) Hayman Grant R GR. Knowledge about using auto-injectable adrenaline: review of patients' case notes and interviews with general practitioners. BMJ: British Medical Journal 2003-12-6;327(7427).

(9) Mehr Sam S. Doctor--how do I use my EpiPen? Pediatric Allergy and Immunology 2007-8;18(5):448-52.

(10) Sicherer SH, Forman JA, Noone SA. Use assessment of self-administered epinephrine among food-allergic children and pediatricians. Pediatrics 2000 Feb;105(2):359-362.

(11) Brown Josephine J. A randomized maternal evaluation of epinephrine autoinjection devices. Pediatric Allergy and Immunology 2013-3;24(2):173-7.

(12) Arkwright Peter D PD. Factors determining the ability of parents to effectively administer intramuscular adrenaline to food allergic children. Pediatric Allergy and Immunology 2006-5;17(3):227-9.

(13) Salter Sandra M SM. Demonstration of epinephrine autoinjectors (EpiPen and Anapen) by pharmacists in a randomised, simulated patient assessment: acceptable, but room for improvement. Allergy, Asthma and Clinical Immunology 2014;10(1).

(14) How to use Jext. Available at: http://www.jext.co.uk/jext-video-demonstrations.aspx, 2015.

(15) How to use Epipen. Available at: https://www.epipen.com/en/about-epipen/how-to-use-epipen, 2015.

(16) Agache, I Ryan, D Rodriguez, M R Yusuf, O Angier,E Jutel, M. Allergy management in primary care across European countries -- actual status. Allergy 2013;68(7):836-843.

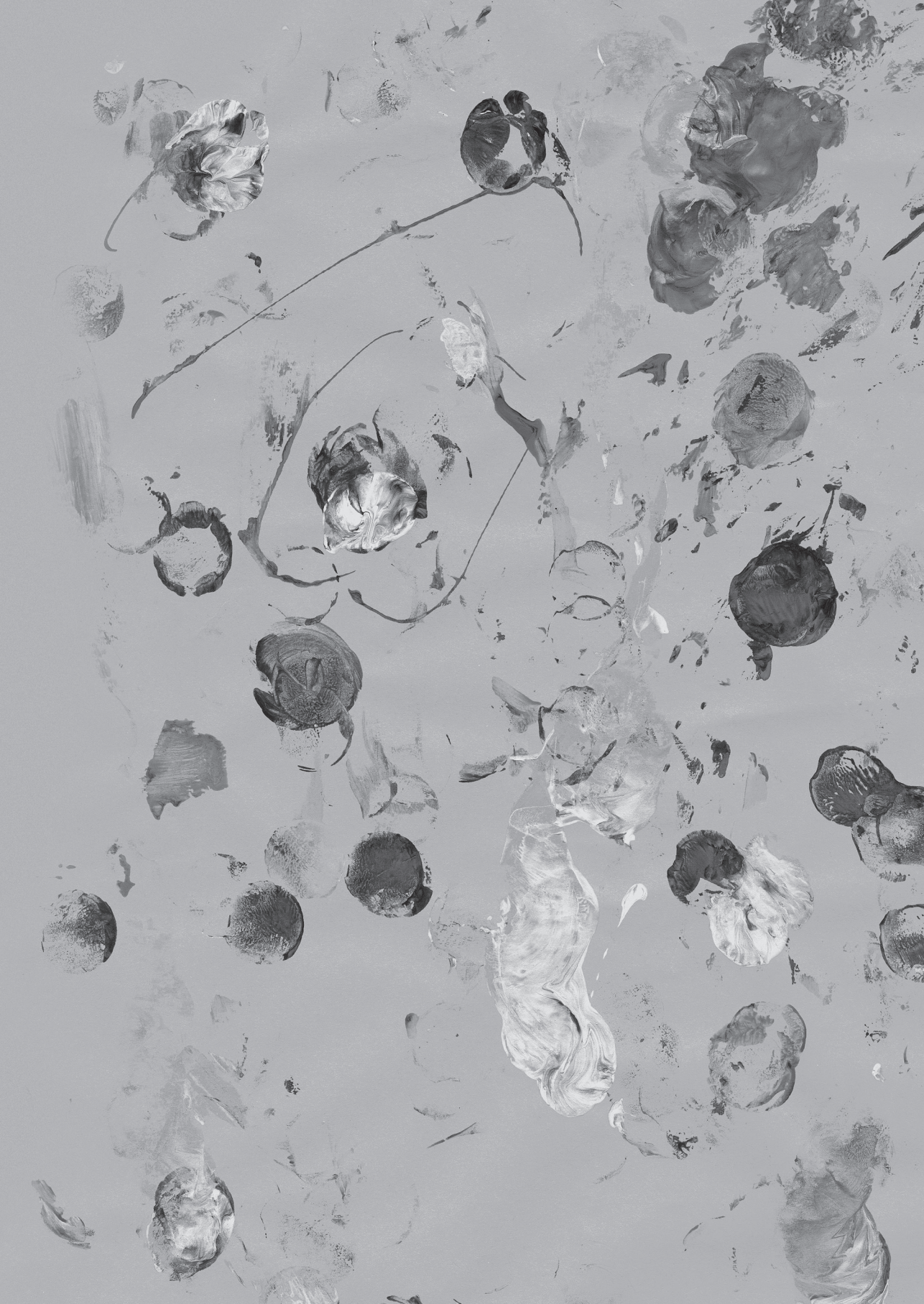
(17) Gupta, Ruchi Springston, Elizabeth Kim, Jennifer Smith, Bridget Pongracic, Jacqueline Wang,Xiaobin Holl, Jane. Food allergy knowledge, attitudes, and beliefs of primary care physicians. Pediatrics 2010;125(1):126-132.

(18) Gupta RS, Springston EE, Smith B, Kim JS, Pongracic JA, Wang X, et al. Food allergy knowledge, attitudes, and beliefs of parents with food-allergic children in the United States. Pediatr Allergy Immunol 2010 Sep;21(6):927-934.

(19) Arga M, Bakirtas A, Catal F, Derinoz O, Harmanci K, Razi CH, et al. Training of trainers on epinephrine autoinjector use. Pediatr Allergy Immunol 2011 Feb 10.

(20) Topal E, Bakirtas A, Yilmaz O, Karagol IH, Arga M, Demirsoy MS, et al. When should we perform a repeat training on adrenaline auto-injector use for physician trainees? Allergol Immunopathol (Madr) 2014 Sep-Oct;42(5):472-475.

(21) van Dijk M, Blom L, Koopman L, Philbert D, Koster E, Bouvy M, et al. Patient-provider communication about medication use at the community pharmacy counter. Int J Pharm Pract 2016 Feb;24(1):13-21.
(22) Simons FE, Lieberman PL, Read EJ,Jr, Edwards ES. Hazards of unintentional injection of epinephrine from autoinjectors: a systematic review. Ann Allergy Asthma Immunol 2009 Apr;102(4):282-287.
(23) van Mil JW, Schulz M. A review of pharmaceutical care in community pharmacy in Europe. Harvard Health Policy Review 2006;1(1):155.
(24) Christensen DB, Farris KB. Pharmaceutical care in community pharmacies: practice and research in the US. Ann Pharmacother 2006 Jul-Aug;40(7-8):1400-1406.
(25) Eickhoff C, Schulz M. Pharmaceutical care in community pharmacies: practice and research in Germany. Ann Pharmacother 2006 Apr;40(4):729-735.
(26) Guignard E, Bugnon O. Pharmaceutical care in community pharmacies: practice and research in Switzerland. Ann Pharmacother 2006 Mar;40(3):512-517.
(27) Noyce PR. Providing patient care through community pharmacies in the UK: policy, practice, and research. Ann Pharmacother 2007 May;41(5):861-868.
(28) Watson MC, Skelton JR, Bond CM, Croft P, Wiskin CM, Grimshaw JM, et al. Simulated patients in the community pharmacy setting. Using simulated patients to measure practice in the community pharmacy setting. Pharm World Sci 2004 Feb;26(1):32-37.



Chapter 7

Late reactions in food-allergic children and adolescents after double-blind, placebo-controlled food challenges

J. Saleh-Langenberg
B.M.J. Flokstra-de Blok
N. AlAgla
B.J. Kollen
A.E.J. Dubois

Allergy. 2016 Jul;71(7):1069-73

ABSTRACT

The time during which children are observed following a double-blind, placebo controlled, food-challenge (DBPCFC) varies in clinical practice. There is little data on late reactions (LRs) following DBPCFCs. Therefore, we determined the prevalence, severity and clinical characteristics of late reactions in food-allergic children and adolescents after DBPCFC, and ascertained which factors are associated with and may predict LRs. Logistic regression analyses were performed to investigate which factors were associated with LRs and to develop association and prediction models.

A total of 1142 children underwent DBPCFCs (child-test combinations). Of these 1142 child-test combinations, 400 reported LRs following the DBPCFC. LRs in food-allergic children after DBPCFC are poorly predictable, and are generally not severe. All LRs, including those on the placebo day, are more frequently reported in younger children. Children who do not experience severe immediate reactions may be safely discharged home 2 hours after a DBPCFC.

INTRODUCTION

IgE-mediated food allergies are known to trigger immediate reactions beginning within minutes to two hours from the time of ingestion. Initial clinical characteristics of anaphylaxis are well documented.[1] Late reactions (LRs) have also been reported and may present with a variety of symptoms, of which anaphylactic symptoms are the most severe. Other variants of the usual monophasic anaphylaxis include biphasic anaphylaxis and protracted anaphylaxis.

Biphasic anaphylaxis is defined as recurrence of symptoms that develop following the apparent resolution of the initial anaphylactic event which may not be ascribed to treatment. Biphasic reactions have been reported to develop in 1 to 20% of anaphylactic reactions and typically occur within one to four hours following the resolution of the initial symptoms,[2-5] although some cases have been reported up to 72 hours later.[6] Protracted anaphylaxis is defined as an anaphylactic reaction that lasts for hours or, in extreme cases, for days.[7]

The gold standard in the diagnosis of food allergies is the double-blind, placebo-controlled food challenge (DBPCFC).[8,9] A DBPCFC can result in immediate onset of symptoms, but late onset of symptoms has also been reported. However, there is little data on LRs following DBPCFCs in food-allergic children and adolescents and which patients are most at risk to develop them. Consequently, the time during which children are observed following a DBPCFC varies in clinical practice. Recommendations vary from between 2 to 24 hours.[10-12] Therefore, the aim of this study was to determine the prevalence, severity and clinical characteristics of late reactions in food-allergic children and adolescents after DBPCFC, and to ascertain which factors are associated with and may predict LRs.

METHODS

Children and adolescents in whom DBPCFCs with cow's milk, egg, peanut, cashew or hazelnut were performed between October 2001 and April 2014 were included. Patients with multiple food allergies were included. Patients whom underwent more than one challenge test for the same food allergen, only the first test was included. Patients were excluded if data were incomplete.

Active and placebo challenges were administered in a random order as determined by computer, and were administered on separate days with at least one week interval in between. Validation of adequate blinding of the test materials was achieved by sensory testing in a dedicated food laboratory.[13]

The challenge procedure included an incremental design in which progressively greater quantities of the same allergen were administered (Appendix I). The challenge was discontinued when objective allergic symptoms (angio)oedema, urticaria, exacerbation of atopic dermatitis, rash, vomiting, diarrhoea, lip or tongue swelling, rhinoconjunctivitis, stridor, coughing, wheezing, hoarseness, collapse, tachycardia and hypotension) occurred, or subjective allergic symptoms (exacerbation of generalized itch, abdominal pain, nausea and/or cramp, oral allergy symptoms, itchy throat or sensation of throat swelling, difficulty in swallowing, drowsiness and irritability) occurred twice on two successive administrations of the challenge material.[9] Forty-eight hours after the second challenge session, the code was broken and the outcome of the DBPCFC was assessed according to a protocol as described previously by Vlieg-Boerstra et al..[14]

Immediate symptoms were defined as symptoms occurring during the challenge or within two hours after the last challenge dose. Late onset symptoms were defined as symptoms occurring between two and forty-eight hours after the last challenge dose. Isolated late reactions were defined as no immediate but only a late reaction after DBPCFC.

Forty-eight hours after each challenge session late reactions were recorded by telephone questionnaire during which the occurrence and type of symptoms were recorded in detail (appendix II).

The presence of symptoms following challenges was used to determine the severity of the reaction. All symptoms were classified into five categories and each of these categories were scored (Table I).[15]

To ascertain which factors were independently associated with LRs, the relationship between LRs and a number of factors were explored, and association models were developed separately for both the active challenge day and for the placebo challenge day.

Prediction models were developed to select the best set of variables to predict LRs, one prediction model for the active challenge day and another for the placebo challenge day.

Data entry and statistical analyses were conducted using SPSS version 20.0 (SPSS Inc. Chicago, IL, USA.). All tests were 2-tailed with the significance level set at $p<0.05$. Univariate logistic regression analysis was used to investigate which factors were associated with LRs. McNemar test was used to assess the difference between LRs on the active challenge day and the placebo challenge day.

This study was approved by the local medical ethics review commission who deemed that permission from the commission was not required.

RESULTS

Study population

Between October 2001 and April 2014 a total of 1396 DBPCFCs (child-test combinations) were performed. In total 1142 child-test combinations were eligible for analysis. Of these 1142 child-test combinations, 400 reported late reactions: 53 (4.6%) reported late reactions both on the active and placebo challenge day, 237 (20.8%) only reported a late reaction on the active challenge day, and 110 children (9.6%) only reported a late reaction on the placebo challenge day.

Out of the 400 child-test combinations, 158 reported isolated late reactions, i.e., no immediate but only a late reaction during DBPCFC. This included 89 reports on the active challenge day and 92 on the placebo challenge day. Descriptive characteristics are shown in Table I.

Late reactions

The frequency of LRS on the active challenge day was significant greater than LRs on the placebo challenge day (p=0.001).

The majority of the food-allergic children and adolescents with LRs reported symptoms of slackening, restlessness, crying, dizziness and/or anxiety for both the active (n=112(47.3%))(Table I) and placebo challenge day (n=56(50.1%)(Table II). The reported symptoms were mild (index score severity of late reaction 1-2). The mean and 95% confidence interval (CI) for the severity score of LRs on active challenge day were 0.26 (0.23-0.28) and on placebo challenge day 0.14 (0.12-0.16).

Table II. Symptoms of late reactions after placebo challenge day (n=110)

Symptoms late reactions, n (%)	Objective symptoms	Subjective symptoms
skin symptoms	38 (34.5)	5 (4.5)
respiratory symptoms (upper and lower)	10(9.0)	1 (0.9)
gastro-intestinal symptoms	45 (40.5)	5 (4.5)
other symptoms	25 (22.7)	31 (28.1)

Table I. Descriptive characteristics food-allergic children and adolescents with late reactions after DBPCFCs (n=400)

	Active challenge day	Placebo challenge day	Both days
Number child-test combinations, n (%)	237 (59.3)	110 (27.5)	53 (13.2)
Sex, boys/girls n (%)	157/80 (66.2/33.8)	59/51 (53.6/46.4)	32/21 (60.3/39.6)
Mean age, years (SD)	5.73 (4.16)	5.30 (4.16)	5.24 (3.52)
Mean level of food specific IgE, kU/L (SD)	16.8 (30.0)	6.03 (16.7)	7.31 (17.3)
Tested foods, n (%)			
cashew nut	23 (9.7)	3 (2.7)	2 (3.7)
hazelnut	16 (6.8)	8 (7.3)	4 (7.5)
egg	41 (17.3)	24 (21.8)	13 (24.5)
milk	76 (32.1)	**51** (46.4)	**20** (37.7)
peanut	**81** (34.2)	23 (21.8)	14 (26.4)
Atopic co-morbidities, n (%)			
atopic dermatitis	215 (90.7)	94 (85.5)	48 (91.0)
asthma	118 (49.8)	40 (36.4)	26 (49.1)
allergic rhinitis	89 (37.6)	32 (29.1)	23 (43.0)
Positive family history of atopic diseases, n (%)			
atopic dermatitis	169 (71.3)	77 (70.0)	34 (64.2)
asthma	138 (58.2)	60 (54.4)	35 (66.0)
allergic rhinitis	169 (71.3)	77 (70.0)	42 (79.2)
food allergies	124 (52.3)	54 (49.0)	23 (43.4)
Late reactions, mean (SD)			
hours to occurrence symptoms of LR	3.46 (7.60)	4.09 (9.36)	7.83 (9.04)
hours to disappearance symptoms of LR	2.09 (5.53)	0.94 (4.74)	1.88 (4.82)
Symptoms late reactions, n (%)			
skin symptoms	79 (33.3)	43 (39.1)	41 (77.4)
respiratory symptoms (upper and lower)	44 (18.6)	11 (10.0)	13 (24.5)
gastro-intestinal symptoms	108 (45.6)	50 (45.4)	42 (79.2)
other symptoms	112 (47.3)	56 (50.1)	33 (62.3)
Index score severity of late reactions*, n (%)			
1-2 (mild)	170 (71.7)	65 (59.1)	18 (34.0)
3-6 (moderate)	60 (25.3)	44 (40.0)	8 (15.0)
7-12 (severe)	7 (3.0)	1 (0.09)	8 (15.0)
Immediate reaction during DBPCFC, n (yes/no) (%)	171/66 (72.2/27.8)	41/69 (37.3/62.7)	30/23 (56.6/43.4)

Table I. (continued)

	Active challenge day	Placebo challenge day	Both days
Symptoms immediate reactions, n (%)			
skin symptoms	157	95	38
respiratory symptoms (upper and lower)	108	7	13
gastro-intestinal symptoms	26	5	14
other symptoms	21	1	3
Index score severity of immediate reactions*, n (%)			
1-2 (mild)	70	45	18
3-6 (moderate)	52	10	8
7-12 (severe)	52	7	8

*Index score severity of late reactions: all symptoms were classified into five categories and each of these categories were scored as followed: skin symptoms (1 point); gastrointestinal symptoms (2 points); (3) upper airway (3 points), lower airway (3 points), other symptoms (3 points). To compute the severity index for the late onset reaction, the total score of the five categories was calculated. This index ranges from one to twelve and was classified into three tertiles: (1) 1-2 (mild); (2) 3-6 (moderate); (3) 7-12 (severe).

Association models of LRs

In the univariate analysis, variables significantly associated with LRs on the active challenge day were: age (p=<0.001); level of food-specific IgE (p=0.005); atopic dermatitis (p=0.008), DBPCFC with hazelnut (p=0.001), DBPCFC with cow's milk (p=<0.001) and severity of the immediate reaction during DBPCFC (p=0.003). For each of these variables a multivariate association model was developed with LR as the dependent variable. Three of these six association models were significant.

In the univariate analysis, variables significantly associated with LRs on the placebo challenge day were: age (p=<0.001) level of food-specific IgE (p=<0.001) asthma (p=0.019) DBPCFC with cashew nut (p=0.003) DBPCFC with hazelnut (p=0.037) DBPCFC with egg (p=0.008) DBPCFC with cow's milk (p=<0.001) and DBPCFC with peanut (p=<0.001). For each of these variables a multivariate association model was developed with LR as the dependent variable. Three of these eight association models were significant.

Prediction models of LRs

The prediction model for the active challenge day accounted for only 8.0% of the variance in LRs. Variables that had a significant and independent contribution to this variance were: age, having rhino-conjunctivitis, having a hazelnut allergy, and the severity of the immediate reaction.

The prediction model for the placebo challenge day accounted for only 12.1% of the variance in LRs. Variables that had a significant and independent contribution to this variance were: age, level of food-specific IgE, having rhino-conjunctivitis, and undergoing a DBPCFC with cashew or milk.

DISCUSSION

This is the first study to show that late reactions in food-allergic children and adolescents after DBPCFC do occur, are poorly predictable and are generally not severe.

There are limited data on LRs after DBPCFC in food-allergic patients. Therefore, comparison to other studies' findings is difficult. A previous study by Wensing et al.,[16] in 26 adults having a peanut allergy showed that no late or delayed reactions (≥2 hours) occurred after DBPFC, apart from the reaction in one patient, who started vomiting 2.5 hours after the last ingestion of peanut. Our study shows that LRs do occur, even when taking the frequency of such "reactions" on placebo challenge days into account. However, isolated LRs occurred with comparable frequency after active and placebo challenges, suggesting that reported LRs in the absence of immediate reactions on the same day are likely to be chance occurrences rather than true allergic reactions.

In this study no severe LRs were reported. Previous studies showed that patients who developed severe immediate reactions may experience severe late or recurrent reactions, even though such reactions may be uncommon. Lee et al.[10] showed that biphasic reactions are rare in children undergoing oral (open) food challenges and may be associated with more severe immediate allergic reactions. Jarvinen et al.[8] reported a single biphasic reaction (2% of cases) which was described as a recurrence of anaphylaxis. Both studies reported higher percentages of severe immediate reactions than we did: we did not have immediate reactions to challenges resulting in anaphylaxis. This suggests that severe late reactions are associated with severe immediate reactions. Therefore, it is probably not necessary to observe food-allergic children for more than 2 hours after DBPCFC except following exceptionally severe immediate reactions**.**

Our data show that age is an important factor predicting the reporting of late reactions on both active and placebo challenge days. A likely explanation for this finding is that parents tend to over-report symptoms in young children, as has been shown for the reporting of (immediate) reactions to placebo by trained health care professionals.[17] Interestingly, this also seems to be true for patients undergoing challenges with milk, even though this effect apparent on placebo days is independent of age. It is possible that this is due to early onset of milk allergy and consequent perseveration of parental beliefs and reporting which do not change as the child becomes older.

The other foods associated with the occurrence of LRs in this study were hazelnut (on active days), peanut, and cashew nut (on placebo days). Previous studies have shown that nut allergy has a significant impact on psychological distress and quality of life in children with a nut allergy.[14-17] One might speculate that patients undergoing challenges with one of these foods are more anxious, and this may therefore contribute to reporting late onset symptoms after a DBPCFC.

In the case of hazelnut, additional factors may be contributing to the occurrence of LRs on active challenge days. Hazelnut allergy is often the result of primary sensitization to cross-reactive birch pollen often resulting in mild oral and upper airway symptoms. Late reactions have been documented in the upper airways[18] and, although it would seem likely that such reactions are responsible for the reactions seen in these patients following oral hazelnut challenges, the reported symptomology was, in fact, quite different. Of the 20 patients reporting LRs on the active hazelnut challenge day, most of them reported gastro-intestinal symptoms (n=11) (stomach cramps, vomiting, diarrhea) and skin symptoms (n=7) (worsening eczema). Four patients reported lower airway symptoms (data not shown). All of the reported symptoms were not severe. The relationship between hazelnut challenges and late reactions is thus only partially explained at present.

In this study, we found a high rate of placebo events 110/400 (27.5%). For most of these events objective symptoms were reported. This is in keeping with the findings of a previous study describing symptoms during challenges with placebo.[14] A variety of symptoms were reported after challenges with placebo in the present study, such as skin symptoms, gastro-intestinal symptoms, lower- and upper airway symptoms. No anaphylaxis was observed. Clinicians conducting DBPCFC tests should thus be aware that various types of symptoms, including objective symptoms, may occur after a placebo challenge day.

A limitation of this study is that the symptoms of the LRs were self- and parent-reported. However this would be likely to lead to overestimation of the frequency and severity of the reactions. Thus the conclusion that such reactions are generally mild would be unlikely to be affected by this limitation. Also, our conclusions are only applicable to centers where the prevalence of severe immediate reactions is low.

Another possible limitation of this study is that the conclusions were based on retrospective data, and that retrospective bias is thus possible. However, all data was collected before the outcome of the oral challenge tests were known, thus limiting this form of bias.

In conclusion, LRs in food-allergic children after DBPCFC are poorly predictable, and are generally not severe. Isolated LRs occur with comparable frequency after active and placebo challenges and are thus unlikely to be true allergic reactions. All LRs, including those on the placebo day, are more frequently reported in younger children. Children who do not experience severe immediate reactions may thus be safely discharged home 2 hours after a DBPCFC.

ACKNOWLEDGEMENTS

This research is supported by the GUIDE Research Institute Groningen, the Netherlands.

APPENDICES

Appendix I. Incremental scale and challenge doses used in double-blind, placebo controlled challenges in children

	Cow's Milk (ml)	Egg (mg)	Protein equivalent (mg)	Peanut (mg)	Hazelnut (mg)	Cashew nut (mg)	Protein equivalent
Dose 1	0.05	13	1.75	6	12	2.3	1.75
Dose 2	0.1	27	3.50	12	25	4.8	3.5
Dose 3	0.4	108	14	48	100	19	14
Dose 4	2.0	538	70	241	500	95	70
Dose 5	10.0	2690	350	480	860	163	130
Dose 6	50.0	13460	1750	1206	2500	475	350
Total	63.0	16830	2190	2000	4000	759	570

Appendix II. Semi-structured interview after DBPCFC

Date: _____

1. Did symptoms occur after the food challenge?

○ Yes

○ No

If yes, what symptoms did occur?

_____

_____

2. At what time did the symptoms occur?

[date, time]

3. For how long did the symptoms persist?

[hours, days]

4. Did you use (extra) medicines to relieve the symptoms?

○ Yes

○ No

If yes, what kind of medicines did you use?

_____

_____

5. Did a reaction occur during the food challenge according to the parents?

○ Yes

○ No

○ Not sure

6. Outcome of the food challenge test?

○ Positive

○ Negative

○ Neither positive nor negative

Appendix III. Univariable associations for late reactions after DBPCFCs in food-allergic children and adolescents on the active challenge day (n=290)

	Odds Ratio	95% CI for Exp (B)	p
Gender	0.837	0.634;1.105	0.210
Age	0.936	0.907;0.966	0.000
Level of food-specific IgE	1.006	1.002;1.011	0.005
Atopic dermatitis	0.531	0.332;0.847	0.008
Asthma	0.954	0.728;1.249	0.731
Allergic rhinitis	0.931	0.691;1.206	0.512
Cashew nut	0.819	0.514;1.305	0.401
Hazelnut	0.443	0.271;0.726	0.001
Egg	1.331	0.937;1.891	0.111
Cow's milk	1.690	1.261;2.264	0.000
Peanut	0.108	0.599;1.052	0.108
FH+* of atopic dermatitis	1.071	0.801;1.431	0.644
FH+ of asthma	1.290	0.984;1.691	0.065
FH+ of allergic rhinitis	1.219	0.906;1.639	0.190
FH+ of food allergies	1.077	0.825;1.406	0.584
Severity of IR** Index score 1-2 (reference) Index score 3-6 Index score 7-12	 0.892 1.826	 0.608;1.309 1.209;2.760	 **0.003** 0.559 0.004

* FH+ = Positive Family History; ** IR = Immediate Reaction during DBPCFC

Associations between independent variables and LRs were tested and, if necessary, corrected for confounding using logistic regression analysis. Added factors were considered confounders if they changed the ß-coefficient of the primary variable by ≥10%. In addition, in logistic regression, a stepwise backward selection procedure (in/out: $p<0.05$) was used to identify factors that significantly predicted LRs following DBPCFCs in food-allergic children and adolescents.

Appendix IV. Univariable associations with late reactions in food-allergic children and adolescents on the placebo challenge day (n=163)

	Odds Ratio	95% CI	p
Gender	1.354	0.969;1.894	0.076
Age	0.904	0.866;0.943	0.000
Level of food-specific IgE	0.975	0.963;0.987	0.000
Atopic dermatitis	0.807	0.472;1.381	0.435
Asthma	1.503	1.070;2.111	0.019
Allergic rhinitis	1.174	0.824;1.673	0.375
Cashew nut allergy	0.255	0.102;0.636	0.003
Hazelnut allergy	0.519	0.280;0.961	0.037
Egg allergy	1.731	1.152;2.601	0.008
Cow's milk allergy	2.694	1.909;3.801	0.000
Peanut allergy	0.477	0.325;0.701	0.000
FH+** of atopic dermatitis	0.957	0.670;1.366	0.808
FH+ of asthma	1.169	0.836;1.635	0.362
FH+ of allergic rhinitis	1.206	0.832;1.749	0.322
FH+ of food allergies	0.908	0.652;1.266	0.570
Severity of IR***			
Index score 1-2 (reference)			0.544
Index score 3-6	0.735	0.395;1.376	0.336
Index score 7-12	0.810	0.394;1.664	0.566

*CI=confidence interval; ** FH+ = Positive Family History; *** IR = Immediate Reaction during DBPCFC
Associations between independent variables and LRs were tested and, if necessary, corrected for confounding using logistic regression analysis. Added factors were considered confounders if they changed the ß-coefficient of the primary variable by ≥10%. In addition, in logistic regression, a stepwise backward selection procedure (in/out: $p<0.05$) was used to identify factors that significantly predicted LRs following DBPCFCs in food-allergic children and adolescents.

Appendix V. Final prediction model for late reactions after DBPCFCs in food-allergic children and adolescents on the active challenge day (n=290)

Variable	OR*	95% CI for OR	p
Constant	1.632		0.261
Age	0.900	0.856;0.945	<0.001
Allergic Rhinitis	0.592	0.394;0.891	0.012
Severity of IR** Index score 1-2 (reference) Index score 3-6 Index score 7-12	 1.225 2.056	 0.803;1.870 1.330;3.181	 0.005 0.347 0.001
Hazelnut allergy	0.447	0.232;0.858	0.016

*OR = Odds Ratio; IR = Immediate Reaction during DBPCFC; Nagelkerke R^2 = 8.0%,

Appendix VI. Final prediction model for late reactions after DBPCFCs in food-allergic children and adolescents on the placebo challenge day (n=163)

Variable	OR*	95% CI for OR	p
Constant	0.612		0.324
Age	0.929	0.878;0.983	0.011
Level of food specific IgE	0.976	0.964;0.988	<0.001
Allergic rhinitis	0.588	0.368;0.940	0.026
Cashew nut allergy	0.363	0.142;0.930	0.035
Cow's milk allergy	2.096	1.362;3.244	0.001

*OR = Odds Ratio, Nagelkerke R^2 = 12.1%.

REFERENCES

(1) Muraro, A., Werfel, T., Hoffmann-Sommergruber, K., Roberts, G., Beyer, K., Bindslev-Jensen, C., et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy 2014;69(8):1008-1025

(2) Alqurashi Waleed W. Epidemiology and clinical predictors of biphasic reactions in children with anaphylaxis. Annals of Allergy, Asthma and Immunology 2015-9;115(3):217-223.

(3) Grunau Brian E BE. Incidence of clinically important biphasic reactions in emergency department patients with allergic reactions or anaphylaxis. Ann Emerg Med 2014-6;63(6):736-44.

(4) Mehr S. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. Clinical and Experimental Allergy 2009-9;39(9):1390-6.

(5) Tole JL. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. Immunology and allergy clinics of North America 2007;27(2):309-26, viii.

(6) Lieberman P. Biphasic anaphylactic reactions. Annals of allergy, asthma, & immunology 2005;95(3):217-26.

(7) Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med 1992 Aug 6;327(6):380-384.

(8) Bindslev Jensen R., C Ballmer Weber, B K Bengtsson, U Blanco, C Ebner, et al. Standardization of food challenges in patients with immediate reactions to foods--position paper from the European Academy of Allergology and Clinical Immunology. Allergy 2004;59(7):690-697.

(9) Sampson HA, Gerth van Wijk R, Bindslev Jensen C, Sicherer S. et. al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol 2012;130(6):1260-1274.

(10) Lee JG, Brown J, Whitehorn T., Spergel, J. Biphasic reactions in children undergoing oral food challenges. Allergy and Asthma Proceedings 2013;34(3):220-226.

(11) Mehr S, Liew WK, Tey D, Tang ML. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. Clin Exp Allergy 2009 Sep;39(9):1390-1396.

(12) Lee, J M Greenes,D S. Biphasic anaphylactic reactions in pediatrics. Pediatrics 2000;106(4):762-766.

(13) Vlieg Boerstra B, Bijleveld C, van der Heide S, Beusekamp B, Wolt-Plompen S, et al. Development and validation of challenge materials for double-blind, placebo-controlled food challenges in children. J Allergy Clin Immunol 2004;113(2):341-346.

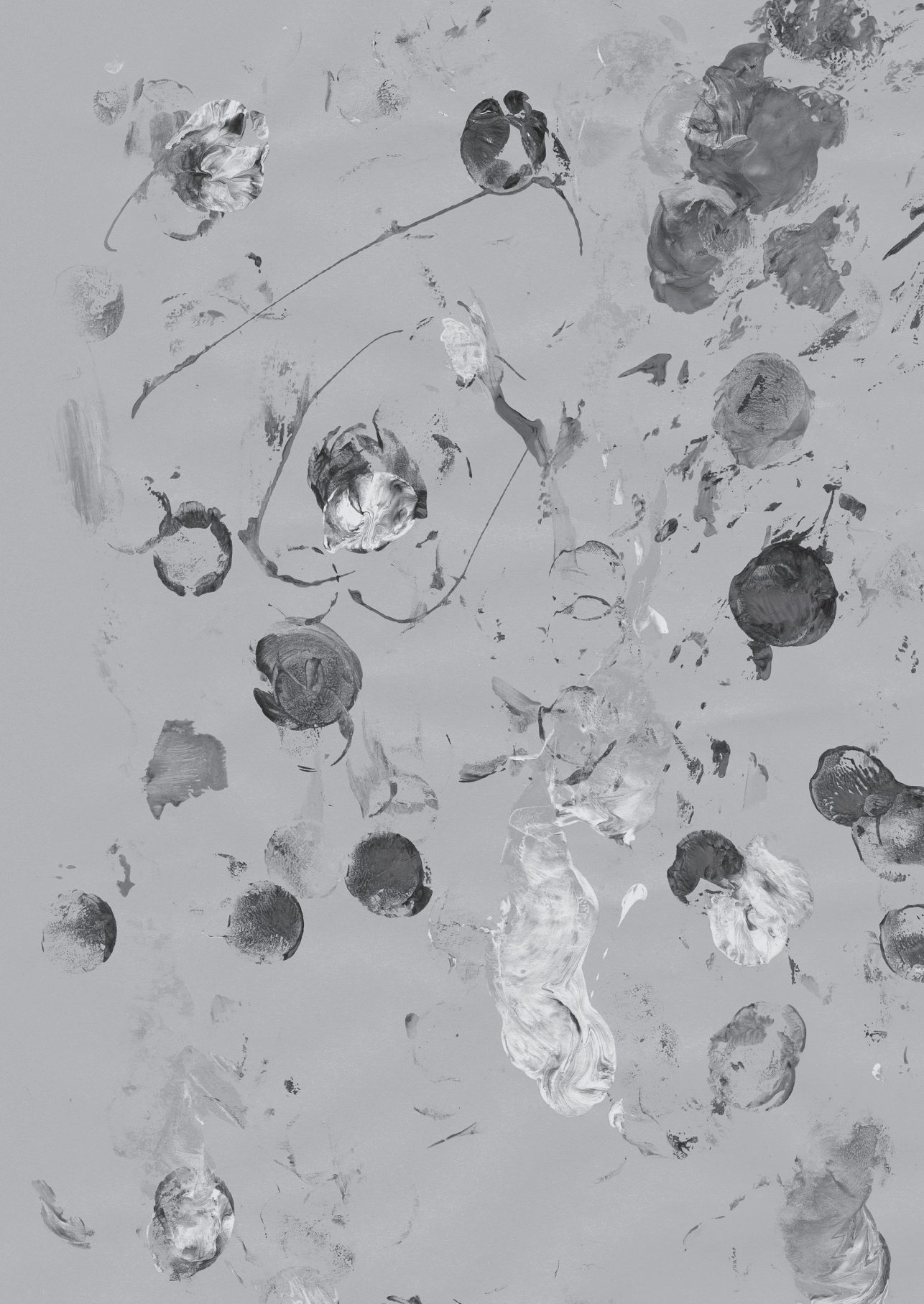
(14) Vlieg Boerstra B, van der Heide S, Bijleveld CM, Kukler J, Duiverman EJ, et al. Placebo reactions in double-blind, placebo-controlled food challenges in children. Allergy 2007;62(8):905-912.

(15) van der Zee T. The eliciting dose of peanut in double-blind, placebo-controlled food challenges decreases with increasing age and specific IgE level in children and young adults. J Allergy Clin Immunol 2011-11;128(5):1031-6.

(16) Wensing, Penninks M, Hefle A, Koppelman S, Bruijnzeel-Koomen C, Knulst, A. The distribution of individual threshold doses eliciting allergic reactions in a population with peanut allergy. J Allergy Clin Immunol 2002;110(6):915-920.

(17) Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Gant C, et al. Comparison of open and double-blind placebo-controlled food challenges in diagnosis of food hypersensitivity amongst children. J Hum Nutr Diet 2007 Dec;20(6):565-579.

(18) Naclerio RM, Proud D, Togias AG, Adkinson NF,Jr, Meyers DA, Kagey-Sobotka A, et al. Inflammatory mediators in late antigen-induced rhinitis. N Engl J Med 1985 Jul 11;313(2):65-70.



Chapter 8

General discussion and future perspectives

J. Saleh-Langenberg

The aims of this thesis were to investigate the reasons for the under-prescription of auto-injectors in food allergic patients at high risk for anaphylaxis, and the reasons for non-compliance and non-use of EAIs by this group of patients. With regard to our first aim, we first determined the prevalence of food allergy and EAI ownership in high-risk food allergic adolescents in the Netherlands (*chapter 2*) and secondly we explored the practice in EAI prescriptions by general practitioners to food allergic patients in the Netherlands (*chapter 3*). Regarding our second aim, we explored the burden of treatment of an EAI and examined the relationship between this burden and compliance with carrying an EAI at all times (*chapter 4*). We also investigated the health-related quality of life in food allergic patients (*chapter 5*). Concerning our third aim, we determined the knowledge, attitudes and beliefs regarding food allergy and anaphylaxis among pharmacists in the Netherlands including how accurately they demonstrated how and when to use an EAI to food allergic patients (*chapter 6*). Finally, we determined the prevalence, severity and clinical characteristics of late reactions in food allergic children and adolescents after DBPCFCs, and ascertained factors that were associated with late reactions after DBPCFCs (*chapter 7*).

Part I. Prevalence of food allergy and under-prescription epinephrine auto-injectors

In this first part of this thesis, *chapter 2* demonstrated that the prevalence of food allergy in high-risk food allergic adolescents, when compared to a previous study in 2009 by Flokstra-de Blok et al.,[1] has not increased in the last six years. In 2009 as well as in 2016 the calculated questionnaire-based prevalence of probable food allergy was 6.2%. This is not in keeping with other studies reporting that the prevalence of self-reported food allergy is increasing.[2-6] These studies report a higher self-reported food allergy prevalence than our study varying from an increase of 1.7% to 4.2% in the community for a time interval of about six years. However, the prevalence of food allergy as diagnosed by the diagnostic gold standard DBPCFC is estimated to be about 3% for all foods together.[7-14] Therefore, the prevalence reported in these self-reported food allergy prevalence studies may be an overestimation.

Chapter 2 also demonstrated that epinephrine auto-injector (EAI) ownership has improved marginally when compared to a previous study in 2009 by Flokstra-de Blok et al.[1] Even though this improvement was not significant and may therefore not be generalizable, there is ultimately still a substantial under-prescription of EAIs in high-risk food allergic adolescents. It remains a fact that when a severe food allergic reaction occurs, prompt administration of epinephrine may be life-saving. Therefore, all food allergic patients at high risk of anaphylaxis should possess an EAI and carry this device at all times.

In our study the adolescents classified as probably food allergic were not referred for further testing for an objective diagnosis of food allergy. However, if all probably food allergic adolescents underwent the diagnostic gold standard DBPCFC, our experience is that approximately half of those adolescents would have a positive test outcome. Ultimately, adolescents reporting having experiences a (severe) allergic reaction would still require an EAI until challenge tests could be done, and overestimation of the need for EAIs would be thus only be apparent after such tests had been completed. Our finding may thus eventually be an overestimation of the problem of under-prescription of EAIs to high risk food allergic patients to some degree.

An overestimation of the prevalence of self-reported food allergy may also be due to an erroneous perception of symptoms of food allergy among the general public. The general public might use the term 'food allergy' to describe any adverse response to foods. Previous studies have shown that the food allergy knowledge among the general public seems to be limited.[15-19] The general public had wide variation in knowledge about food allergy with many misconceptions of key concepts related to prevalence, definition, and triggers of food allergy. Food allergy knowledge among parents of food allergic children from the Netherlands was suboptimal when compared with their counterparts from the USA,[19] although Dutch parents tend to be more optimistic toward food allergy than parents from the USA. This optimism may be explained by an underestimation of the severity and risks of having an accidental food allergic reaction.[15,19]

The limited knowledge about food allergy and underestimation of the severity and risk of a food allergic reaction mentioned in the previous paragraph may contribute to the under-prescription of EAIs in food allergic patients. Adolescents with problems with food may not visit their general practitioner, and may consequently be ignorant of the fact that they are at high risk for food-induced anaphylaxis. We also have to take into account the role of puberty in the developing adolescent brain. Adolescence is a period of developmental transition between childhood and adulthood, involving multiple physical, intellectual, personality, and social development changes.[20-26] Therefore there may be a variety of (unknown) reasons why food allergic adolescents behave the way they do. Details about these reasons will be discussed further on in this general discussion (*chapter 4*).

Most food allergic accidents and anaphylaxis fatalities in children and adolescents take place at schools.[27-29] Previous studies showed that six to eighteen per cent of children with food allergy experience an allergic reaction at school,[30,31] and four to six fatal anaphylactic reactions in children occurred at school.[32] It is therefore important that schools are prepared for the management of food allergic children. However, previous studies have also shown that in reality many schools are poorly prepared: preventive measures of food allergen exposure are absent, teachers have little knowledge of food

allergy, anaphylaxis, and EAIs.[27,33-36] To our knowledge, the preparedness of Dutch high schools have not yet been investigated,[35] and it would thus be of interest to investigate how prepared they are. Le et al. investigated 37 primary schools in the Netherlands.[35] Their study showed that there is a low preparedness for food allergy as perceived by school staff, as is the case for other primary schools across Europe.[35] Not every school's staff was aware of symptoms associated with food and not all schools identified children with food allergy.[35] Few schools had written operating procedures that included how to deal with food allergy. This may also be the case for (Dutch) high schools. This lack of precautionary measures for food allergic children may give rise to food allergic accidents and (fatal) anaphylaxis.

Le et al. proposed that their findings warrants the preparation of guidelines for a standardized approach to identifying children at risk and to preventing and managing the effects of food allergies.[35] Guidelines have been developed and are intended to assist those working in school and early childhood. Guidelines of the European Academy of Allergy and Clinical Immunology (EAACI),[27,33] the American Academy of Allergy, Asthma, and Immunology (AAAAI)[37] and the Australasian Society of Clinical Immunology and Allergy (ASCIA)[38-40] have outlined the roles and responsibilities of schools, namely (1) identification of children with food allergy; (2) avoidance strategies that create a safe environment for children with food allergy; and (3) treatment strategies to educate the staff. Unfortunately, these guidelines are not yet sufficiently implemented in Dutch schools.[35] In addition, there are no laws in the Netherlands as there are in Canada,[41] in the United States of America (USA)[42] or Ireland[43] that focus specifically on the preparedness of schools for medical emergencies, such as food-induced anaphylaxis.

In the Netherlands, safety, health-care and welfare for students at schools results from several laws: 'Wet op het Primair Onderwijs' *(Primary Education Law),* 'Wet op het Voorgezet Onderwijs' *(Secondary Education Law') and* 'Wet Ondersteuning Onderwijs Zieke leerlingen' (*Assistance of Education for Diseased Students Law)'.*[44-46] Regarding the safety, health-care and welfare for students at schools, these laws demand from schools that they take preventive measures for creating a healthy and safe learning environment for their students. Schools should understand that certain chronic conditions are serious and can be potentially life threatening, particularly if not correctly managed or misunderstood. Schools should have a personal record about each student that has a (chronic) disease.

This record should state which measures should be taken for these individual students.[44-47] Schools should have a clear communication plan for staff and parents to ensure the safety of these students. Parents have a duty to inform the school of their child's condition and provide the necessary medical equipment to respond to emergencies. School staff should be provided with training to learn more about these (chronic) diseases and what to do in case of emergencies. Nevertheless, (severe) allergic reactions may occur

in previously undiagnosed children.[30] Therefore, the availability of epinephrine in schools is important for emergency treatment. However, according to Dutch law, medication may only be prescribed to individuals.[48,49] This means that children that have a (severe) allergic reaction at school may only be treated with their own personal EAI. This also means that schools in the Netherlands are not allowed to have undesignated EAIs available. In the USA there is a law since 2013 that permits schools to have an undesignated EAI available for any student or staff member experiencing anaphylaxis.[50] The undesignated EAI may be available in unlocked an easily accessible places in schools and may be used by trained personnel. Such a law might also be helpful in the Netherlands in order to protect food allergic children who experience anaphylaxis when their personal EAI is not easily accessible and those who experience anaphylaxis and do not have an EAI. Currently, in Ireland, regulations about to be changed "to provide for the supply and administration of specified prescription-only medicinal products without a prescription to a person by a pharmacist or by an individual appointed by a listed organisation for the purpose of saving life or reducing severe distress in emergency situations".[51] The EAI is one of these products. However, that pharmacist or individual must have completed an approved course of training regarding the administration of such products and the management of any adverse reaction.[51]

In the Netherlands the safety of school staff is provided for in the 'Arbeidsomstandighedenwet' *(Working Conditions Act)* and regulated in collective employment agreements of schools.[47] When school staff administer an EAI for emergency treatment in a food allergic child or adolescent they are legally protected by this law and related regulations. But they are only legally protected if their school did take all preventive measures necessary to ensure a healthy and safe environment and trained their school staff to handle these emergencies.

The cornerstones of food allergy and anaphylaxis management should include training of staff members to improve understanding of food allergy and anaphylaxis and establishing management and emergency plans to minimize risks, and to provide a safe educational environment.[27,33,35] However, the board of management of schools and school staff face problems with the implementation of laws to create a safe and supportive learning environment for students.[52] It is often unclear which preventive measures should be taken and school staff experience problems caring for students with special health requirements.[52] This may explain that school staff are unprepared and do not want to take responsibility for these emergency treatments.[35] This suggests that there is room for improvement of existing practices. A combination of initiatives undertaken in Canada, Australia and Ireland may be suitable for schools in the Netherlands. For example, in Canada, Sabrina's Law signed into effect on January 1st, 2006, requires that every school board establish and maintain an anaphylaxis policy to help students with serious allergies.

It also requires that schools create individual plans for each student at risk of anaphylaxis.[41] In Australia, there are guidelines to assist staff in school and childcare settings to plan and implement appropriate risk minimisation strategies, taking into consideration the needs of the allergic child, the likely effectiveness of measures and the practicality of implementation.[40,53] And in Ireland there is a resource pack 'Managing Chronic Health Conditions at School' to help teachers and parents to work together and provide a safe and enjoyable school environment for students with (food) allergies.[43]

Another problem where food allergic children and adolescents stumble upon is bullying, teasing, and harassment because of their food allergy.[54,55] Low preparedness of schools for food allergic children and adolescents may contribute to this as well. All this may also have a potential negative impact on a child's quality of life. Schools must therefore be assisted through government in the implementation of laws to care for food allergic children in case of emergency. National regulations may therefore be required in order to improve food allergy and anaphylaxis knowledge of school staff, to improve anaphylaxis preparedness and to improve health-related quality of life (HRQL) of food allergic children, adolescents and their families.

General practitioners (GPs) play an important role in diagnosing and treating food allergic patients. In the Netherlands, the GP is the gatekeeper of the Dutch health-care system controlling access to specialized medical care. *Chapter 3* described and evaluated the practice in EAI prescriptions by GPs to food allergic patients in the Netherlands. Although the knowledge of GPs regarding food allergy and anaphylaxis has previously been studied using questionnaires and hypothetical cases,[56-59] this study is the first to examine actual EAI prescription practices and the first to make use of data collected by GPs themselves. Our study showed with data recorded by GPs themselves that those food allergic patients at high risk for anaphylaxis that do visit their GPs are often not prescribed an EAI, even to those with a previous severe anaphylactic reaction. This shows that previously identified low rates of EAI ownership may be partly due to GPs not prescribing this medication to patients for whom it would be appropriate to do so.

The management of food allergy and anaphylaxis should be familiar to GPs. However, previous studies showed that there is a lack of food allergy knowledge in primary care, especially the recognition and treatment of anaphylaxis were problematic and that (inter) national guidelines were often not followed.[29,60-64] Knowledge and/or practice behavior gaps in GPs may be explained by the fact that anaphylaxis is relatively uncommon and that therefore they do not see and treat them that often. However, there are guidelines and algorithms for the diagnosis and management of food allergy and anaphylaxis in case food allergic patients do visit the GP. Primary care guidelines in the Netherlands, the *food allergy guidelines of the Dutch College of General Practitioners* (NHG) guidelines differ from the internationally accepted guidelines for the diagnosis and management of food

allergy and anaphylaxis.[29,64-66] Surprisingly, the NHG guidelines recommend that an EAI should only be prescribed after a previous case of anaphylaxis. Significantly, risk factors for a life-threatening food-induced anaphylactic reaction are mentioned, but are not put forward as a reason to prescribe an EAI in the absence of a previous anaphylactic reaction. Although in our study it may therefore be argued that GPs are simply following their own guidelines to whom prescribing an EAI, this, however, does not seem to explain the lack of EAI prescription in high risk patients who had experienced prior anaphylaxis as well as in patients presenting with anaphylaxis to their GP. The latter situation is in agreement with previous studies of anaphylaxis management in emergency rooms, where patients presenting with anaphylaxis are not always prescribed an EAI or referred to appropriate specialist care.[58,67-69]

In our study, a limitation is the number of patients excluded from analysis due to inaccessible or incomplete patient's medical records. The incomplete data might be due to under-reporting of patients (or their parents), under-documentation of clinical information by GPs or lack of knowledge and/or practice behavior gaps experienced by GPs. In this regard, it may be expected there would be more food allergic patients at high risk for anaphylaxis not being prescribed an EAI. We did not find patients who had been prescribed an EAI who were not high risk patients. Ultimately, some of these patients would probably show no reactions when challenged with the food in question. However, such patients would still require an EAI until challenge tests could be done, and overestimation of the need for EAIs would thus only be apparent after such tests had been completed. Our findings may thus eventually be an overestimation of the problem of inadequate EAI prescription to high-risk food allergic patients to some degree. More urgent, however, is the obvious extent to which high risk food allergic patients are not prescribed an EAI by their GPs.

It is important that GPs in the Netherlands become prepared for high risk food allergic patients. Our study highlights that there is a need for improvement of the quality of care for these patients in primary care and that the NHG guidelines should be revised.

Part II. Non-compliance, burden of treatment and HRQL

Food allergic patients at high risk for (fatal) anaphylaxis should carry an EAI at all times. Compliance with EAI carriage is a major clinical problem and important contributor to anaphylactic deaths.[22,25,70-73] Carriage of an EAI may be perceived as burdensome and this may affect compliance. In the second part of this thesis, we examined in *chapter 4* the relationship between self-reported compliance with carrying the EAI and the burden of treatment as perceived by food allergic adolescents and their parents. We found that the majority of food allergic adolescents and their parents were positive about the EAI which means that the burden of treatment was low. Parents were even more positive about the EAI than the adolescents themselves. This is in keeping with a previous study that showed that a prescription of an EAI did not increase the parental burden of food allergic children.[74] In contrast to the low burden of treatment we found in food allergic patients, it was previously shown that patients with vespid allergy carrying an EAI reported a high burden of treatment.[75] This may be due to the fact that an EAI is much more likely to be perceived as burdensome in vespid allergy, where it is a temporary measure until curative treatment makes the EAI superfluous. In food allergy it is the only meaningful measure offering protection when accidental food allergic reactions occur. Also, vespid exposure is usually limited to certain seasons while food allergen exposure may occur every day.

However, for food allergic adolescents, a higher burden of treatment was associated with self-reported non-compliance with carrying an EAI at all times. There may be a variety of reasons for non-compliance with carrying an EAI at all times by food allergic adolescents. As mentioned before we have to take into account the role of puberty in the developing adolescent brain. Adolescents are the age-group with the highest risk for food allergy fatalities.[76-78] Food allergic adolescents take risks pertaining to their food allergy, including not carrying their EAI at all times.[21,23,79] One reason for this may be caused by problems occurring at the time of the transfer of responsibility for managing their food allergy from their parents to themselves. They have to make decisions for themselves, which might be difficult and they may find risks difficult to judge, particularly with regard to eating outside home, buying food and reading and interpreting food labels (e.g. 'may contain'). In our study, as in previous studies,[22,71] we found that compliance is often selective, where food allergic adolescents report having the EAI with them in restaurants and during holidays more often than at other times. Reasons given by adolescents for eating 'may contain' food include low perceived risk of reaction and having previously eaten such foods before without developing allergic symptoms.[80] A reason for not carrying an EAI at all times may be due to the design of the EAI itself.[21] However in our study the inconvenience, shape and size of the EAI were not associated with self-reported non-compliance with carrying the device. Food allergic adolescents should be advised how best to ensure EAIs are accessible at all times, and should not vary such compliance according to their convenience.[21,22,80] It is

important to develop interventions for food allergic adolescents to engage effective self-management of food allergy and anaphylaxis.

In *chapter 4* we also analyzed which factors contribute to the burden of treatment of the EAI as perceived by food allergic adolescents and their parents. Remarkably, the burden of treatment scores of both adolescents and their parents were not associated with health-related quality of life, trait anxiety, illness perception or perceived disease severity. However, our study showed that individuals not using available epinephrine perceived their disease as being less severe than those who did. Reasons given for non-use of the EAI were "other medication used", "unsure if it was necessary", "didn't seem severe enough", "unsure they ingested the food" and one patient did not dare to use the EAI. These explanations for the non-use of the EAI are similar to those found in a previous study.[81] This suggests that perceived disease severity is a motivating factor for use of the EAI during an allergic reaction to foods.

The burden of treatment measure seems to measure a distinct concept related to compliance behavior and relatively subtle differences in burden of treatment have an impact on compliance. Further studies on factors influencing the burden of treatment of food allergic adolescents may be helpful in order to improve compliance.

Health-related quality of life is increasingly being recognized as an important outcome measurement for both research and clinical practice.[82,83] Even though we demonstrated in *chapter 4* that the majority of food allergic adolescents and their parents perceived a low burden of treatment with carrying an EAI at all times, the burden of treatment was not associated with HRQL. In *chapter 5* we demonstrated that experiencing anaphylaxis or being prescribed an EAI did not seem to be related to HRQL of neither food allergic adults (≥ 18 years) nor children (8-12 years). We were surprised to find the limited impact of being prescribed an EAI on HRQL in food allergic children. A previous study by Pinczower et al.,[84] who used parent-proxy-reports to determine HRQL of food allergic children, found more impaired HRQL in children being prescribed an EAI compared to those who were not prescribed an EAI. However, they did not adjust the inverse relationship between EAI prescription and HRQL for self-perceived disease severity (FAIM). Their proposed relationship between EAI prescription and HRQL may thus be confounded by this self-perceived disease severity.

Chapter 5 also demonstrated that important predictors other than self-perceived disease severity for HRQL of food allergic adults in Europe were type of allergenic food, type of symptoms, and gender. For children important predictors were type of allergenic food and country of origin. However, the explained variance in adults was high, suggesting that the factors discovered here are important predictors of HRQL in food allergic adults. Further study will be necessary to improve prediction in children. Moreover, an important issue is whether clinicians can use the factors identified in our study to manage their

food allergic patients. In principle, knowledge of factors contributing to poor HRQL could assist clinicians to identify at risk patients and might inform preventive and/or therapeutic interventions. Therefore, further research is required in this area.

Part III. Non-use

Successful treatment of anaphylaxis in the community relies on early and correct use of EAIs. In the Netherlands pharmacists supply EAIs to patients and have a crucial role in instructing patients in how and when to use EAI. In the last part of this thesis, *chapter 6* demonstrated that there are knowledge gaps about food allergy and its management among pharmacists in the Netherlands, and that they often give incorrect and incomplete demonstration of EAI use. Anaphylaxis usually occurs in the community, and thus all food allergic patients and their families should be provided with educational resources and training about when and how to administer an EAI. However, in *chapter 3* we showed that GPs in the Netherlands feel that giving instructions about how to use an EAI is the responsibility of the pharmacist, even though the NHG guidelines recommends giving clear instructions about the use of an EAI.[85] The reason for not giving instructions about how to use an EAI may be due to the limited time available to the GP to see a patient. Another reason might be that the knowledge and/or practice behavior gaps of GPs in the management of food allergy. Therefore, it is important and necessary that pharmacists in the Netherlands know about food allergy and can demonstrate how and when to use an EAI to food allergic patients. Studies in this area are limited to evaluation of EAI demonstration rates and open assessment of EAI demonstration steps.[57,86-91] There is, to our knowledge, no study assessing real-world EAI instructions and demonstrations by pharmacist in Europe. One study by Salter et al. assessed real-world community pharmacist demonstrations of EAIs in Australia.[92] They showed that it was disappointing that only 18% of the pharmacist in Australia accurately demonstrated all four steps for auto-injector administration listed on the ASCIA action plan for anaphylaxis.[53,92] This is a better result than our study, as our study showed that of the pharmacists in the Netherlands who agreed to demonstrate how to use an EAI, none of them demonstrated the device correctly according to a ten step scoring system. This is worrisome given the importance of timely and correct administration of epinephrine in case of a (severe) food allergic reaction.

The errors in demonstration in our study were similar to those observed in other studies.[86-88,93-95] The most frequent errors in demonstration in our study were 'massage injection site after use' (100%) and 'call the emergency number to ask for an ambulance and say 'anaphylaxis'' (100%). Other common errors were failure to state to press the tip of EAI firmly into mid-anterolateral thigh until a 'click' is heard confirming the injection has started, and incorrect positioning of the thumb over the needle of the EAI. The instructions given by the pharmacist in our study may lead to a patient not receiving epinephrine or unintentional injection of epinephrine. Although the true rate of occurrence of unintentional injection of epinephrine from auto-injectors is unknown, it is said to be increasing.[96] Although dealing with the errors in device technique is very important, it may be difficult to achieve because aspects critical for correct epinephrine injection are

not intuitive.[92] New approaches should be developed for EAI training. One may speculate that opportunities to improve EAI demonstrations by pharmacists to food allergic patients may be of international concern.

The gold standard in the diagnosis of food allergies is the DBPCFC. A DBPCFC can result in immediate onset of symptoms, but late onset of symptoms has also been reported. The time during which children are observed following a DBPCFC varies in clinical practice. Recommendations vary from between 2 to 24 hours.[97-99] There is little data on late reactions (LRs) following DBPCFCs. Therefore, to compare our data about LRs following DBPCFCs (*chapter 7*) to other studies was difficult. A previous study by Wensing et al.,[97-99] in 26 adults having a peanut allergy, showed that no late or delayed reactions (≥2 hours) occurred after DBPCFC, apart from the reaction in one patient, who started vomiting 2.5 hours after the last ingestion of peanut. In *chapter 7* we demonstrated that LRs in food allergic children and adolescents after DBPCFC do occur, even when taking the frequency of such "reactions" on placebo challenge days into account. However, isolated LRs occurred with comparable frequency after active and placebo challenges, suggesting that reported LRs in the absence of immediate reactions on the same day are likely to be chance occurrences rather than true allergic reactions.

In *chapter 7* we also demonstrated that LRs are poorly predictable. The prediction model for the active challenge day accounted for only 8.0% of the variance in LRs. Variables that had a significant and independent contribution to this variance were: age, having rhino-conjunctivitis, having a hazelnut allergy, and the severity of the immediate reaction. Previous studies showed that patients who developed severe immediate reactions may experience severe late or recurrent reactions.[86,89] This suggests that severe late reactions are associated with severe immediate reactions. Therefore, it is probably not necessary to observe food allergic children for more than 2 hours after DBPCFC except following exceptionally severe immediate reactions.

In chapter 7 we also demonstrated that the prediction model for the placebo challenge day accounted for only 12.1% of the variance in LRs. Variables that had a significant and independent contribution to this variance were: age, level of food-specific IgE, having rhino-conjunctivitis, and undergoing a DBPCFC with cashew or milk. In our study, we found a high rate of placebo events 110/400 (27.5%). For most of these events objective symptoms were reported. This is in keeping with the findings of a previous study describing symptoms during challenges with placebo.[100] A variety of symptoms were reported after challenges with placebo in the present study, such as skin symptoms, gastro-intestinal symptoms, lower- and upper airway symptoms. No anaphylaxis was observed. Clinicians conducting DBPCFC tests should thus be aware that various types of symptoms, including objective symptoms, may occur after a placebo challenge day.

In conclusion, LRs in food allergic children after DBPCFC are poorly predictable, and

are generally not severe. Isolated LRs occur with comparable frequency after active and placebo challenges and are thus unlikely to be true allergic reactions. All LRs, including those on the placebo day, are more frequently reported in younger children. Children who do not experience severe immediate reactions may thus be safely discharged home 2 hours after a DBPCFC.

Recommendations for future research, policy and clinical practice

1. Food allergy and anaphylaxis today: the extent of the problem?

Although it is suggested that the prevalence of food allergy has increased, we have to keep in mind that reliable population-based data are limited.[2,5,7,102] In the Netherlands, food allergies are thought to be responsible for several hundred hospital admissions every year.[103] Although anaphylaxis to food is not uncommon, fatal food-induced anaphylaxis is very rare.[104] Overall, the case fatality rate is low, below 0.0001%.[104] However, the social impact of a fatality is enormous. Estimates of the actual prevalence of anaphylaxis are uncertain. For ethical reasons, it is not possible to conduct randomized, placebo-controlled trials in anaphylaxis. Therefore, to get a better insight in the physician visits for food allergies and anaphylaxis, hospital admissions and fatalities caused by anaphylaxis in the Netherlands, the first recommendation would therefore be to register them in a national database or to collaborate with an established international database. In 2006 an anaphylaxis registry was established in German-speaking countries and since 2011 several other European countries started to participate as well. [105-107] The data can only be entered by an allergist from participating countries.[106] The data cover demographical data, data on the elicitors, concomitant diseases, circumstances of the allergic reactions, and information about the treatment of affected patients.[106] This registry is an important clinical epidemiological tool which allows the generation of research but also disease management-related questions.[105] It may be of interest for health-care professionals and researchers in the Netherlands to participate in this anaphylaxis registry to know more about food allergies and anaphylaxis in the Netherlands, and to be able to make cross cultural comparisons. It would be recommended to allow also other health-care professionals than allergist to enter data in this anaphylaxis registry because not only allergist see food allergic patients. This will provide data about to whom patients turn to in case of allergic reactions (e.g. general practitioners, emergency departments, pediatricians, etcetera), and it will also possibly provide interesting data about EAI prescription practices by different health-care professionals and referral patterns.[105]

2. Improvement of the diagnosis and management of food allergy and anaphylaxis in clinical practice

The management of food allergy and anaphylaxis is suboptimal by patients and their families, GPs, pharmacists, and schools. In addition, the general public has also significant variations in their knowledge about food allergy with many misconceptions.[108] Therefore, until a cure is found for food allergies or better treatments developed, improving knowledge of symptoms, acute and long-term treatment, and prevention is the best strategy to protect food allergic patients from potentially fatal food allergic reactions. Interventions aimed specifically at knowledge gaps may help improve the quality of life of food allergic patients and their families.

Food allergic patients and their families

Food allergy is the trigger of anaphylaxis in the community. Therefore, it is of utmost importance to provide food allergic patients and their families with comprehensive information on food allergen avoidance, and prompt recognition and management of allergic reactions. Provision of an EAI and education on how and when to use it are also very important. Better knowledge is likely to diminish undiagnosed and untreated food allergy as well as inappropriate self-diagnosed food allergy. Moreover, food allergic patients and their families at high risk for anaphylaxis may become aware of the risk factors, allergic symptoms and potential severity of reactions. Educating food allergic patients to recognize severe allergic symptoms and when use an EAI and to seek medical help may lead to a better compliance and HRQL. Furthermore, when EAIs are prescribed, patients should be educated properly about the need to carry an EAI at all times, and about how and when to use this device. Patient education should also identify and correct patients' fears regarding EAI use to increase compliance. Using self-administration of an EAI (when needed) as a didactic tool (training program) may be more effective in alleviating fear and uncertainty incurred by the prospect of using the device. This may, in turn, lead to improved HRQL. Further research is needed and interesting to ascertain whether EAI self-administration does indeed have these effects. Patient education should also include instructions about how to read food ingredient labels. Patients can be referred to a dietician for education about this. It has been shown that correct food ingredient label identification was associated with prior instruction by a dietician.[17] In addition, there is an increased use of defensive precautionary food labelling, such as 'may contain' or 'may contain traces of'. Food allergic patients are advised to avoid these products, which limits them in their food choices and may also impair their HRQL.[109] It has been previously reported that patients ignore warnings on the labels of pre-packed foods.[110] This may be due to over-use of precautionary food labelling.[111] Therefore, over-use of precautionary labelling should be avoided whenever possible, since every additional *'may contain'* or

'may contain traces of' warning diminishes the impact, and thereby increasing the risk of unnecessary risk taking by food allergic patients and hence exposure.[112] The food industry plays an important role in the safety of patients with food allergies. There are differences between countries regarding food labeling regulations, with a different level of mandatory allergen information and different allergens that require labeling.[112] It would be advisable to harmonize food labeling regulations in the food industry worldwide in order to avoid unnecessary avoidance of food products and possibly increase the HRQL of food allergic patients.[113] The food industry suffers from a lack of knowledge on the level of allergen required to elicit a significant allergic reaction, and also there are no analytical systems to detect small amounts of allergenic food.[112] This may explain their defensive precautionary food labelling.[111,112,114,115] To guarantee an absolute safety of food allergic patients seems impossible, however, evidence-based references are urgently needed to determine threshold levels for all allergenic food.[112] With these evidence-based references food allergy management systems can be improved.[116] If food allergen management by the food industry improves this may ultimately lead to decrease risk taking behavior in patients and may help improve their HRQL.

General practitioners

Not only food allergic patients and their families but also general practitioners (GPs) and other health-care professionals should know about food allergen avoidance, and prompt recognition and management of (severe) allergic reactions. The management of anaphylaxis requires special attention of GPs and they should be familiar with it. To GPs there is limited time to record the patient's symptoms during a consultation and to think of a management plan. An allergy service is currently being developed to assist GPs to diagnose and treat food allergic patients.[112] This allergy service may be useful to GPs in the management of food allergic patients.

Primary care guidelines in the Netherlands, the *food allergy guidelines of the Dutch College of General Practitioners* (NHG) guidelines differ from the internationally accepted guidelines for the diagnosis and management of food allergy and anaphylaxis.[117] The NHG guidelines recommend that an EAI should only be prescribed after a previous case of anaphylaxis. The main difference that needs urgent attention is that risk factors for a life-threatening food-induced anaphylactic reaction are mentioned, but are not put forward as a reason to prescribe an EAI in the absence of a previous anaphylactic reaction. This implies that food allergic patients at high risk for anaphylaxis are not being prescribed an EAI, and put them at serious risk for a fatal allergic reaction. It would therefore be recommended to revise the NHG guidelines and put risk factors for a life-threatening food-induced anaphylactic reaction forward as a reason to prescribe an EAI. Furthermore, educational programs for general practitioners are needed to get acquainted with these

(inter)national guidelines. The educational programs should consist of at least the following items: (1) diagnosis of food allergy and anaphylaxis; (2) acute management of food allergy and anaphylaxis; and (3) long-term management of food allergy and anaphylaxis. The latter should preferably consist of prescription of EAI, including education on when and how to use it. This in turn may improve EAI use in the community and save lives. Also, it would be beneficial to implement clear referral criteria to assist GPs to refer patients to a specialist with specific expertise on allergology when this is needed.

Pharmacists

The EAACI food allergy and anaphylaxis guidelines, in the section on managing patients with food allergy in the community, intend to provide guidance to reduce the risk of accidental allergic reactions to foods in the community.[29,64-66] Although these recommendations target numerous health-care professionals relevant to food allergy, pharmacists are surprisingly not included. Pharmacist play an important role in the management of food allergic patients, at least in the Netherlands. Here pharmacists and pharmacy staff dispense EAIs to food allergic patients, and are required to provide all the appropriate medication-related information and instruction. However, Van Dijk et al.[33] showed that when dispensing first (or repeat) prescription medications, pharmacy staff do provide medication-related information, but this information is incomplete according to the professional guidelines of the pharmacist organization. In addition, GPs in the Netherlands feel that giving instructions about how to use an EAI is the responsibility of the pharmacist. Therefore, it is necessary that pharmacists in the Netherlands know about food allergy and its management in order to give patients proper instructions on when and how to use an EAI. Therefore, the same recommendation is relevant as for GPs and other health-care professionals, educational programs are needed for pharmacists and pharmacy staff.

Pharmaceutical care in European countries are quite diverse because of differences in legal and political aspects of health-care systems and because practices have developed in different ways and at different paces.[118] It may therefore be that the roles and responsibilities of pharmacists and pharmacy staff differ between European countries. According to '*Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie* (KNMP)' (The Royal Dutch Pharmacists Association), the roles and responsibility of pharmacist do differ between European countries, mainly because of the different health-care systems. The roles and responsibilities have been evolving from product-oriented to patient-oriented service provision in the last two decades.[118-123] Extended and new roles for pharmacists, as professionals of health care services and as scientists, are increasingly being recognized and valued.[124] It would be of interest to investigate to what extent the roles and responsibilities differ between the different countries differ. According to KNMP,

pharmacists within Europe should be able to provide essential medicines expertise, and in case of an EAI they should be able to explain to a food allergic patients how to use an EAI. However, to our knowledge there are no studies investigating the knowledge, attitudes, and beliefs and management regarding food allergy and anaphylaxis among pharmacists elsewhere in Europe. It would be of interest to further investigate the cross-cultural differences in these areas, so that the management of food allergic patients by pharmacists may eventually be optimized and that guidelines for pharmacies can be developed and implemented.

Schools and other public places

Schools in the Netherlands all should have a system to identify food allergic children and should know how to manage food allergies and anaphylaxis. Pro-active management is important. School staff responsible for student supervision should be properly instructed to recognize the onset of an allergic reaction, including anaphylaxis, should know how and when to use an EAI and when to seek medical help. Schools should be allowed to have undesignated EAIs available for use in students not being prescribed an EAI who experience a (severe) allergic reaction. In order to implement this, national legislation is needed. There should be a law for schools (and possibly also for all other public places) to ensure that all school boards have policies or procedures in place to address anaphylaxis in schools, which includes providing instruction to staff and guidance on the administration of medication. School, families, health-care professionals and the government should work together to create a safe educational environment.[124] It would be of interest to investigate further the preparedness of schools for food allergy and anaphylaxis after implementing such a law. After this implementation it would be of interest to investigate whether or not this law caused a decrease in food allergy accidents in schools and whether or not the HRQL of food allergic children and their families improved.

There should also be a law that permits schools and other public places to have an undesignated EAI available for individuals experiencing anaphylaxis. The undesignated EAI should be available in unlocked an easily accessible places in schools and other public places and may be used by trained individuals. Preferably, it should be next to the Automatic External Defibrillators (AED) available in public places. In addition, companies who provide first-aid training courses for the general public should also cover food allergies, anaphylaxis and its management including how and when to use an EAI. This may lead to a better understanding of the seriousness of food allergies and anaphylaxis among the general public and better treatment of food allergic patients in case of emergency.

General public

Improved food allergy and anaphylaxis knowledge among the general public is desirable as the general public plays a significant role in the well-being of food allergic patients.[27,33,125] Many people believe that they are allergic to foods or food ingredients. Estimates range from five to twenty per cent.[33] This means that between one and three million Dutch people believe, rightly or wrongly, that they are allergic to specific foods.[103] Besides this, food allergic patients are often misunderstood, ignored, bullied or not taken seriously, which may considerably affect their physical and psychological well-being. Therefore, raising public awareness about food allergy and anaphylaxis is needed. In recent years, the Dutch government has made an effort to increase the public awareness of several health-related topics by using campaigns.[103] Surprisingly, food allergy and anaphylaxis has never been a topic until now. Food allergy and anaphylaxis may be particularly suitable for a governmental campaign as they seem to increase knowledge and change attitudes and behaviors.[126,127]

Epinephrine auto-injectors

Worryingly, food allergic patients, food allergic adolescents in particular, are often poorly compliant and do not always carry and use their EAI. There are a number of possible reasons why poor compliance and non-use is so prevalent with EAIs amongst food allergic adolescents. An area of interest is the device itself to determine the ideal features of an EAI from a food allergic patient's perspective. Interestingly, the ideal features from a patient's perspective have not been investigated. Even though, in our study (*chapter 4*), the inconvenience, shape and size of the EAI were not associated with self-reported non-compliance with carrying the device, other studies showed that the size and shape discourages adolescents from carrying the EAI at all times.[126] Therefore, research is needed to investigate the ideal features from a food allergic patient's perspective, and researcher and pharmaceutical companies should together with food allergic patients to focus on a new design for an EAI. Further research is also needed regarding the impact of EAI prescription on HRQL. It may be interesting to investigate this prospectively and longitudinally. It would also be interesting to investigate the effects of the newly designed EAIs on compliance, non-use and HRQL of food allergic patients.

Prescription practices of EAIs differ considerably. There is data about absolute indications for a prescription of an EAI, however, there is no high quality data to help decide how many EAIs should be available to individual patients.[21,128] A decision to prescribe one, two or more devices will be influenced by a number of factors (e.g. previous severity, access to medical care). The EAACI task force on anaphylaxis suggested indications for prescription of a second EAI.[66] However, as mentioned above, food allergic adolescents are poorly compliant and do not always carry and use their EAI. It would

therefore be of interest to see whether or not prescribing more than one EAI has an effect on compliance, non-use and HRQL. Food-allergic patients are instructed to use their EAIs if they have signs of an allergic reaction. However, there are different recommendations given by health-care professionals and manufacturers of EAIs as to when an EAI should be administered. Administering an EAI after a patient has ingested the culprit food but is not yet experiencing allergic symptoms is unlikely to be necessary. However, to wait and see whether an allergic reaction progresses from mild to severe is not advisable. The reasons for the different recommendations are due to lack of studies evaluating acute interventions in anaphylaxis and making it therefore difficult to generate evidence based recommendations. For ethical reasons, it is not possible to conduct randomized, placebo-controlled trials in anaphylaxis. Therefore, even though fatal anaphylaxis is rare, early administration of an EAI may therefore be justified until experience proves otherwise.

3. Health related quality of life for patients with food allergy and minimal clinical important difference

Living with a food allergy may influence daily life in a negative way and may affect HRQL. The *Food Allergy Quality of Life Questionnaires* (FAQLQs) are disease-specific health-related quality of life questionnaires to may be used to measure the impact of food allergy on a patient's HRQL. These reliable and validated questionnaires are important tools to measure a statistically significant differences or changes in HRQL. However, this does not necessarily mean that the observed change in quality of life is worthwhile or important to the patient. In order to understand, determine and interpret the magnitude of change, one requires an understanding of the minimal clinical important difference (MCID). A MCID is introduced as a threshold value for the smallest change in HRQL score that is actually perceived by the patient as being clinically meaningful. The MCID is defined as '*the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive costs, a change in the patient's management*'.[66] The specific MCID of the FAQLQs has not been determined in earlier studies. The MCID of the disease-specific health-related quality-of-life questionnaires with a 7-point scale was commonly close to 0.5.[129] We therefore recommend to determine the MCID of the FAQLQs, because it may give clinicians and researchers a better insight into whether a change in the FAQLQ score, for example before and after an intervention, is also a clinically important change.

4. Late reactions following DBPCFCs

An important point in the management of food allergic patients is the observation period after an allergic reaction. Besides immediate reactions, late reactions (LRs) have also been reported and may present with a variety of symptoms, of which anaphylactic symptoms are the most severe. Other variants of the usual monophasic anaphylaxis include biphasic anaphylaxis and protracted anaphylaxis. Position papers on anaphylaxis recommend that the observation should be individualized on the basis of the severity of the reaction.[129] These recommendations for the observation period are for allergic reactions that occur in the community. A DBPCFC can also result in late onset of symptoms. The time during which children are observed following a DBPCFC varies also in clinical practice. Previous studies showed that patients who developed severe immediate reactions may experience severe late or recurrent reactions, even though such reactions may be uncommon. In our study no severe LRs were reported. Therefore, it is probably not necessary to observe food allergic children for more than two hours after DBPCFC except following exceptionally severe immediate reactions**.**

The prediction model for the active and placebo challenge day in our study accounted for only 8.0% and 12.1% respectively of the variance in LRs. Even though the LRs in food allergic children after DBPCFC in our study were not severe, they were poorly predicable. It would therefore be of interest to further investigate predictors of LRs after DBPFCFC to be able to predict which food allergic patients are more at risk for LRs.

Concluding remarks

This thesis showed that the prevalence of food allergy in Dutch high-risk food allergic adolescents has not increased appreciably in the last six years. The calculated questionnaire-based prevalence of probable food allergy was 6.2%. It also showed that even though EAI ownership has improved marginally, there is still a substantial under-prescription of EAIs in high-risk food allergic adolescents in the Netherlands. The under-prescription of EAIs may be partly due to GPs not prescribing this medication to patients for whom it would be appropriate to do so. In this thesis we showed that food allergic patients at high risk for anaphylaxis who visit their GP are often not prescribed an EAI, even those with a previous allergic reaction. To those food allergic patients who are prescribed an EAI, this treatment may be perceived as burdensome and this may affect compliance. In this thesis we showed that the majority of food allergic adolescents and their parents were positive about the EAI. The perceived burden was thus low. However, for food allergic adolescents, a higher burden of treatment was associated with self-reported non-compliance with carrying an EAI at all times. The burden of treatment measure seems to measure a distinct concept related to compliance behavior and relatively subtle differences in burden of treatment have an impact on compliance.

In this thesis we showed that experiencing anaphylaxis or being prescribed an EAI did not seem to be related to HRQL of either food allergic adults (≥ 18 years) or children (8-12 years). We also showed that important predictors other than self-perceived disease severity for HRQL of food allergic adults in Europe were type of allergenic food, type of symptoms, and gender. For children important predictors were type of allergenic food and country of origin.

Food allergic patient being prescribed an EAI should receive training that covers avoidance strategies, recognition of symptoms, and most importantly when and how to administer an EAI. This thesis showed that there are knowledge gaps about food allergy and its management among pharmacists in the Netherlands. It also showed that food allergic patients at high risk for anaphylaxis who receive their EAI from a pharmacy in the Netherlands are often not or incorrectly instructed on how to use an EAI.

The time during which children are observed following a DBPCFC varies in clinical practice. Recommendations vary from between 2 to 24 hours. This thesis showed that late reactions in food allergic children and adolescents after DBPCFC do occur, are poorly predictable and are generally not severe. In our study no severe late reactions were reported. Therefore, it is probably not necessary to observe food allergic children for more than two hours after DBPCFC except following exceptionally severe immediate reactions.

REFERENCES

(1) Flokstra-de Blok BM, Doriene van Ginkel C, Roerdink EM, Kroeze MA, Stel AA, van der Meulen GN, et al. Extremely low prevalence of epinephrine autoinjectors in high-risk food-allergic adolescents in Dutch high schools. Pediatr Allergy Immunol 2011 Jun;22(4):374-377.

(2) Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy 2014 Jan;69(1):62-75.

(3) Steinke M, Fiocchi A, Kirchlechner V, Ballmer-Weber B, Brockow K, Hischenhuber C, et al. Perceived food allergy in children in 10 European nations. A randomised telephone survey. Int Arch Allergy Immunol 2007;143(4):290-295.

(4) Koplin JJ, Mills EN, Allen KJ. Epidemiology of food allergy and food-induced anaphylaxis: is there really a Western world epidemic? Curr Opin Allergy Clin Immunol 2015 Oct;15(5):409-416.

(5) Sicherer SH. Epidemiology of food allergy. J Allergy Clin Immunol 2011 Mar;127(3):594-602.

(6) McGowan EC, Keet CA. Prevalence of self-reported food allergy in the National Health and Nutrition Examination Survey (NHANES) 2007-2010. J Allergy Clin Immunol 2013 Nov;132(5):1216-1219.e5.

(7) Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy 2014 Aug;69(8):992-1007.

(8) Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. J Allergy Clin Immunol 2007 Sep;120(3):638-646.

(9) Zuidmeer L, Goldhahn K, Rona RJ, Gislason D, Madsen C, Summers C, et al. The prevalence of plant food allergies: a systematic review. J Allergy Clin Immunol 2008 May;121(5):1210-1218.e4.

(10) Venter C, Pereira B, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. Pediatr Allergy Immunol 2006 Aug;17(5):356-363.

(11) Zuberbier T, Edenharter G, Worm M, Ehlers I, Reimann S, Hantke T, et al. Prevalence of adverse reactions to food in Germany - a population study. Allergy 2004 Mar;59(3):338-345.

(12) Roehr CC, Edenharter G, Reimann S, Ehlers I, Worm M, Zuberbier T, et al. Food allergy and non-allergic food hypersensitivity in children and adolescents. Clin Exp Allergy 2004 Oct;34(10):1534-1541.

(13) Jansen JJ, Kardinaal AF, Huijbers G, Vlieg-Boerstra BJ, Martens BP, Ockhuizen T. Prevalence of food allergy and intolerance in the adult Dutch population. J Allergy Clin Immunol 1994 Feb;93(2):446-456.

(14) Pereira B, Venter C, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization to food allergens, reported adverse reaction to foods, food avoidance, and food hypersensitivity among teenagers. J Allergy Clin Immunol 2005 Oct;116(4):884-892.

(15) Goossens NJ, Flokstra-de Blok BM, van der Meulen GN, Botjes E, Burgerhof HG, Gupta RS, et al. Food allergy knowledge of parents - is ignorance bliss? Pediatr Allergy Immunol 2013 Sep;24(6):567-573.

(16) Gupta RS, Springston EE, Smith B, Kim JS, Pongracic JA, Wang X, et al. Food allergy knowledge, attitudes, and beliefs of parents with food-allergic children in the United States. Pediatr Allergy Immunol 2010 Sep;21(6):927-934.

(17) Gupta RS, Kim JS, Barnathan JA, Amsden LB, Tummala LS, Holl JL. Food allergy knowledge, attitudes and beliefs: focus groups of parents, physicians and the general public. BMC Pediatr 2008 Sep 19;8:36-2431-8-36.

(18) Gupta RS, Kim JS, Springston EE, Smith B, Pongracic JA, Wang X, et al. Food allergy knowledge, attitudes, and beliefs in the United States. Ann Allergy Asthma Immunol 2009 Jul;103(1):43-50.
(19) Goossens NJ, Flokstra-de Blok BMJ, Gupta RS, Springston EE, Smith B, Duiverman EJ, et al. Knowledge, attitudes and beliefs regarding food allergy among general public in the Netherlands - a cross-cultural comparison with the USA. submitted .
(20) Jones CJ, Llewellyn CD, Frew AJ, Du Toit G, Mukhopadhyay S, Smith H. Factors associated with good adherence to self-care behaviours amongst adolescents with food allergy. Pediatr Allergy Immunol 2015 Mar;26(2):111-118.
(21) Marrs T, Lack G. Why do few food-allergic adolescents treat anaphylaxis with adrenaline?--Reviewing a pressing issue. Pediatr Allergy Immunol 2013 May;24(3):222-229.
(22) Sampson MA, Munoz-Furlong A, Sicherer SH. Risk-taking and coping strategies of adolescents and young adults with food allergy. J Allergy Clin Immunol 2006 Jun;117(6):1440-1445.
(23) Rolison MR, Scherman A. Factors influencing adolescents' decisions to engage in risk-taking behavior. Adolescence 2002 Fall;37(147):585-596.
(24) Lyons AC, Forde EM. Food allergy in young adults: perceptions and psychological effects. J Health Psychol 2004 Jul;9(4):497-504.
(25) Greenhawt MJ, Singer AM, Baptist AP. Food allergy and food allergy attitudes among college students. J Allergy Clin Immunol 2009 Aug;124(2):323-327.
(26) Blakemore SJ, Burnett S, Dahl RE. The role of puberty in the developing adolescent brain. Hum Brain Mapp 2010 Jun;31(6):926-933.
(27) Muraro A, Clark A, Beyer K, Borrego LM, Borres M, Lodrup Carlsen KC, et al. The management of the allergic child at school: EAACI/GA2LEN Task Force on the allergic child at school. Allergy 2010 Jun 1;65(6):681-689.
(28) Simons FE, World Allergy Organization. Epinephrine auto-injectors: first-aid treatment still out of reach for many at risk of anaphylaxis in the community. Ann Allergy Asthma Immunol 2009 May;102(5):403-409.
(29) Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy 2007 Aug;62(8):857-871.
(30) Sicherer SH, Furlong TJ, DeSimone J, Sampson HA. The US Peanut and Tree Nut Allergy Registry: characteristics of reactions in schools and day care. J Pediatr 2001 Apr;138(4):560-565.
(31) Nowak-Wegrzyn A, Conover-Walker MK, Wood RA. Food-allergic reactions in schools and preschools. Arch Pediatr Adolesc Med 2001 Jul;155(7):790-795.
(32) Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med 1992 Aug 6;327(6):380-384.
(33) Muraro A, Agache I, Clark A, Sheikh A, Roberts G, Akdis CA, et al. EAACI food allergy and anaphylaxis guidelines: managing patients with food allergy in the community. Allergy 2014 Aug;69(8):1046-1057.
(34) Polloni L, Baldi I, Lazzarotto F, Bonaguro R, Toniolo A, Celegato N, et al. School personnel's self-efficacy in managing food allergy and anaphylaxis. Pediatr Allergy Immunol 2016 Feb 17.
(35) Le TM, Kummeling I, Dixon D, Barreales Tolosa L, Ballmer-Weber B, Clausen M, et al. Low preparedness for food allergy as perceived by school staff: a EuroPrevall survey across Europe. J Allergy Clin Immunol Pract 2014 Jul-Aug;2(4):480-82, 482.e1.
(36) Morris P, Baker D, Belot C, Edwards A. Preparedness for students and staff with anaphylaxis. J Sch Health 2011 Aug;81(8):471-476.
(37) Anaphylaxis in schools and other childcare settings. AAAAI Board of Directors. American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 1998 Aug;102(2):173-176.

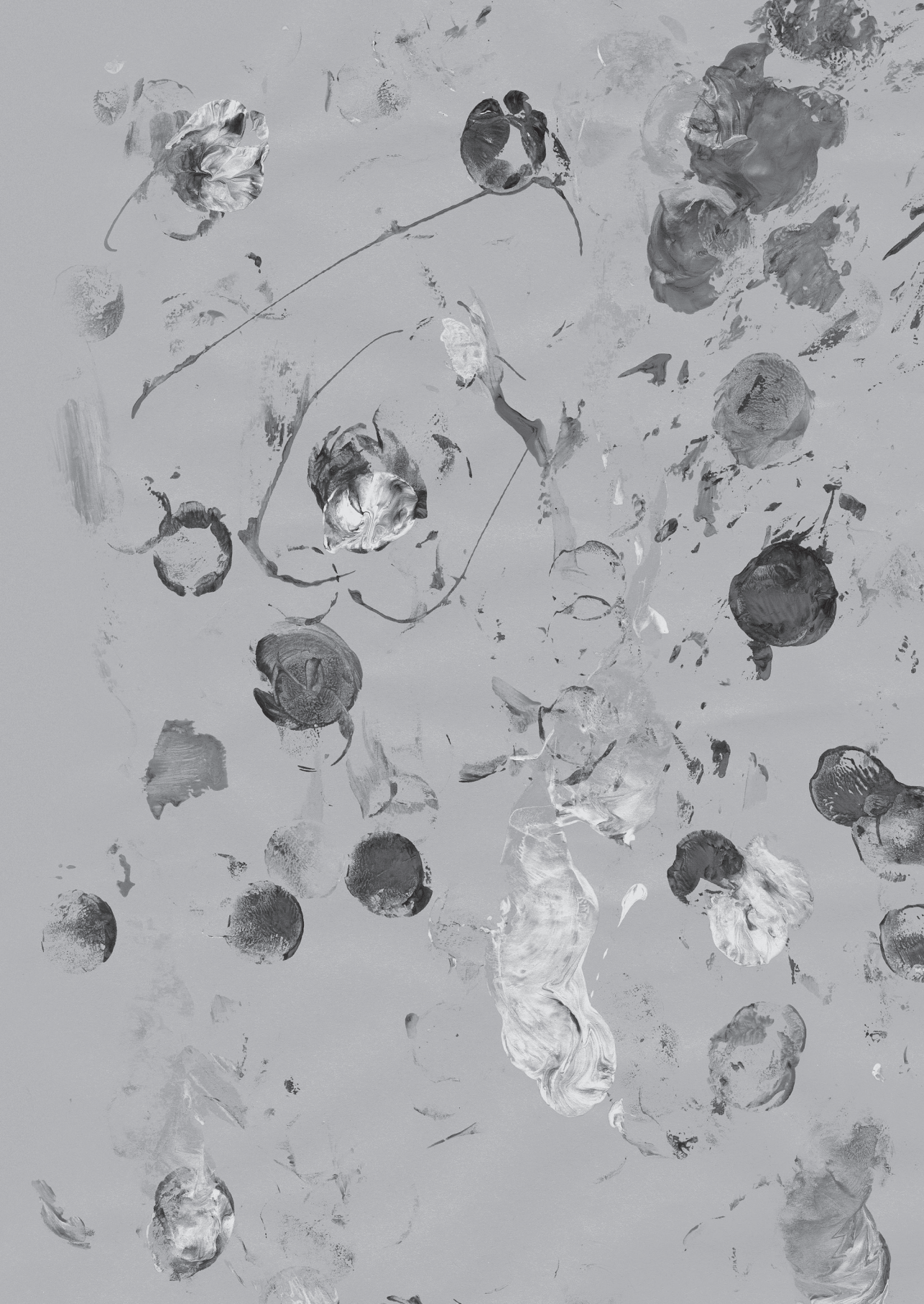
(38) Baumgart K, Brown S, Gold M, Kemp A, Loblay R, Loh R, et al. ASCIA guidelines for prevention of food anaphylactic reactions in schools, preschools and child-care centres. J Paediatr Child Health 2004 Dec;40(12):669-671.
(39) Vale S, Smith J, Said M, Dunne G, Mullins R, Loh R, et al. ASCIA guidelines for prevention of anaphylaxis in schools, pre-schools and childcare: 2012 update. J Paediatr Child Health 2013 May;49(5):342-345.
(40) Vale S, Smith J, Said M, Mullins RJ, Loh R. ASCIA guidelines for prevention of anaphylaxis in schools, pre-schools and childcare: 2015 update. J Paediatr Child Health 2015 Oct;51(10):949-954.
(41) Sabrina's Law, 2005, S.O. 2005, c. 7. Available at: https://www.ontario.ca/laws/statute/05s07. Accessed 06/08, 2016.
(42) Food Allergy Research & Education (FARE). School access to Epinephrine. Available at: http://www.foodallergy.org/advocacy/epinephrine-at-school. Accessed 06/08, 2016.
(43) Managing chronic health conditions at school. A resource pack for teachers and parents. Available at: www.into.ie. Accessed 06/29, 2016.
(44) Ministerie van Onderwijs, Cultuur en en Wetenschap. Wet- en regelgeving. Wet op het Primair Onderwijs. Available at: http://wetten.overheid.nl/BWBR0003420/2016-01-18. Accessed 06/29, 2016.
(45) Ministerie van Onderwijs, Cultuur en en Wetenschap. Wet- en regelgeving. Wet op het Voorgezet Onderwijs. Available at: http://wetten.overheid.nl/BWBR0002399/2016-01-18. Accessed 06/29, 2016.
(46) Ministerie van Onderwijs, Cultuur en Wetenschap. Wet- en regelgeving. Wet Ondersteuning Onderwijz Zieke Leerlingen. Available at: http://wetten.overheid.nl/BWBR0014940/2003-04-23. Accessed 06/29, 2016.
(47) Wet- en regelgeving. Arbeidsomstandighedenwet. Available at: http://wetten.overheid.nl/BWBR0010346/2016-01-01#Hoofdstuk2_Paragraaf_8_Artikel10. Accessed 06/29, 2016.
(48) Wet- en regelgeving. Wet op de beroepen in de individuele gezondheidszorg. Available at: http://wetten.overheid.nl/BWBR0006251/2016-01-18. Accessed 06/08, 2016.
(49) Ministerie van Volksgezondheid, Welzijn en Sport (Ministery of Health, Welfare and Sports). Wet op de beroepen in de individuele gezondheidszorg (Wet BIG). Available at: http://www.igz.nl/onderwerpen/handhaving_en_toezicht/wetten/wet_big/. Accessed 06/08, 2016.
(50) US Government. Public Law 113–48. School Access to Emergency Epinephrine Act. 2013; Available at: https://www.gpo.gov/fdsys/pkg/PLAW-113publ48/pdf/PLAW-113publ48.pdf. Accessed 06/29, 2016.
(51) Ministery of Health. Irisch Statute Book. S.I. No. 449/2015 - Medicinal Products (Prescription and Control of Supply) (Amendment) (No. 2) Regulations 2015. 2015; Available at: http://www.irishstatutebook.ie/eli/2015/si/449/made/en/print. Accessed 07/01, 2016.
(52) Van der Wel J, Schmidt J, Van der Ploeg S. Evaluatie Wet Ondersteuning Onderwijs Zieke Leerlingen. 2003; Available at: http://parlis.nl/pdf/bijlagen/BLG820.pdf. Accessed 06/29, 2016.
(53) Australasian Society of Clinical Immunology and Allergy: ASCIA Action Plans for Anaphylaxis. Available at: http://www.allergy.org.au/health-professionals/ascia-plans-action-and-treatment. Accessed 06/09, 2016.
(54) Egan M, Sicherer S. Doctor, my child is bullied: food allergy management in schools. Curr Opin Allergy Clin Immunol 2016 Jun;16(3):291-296.
(55) Oppenheimer J, Bender B. The impact of food allergy and bullying. Ann Allergy Asthma Immunol 2010 Dec;105(6):410-411.
(56) Klemans RJ, Le TM, Sigurdsson V, Enters-Weijnen CF, van Hoffen E, Bruijnzeel-Koomen CA, et al. Management of acute food allergic reactions by general practitioners. Eur Ann Allergy Clin Immunol 2013 Apr;45(2):43-51.

(57) Hayman Grant R GR. Knowledge about using auto-injectable adrenaline: review of patients' case notes and interviews with general practitioners. BMJ: British Medical Journal 2003-12-6;327(7427).
(58) Le TM, van Hoffen E, Pasmans SG, Bruijnzeel-Koomen CA, Knulst AC. Suboptimal management of acute food-allergic reactions by patients, emergency departments and general practitioners. Allergy 2009 Aug;64(8):1227-1228.
(59) Lowe, G Kirkwood,E Harkness, S. Survey of anaphylaxis management by general practitioners in Scotland. Scott Med J 2010;55(3):11-14.
(60) Gupta RS, Springston EE, Kim JS, Smith B, Pongracic JA, Wang X, et al. Food allergy knowledge, attitudes, and beliefs of primary care physicians. Pediatrics 2010 Jan;125(1):126-132.
(61) Agache I, Ryan D, Rodriguez MR, Yusuf O, Angier E, Jutel M. Allergy management in primary care across European countries -- actual status. Allergy 2013 Jul;68(7):836-843.
(62) Jutel M, Angier L, Palkonen S, Ryan D, Sheikh A, Smith H, et al. Improving allergy management in the primary care network--a holistic approach. Allergy 2013 Nov;68(11):1362-1369.
(63) Waserman S, Chad Z, Francoeur MJ, Small P, Stark D, Vander Leek TK, et al. Management of anaphylaxis in primary care: Canadian expert consensus recommendations. Allergy 2010 Sep;65(9):1082-1092.
(64) Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy 2014 Aug;69(8):1008-1025.
(65) Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF,Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006 Feb;117(2):391-397.
(66) Muraro A, Roberts G, Worm M, Bilo MB, Brockow K, Fernandez Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014 Aug;69(8):1026-1045.
(67) Campbell RL, Luke A, Weaver AL, St Sauver JL, Bergstralh EJ, Li JT, et al. Prescriptions for self-injectable epinephrine and follow-up referral in emergency department patients presenting with anaphylaxis. Ann Allergy Asthma Immunol 2008 Dec;101(6):631-636.
(68) Melville N, Beattie T. Paediatric allergic reactions in the emergency department: a review. Emerg Med J 2008 Oct;25(10):655-658.
(69) Consultation and referral guidelines citing the evidence: how the allergist-immunologist can help. J Allergy Clin Immunol 2006;117(2 Suppl Consultation):S495-S523.
(70) Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Epinephrine auto-injector use in adolescents at risk of anaphylaxis: a qualitative study in Scotland, UK. Clin Exp Allergy 2011 Jun;41(6):869-877.
(71) Gallagher M, Worth A, Cunningham-Burley S, Sheikh A. Strategies for living with the risk of anaphylaxis in adolescence: qualitative study of young people and their parents. Prim Care Respir J 2012 Dec;21(4):392-397.
(72) Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 2000 Aug;30(8):1144-1150.
(73) Pumphrey RS. Fatal anaphylaxis in the UK, 1992-2001. Novartis Found Symp 2004;257:116-28; discussion 128-32, 157-60, 276-85.
(74) Allen CW, Bidarkar MS, vanNunen SA, Campbell DE. Factors impacting parental burden in food-allergic children. J Paediatr Child Health 2015 Jan 15.
(75) Oude Elberink JN, van der Heide S, Guyatt GH, Dubois AE. Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis. J Allergy Clin Immunol 2006 Sep;118(3):699-704.

(76) Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 2001 Jan;107(1):191-193.
(77) Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol 2007 Apr;119(4):1016-1018.
(78) MacKenzie H, Roberts G, van Laar D, Dean T. Teenagers' experiences of living with food hypersensitivity: a qualitative study. Pediatr Allergy Immunol 2010 Jun;21(4 Pt 1):595-602.
(79) Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. J Allergy Clin Immunol 2007 Apr;119(4):1018-1019.
(80) Monks H, Gowland MH, MacKenzie H, Erlewyn-Lajeunesse M, King R, Lucas JS, et al. How do teenagers manage their food allergies? Clin Exp Allergy 2010 Oct;40(10):1533-1540.
(81) Simons KJ, Simons FE. Epinephrine and its use in anaphylaxis: current issues. Curr Opin Allergy Clin Immunol 2010 Aug;10(4):354-361.
(82) Lieberman JA, Sicherer SH. Quality of life in food allergy. Curr Opin Allergy Clin Immunol 2011 Jun;11(3):236-242.
(83) Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol 2010 Feb;125(2 Suppl 2):S116-25.
(84) Pinczower GD, Bertalli NA, Bussmann N, Hamidon M, Allen KJ, DunnGalvin A, et al. The effect of provision of an adrenaline autoinjector on quality of life in children with food allergy. J Allergy Clin Immunol 2013 1;131(1):238-240.e1.
(85) Lucassen P, Albeda F, Van Reisen M, Silvius A, Wensing C, Luning-Koster M. NHG guideline Food Hypersensitivity. 2010(53):537-553.
(86) Grouhi M, Alshehri M, Hummel D, Roifman CM. Anaphylaxis and epinephrine auto-injector training: who will teach the teachers? J Allergy Clin Immunol 1999 Jul;104(1):190-193.
(87) Mehr Sam S. Doctor--how do I use my EpiPen? Pediatric Allergy and Immunology 2007-8;18(5):448-52.
(88) Sicherer SH, Forman JA, Noone SA. Use assessment of self-administered epinephrine among food-allergic children and pediatricians. Pediatrics 2000 Feb;105(2):359-362.
(89) Brown Josephine J. A randomized maternal evaluation of epinephrine autoinjection devices. Pediatric Allergy and Immunology 2013-3;24(2):173-7.
(90) Arkwright Peter D PD. Factors determining the ability of parents to effectively administer intramuscular adrenaline to food allergic children. Pediatric Allergy and Immunology 2006-5;17(3):227-9.
(91) Barnett CW. Need for community pharmacist-provided food-allergy education and auto-injectable epinephrine training. J Am Pharm Assoc (2003) 2005 Jul-Aug;45(4):479-485.
(92) Salter SM, Loh R, Sanfilippo FM, Clifford RM. Demonstration of epinephrine autoinjectors (EpiPen and Anapen) by pharmacists in a randomised, simulated patient assessment: acceptable, but room for improvement. Allergy Asthma Clin Immunol 2014 Sep 19;10(1):49-1492-10-49. eCollection 2014.
(93) Topal E, Bakirtas A, Yilmaz O, Karagol IH, Arga M, Demirsoy MS, et al. When should we perform a repeat training on adrenaline auto-injector use for physician trainees? Allergol Immunopathol (Madr) 2014 Sep-Oct;42(5):472-475.
(94) Bakirtas A, Arga M, Catal F, Derinoz O, Demirsoy MS, Turktas I. Make-up of the epinephrine autoinjector: the effect on its use by untrained users. Pediatr Allergy Immunol 2011 Jul 13.
(95) Arga M, Bakirtas A, Catal F, Derinoz O, Harmanci K, Razi CH, et al. Training of trainers on epinephrine autoinjector use. Pediatr Allergy Immunol 2011 Feb 10.
(96) Simons FE, Lieberman PL, Read EJ,Jr, Edwards ES. Hazards of unintentional injection of epinephrine from autoinjectors: a systematic review. Ann Allergy Asthma Immunol 2009 Apr;102(4):282-287.
(97) Lee J, Garrett JP, Brown-Whitehorn T, Spergel JM. Biphasic reactions in children undergoing oral food challenges. Allergy Asthma Proc 2013 May-Jun;34(3):220-226.

(98) Mehr S, Liew WK, Tey D, Tang ML. Clinical predictors for biphasic reactions in children presenting with anaphylaxis. Clin Exp Allergy 2009 Sep;39(9):1390-1396.
(99) Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. Pediatrics 2000 Oct;106(4):762-766.
(100) Wensing M, Penninks AH, Hefle SL, Koppelman SJ, Bruijnzeel-Koomen CA, Knulst AC. The distribution of individual threshold doses eliciting allergic reactions in a population with peanut allergy. J Allergy Clin Immunol 2002 Dec;110(6):915-920.
(101) Vlieg-Boerstra BJ, van der Heide S, Bijleveld CM, Kukler J, Duiverman EJ, Dubois AE. Placebo reactions in double-blind, placebo-controlled food challenges in children. Allergy 2007 Aug;62(8):905-912.
(102) Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, et al. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy 2013 Nov;68(11):1353-1361.
(103) Gezondheidsraad. Voedselallergie. 2007; Available at: http://www.gezondheidsraad.nl/sites/default/files/200707.pdf.
(104) Umasunthar T, Leonardi-Bee J, Hodes M, Turner PJ, Gore C, Habibi P, et al. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. Clin Exp Allergy 2013 Dec;43(12):1333-1341.
(105) Worm M, Hompes S. The registry for severe allergic reactions in German-speaking countries. Recent data and perspectives. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2012 Mar;55(3):380-384.
(106) Worm M, Edenharter G, Rueff F, Scherer K, Pfohler C, Mahler V, et al. Symptom profile and risk factors of anaphylaxis in Central Europe. Allergy 2012 May;67(5):691-698.
(107) Hompes S, Kohli A, Nemat K, Scherer K, Lange L, Rueff F, et al. Provoking allergens and treatment of anaphylaxis in children and adolescents--data from the anaphylaxis registry of German-speaking countries. Pediatr Allergy Immunol 2011 Sep;22(6):568-574.
(108) Jones RB, Hewson P, Kaminski ER. Referrals to a regional allergy clinic - an eleven year audit. BMC Public Health 2010 Dec 29;10:790-2458-10-790.
(109) Joshi P, Mofidi S, Sicherer SH. Interpretation of commercial food ingredient labels by parents of food-allergic children. J Allergy Clin Immunol 2002 Jun;109(6):1019-1021.
(110) Cornelisse-Vermaat JR, Voordouw J, Yiakoumaki V, Theodoridis G, Frewer LJ. Food-allergic consumers' labelling preferences: a cross-cultural comparison. Eur J Public Health 2008 Apr;18(2):115-120.
(111) Hefle SL, Furlong TJ, Niemann L, Lemon-Mule H, Sicherer S, Taylor SL. Consumer attitudes and risks associated with packaged foods having advisory labeling regarding the presence of peanuts. J Allergy Clin Immunol 2007 Jul;120(1):171-176.
(112) Muraro A, Hoffmann-Sommergruber K, Holzhauser T, Poulsen LK, Gowland MH, Akdis CA, et al. EAACI Food Allergy and Anaphylaxis Guidelines. Protecting consumers with food allergies: understanding food consumption, meeting regulations and identifying unmet needs. Allergy 2014 Nov;69(11):1464-1472.
(113) Taylor SL, Hefle SL. Food allergen labeling in the USA and Europe. Curr Opin Allergy Clin Immunol 2006 Jun;6(3):186-190.
(114) Ford LS, Taylor SL, Pacenza R, Niemann LM, Lambrecht DM, Sicherer SH. Food allergen advisory labeling and product contamination with egg, milk, and peanut. J Allergy Clin Immunol 2010 Aug;126(2):384-385.
(115) Robertson ON, Hourihane JO, Remington BC, Baumert JL, Taylor SL. Survey of peanut levels in selected Irish food products bearing peanut allergen advisory labels. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2013;30(9):1467-1472.
(116) Crevel RW, Baumert JL, Luccioli S, Baka A, Hattersley S, Hourihane JO, et al. Translating reference doses into allergen management practice: challenges for stakeholders. Food Chem Toxicol 2014 May;67:277-287.

(117) Brakel T, Flokstra-de Blok B, van der Molen T, Dubois A. Developing a decision support system for the management of allergy in primary care: system requirements as reported by general practitioners. Allergy 2012;67(11.2012):108.
(118) van Dijk M, Blom L, Koopman L, Philbert D, Koster E, Bouvy M, et al. Patient-provider communication about medication use at the community pharmacy counter. Int J Pharm Pract 2016 Feb;24(1):13-21.
(119) Christensen DB, Farris KB. Pharmaceutical care in community pharmacies: practice and research in the US. Ann Pharmacother 2006 Jul-Aug;40(7-8):1400-1406.
(120) Eickhoff C, Schulz M. Pharmaceutical care in community pharmacies: practice and research in Germany. Ann Pharmacother 2006 Apr;40(4):729-735.
(121) Guignard E, Bugnon O. Pharmaceutical care in community pharmacies: practice and research in Switzerland. Ann Pharmacother 2006 Mar;40(3):512-517.
(122) van Mil JW, Schulz M. A review of pharmaceutical care in community pharmacy in Europe. Harvard Health Policy Review 2006;1(1):155.
(123) Westerlund LT, Bjork HT. Pharmaceutical care in community pharmacies: practice and research in Sweden. Ann Pharmacother 2006 Jun;40(6):1162-1169.
(124) International Pharmaceutical Federation (FIP). 2013 FIPEd Global Education Report. 2013; Available at: http://fip.org/static/fipeducation/2013/2013-FIPEd-GlobalEducationReport/data/FIPEd%20Global%20Education%20Report%202013.pdf. Accessed 07/01, 2016.
(125) Young MC, Munoz-Furlong A, Sicherer SH. Management of food allergies in schools: a perspective for allergists. J Allergy Clin Immunol 2009 Aug;124(2):175-82, 182.e1-4; quiz 183-4.
(126) Rijksoverheid (Dutch Government). Campagnes. Available at: https://www.rijksoverheid.nl/onderwerpen/campagnes. Accessed 06/10, 2016.
(127) SIRE. Campagne overzicht. Available at: http://sire.nl/campagne-overzicht?tid%5B%5D=8. Accessed 06/10, 2016.
(128) Macadam C, Barnett J, Roberts G, Stiefel G, King R, Erlewyn-Lajeunesse M, et al. What factors affect the carriage of epinephrine auto-injectors by teenagers? Clin Transl Allergy 2012 Feb 2;2(1):3.
(129) Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989 Dec;10(4):407-415.
(130) Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005 Mar;115(3 Suppl 2):S483-523.
(131) Simons FE. Anaphylaxis. J Allergy Clin Immunol 2010 Feb;125(2 Suppl 2):S161-81.



Chapter 9

LIST OF ABBREVIATIONS

AA	Allergen Avoidance
AAAAI	American Academy of Allergy, Asthma & Immunology
ASCIA	Australasian Society of Clinical Immunology and Allergy
ATC	Anatomical Therapeutic Chemical
BoT	Burden of Treatment
DBPCFC(s)	Double-blind, Placebo Controlled Food Challenge(s)
DR	Dietary Restrictions
EAACI	European Academy of Allergy and Clinical Immunology
EI	Emotional Impact
EAI(s)	Epinephrine Auto-Injector(s)
EU	European Union
FAAN	Food Allergy & Anaphylaxis Network
FAH	Food Allergy related Health
FAIM	Food Allergy Independent Measure
- TF	- Teenager Form
- PFT	- Parent Form Teenager
FAQLQ(s)	Food Allergy Quality of Life Questionnaire(s)
- AF	- Adult Form
- TF	- Teenager Form
- CF	- Child Form
- PFT	- Parent Form Teenager
- PF	- Parent Form
FAV	Friese Apotheken Vereniging (Frisian Pharmacists Association)
GAV	Groningen Apotheken Vereniging (Groningen Pharmacists Association)
GP(s)	General Practitioner(s)
HRQL	Health Related Quality of Life
IR(s)	Immediate Reaction(s)
KNMP	Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (The Royal Dutch Pharmacists Association)
LR(s)	Late Reaction(s)
ICPC	International Classification of Primary Care
IPQ	Illness Perception Questionnaire
METc	Medical Ethics review commission
MID	Minimal Important Difference
NHG	Nederlandse Huisarts Genootschap (Dutch College of General Practitioners)
RAE	Risk of Accidental Exposure
RNG	Registration Network Groningen
STAI	State Trait Anxiety Inventory
UMCG	University Medical Center Groningen
WHO	World Health Organization

SUMMARY

Food allergy is an abnormal response of the body involving the immune system to otherwise harmless foods. Allergic symptoms vary from mild localized to severe systemic and even life-threatening reactions (anaphylaxis). Symptoms and signs of anaphylaxis can occur within minutes to hours after ingesting the culprit food. The severity of the reaction depends on a complex interplay between various factors. Risk factors for a food-induced anaphylactic reaction that are recognized from epidemiological studies are a previously severe anaphylactic reaction to a food requiring emergency treatment or hospitalization as a result, asthma or asthmatic reactions to food, adolescent or young adult age, systemic reaction to traces of the food allergen, and being allergic to peanut or (tree) nut. Also, co-factors increase the risk of an allergic reaction occurring or its severity. Co-factors are life style factors, medication, patient specific factors and pre-existing conditions.

Foods that most commonly cause serious allergic reactions in children and adolescents are cow's milk, hen's eggs, peanuts and tree nuts, while in adulthood they are commonly caused by peanuts, tree nuts and fruits. Allergies to fish and shellfish are less common but can also be quite severe.

Food allergy is a growing health issue in countries with a Western lifestyle. Food allergy affects about six to eight percent of children in the first year of life. Most of the children outgrow their sensitivity to certain foods, and approximately two to three per cent of the adult population have food allergies. It is generally assumed that the prevalence of food allergy and anaphylaxis is increasing, although reliable population-based data are limited and (with few exceptions) time series are lacking.

The diagnosis of food allergy is primarily based on a detailed patient's clinical history and can be supported by physical examination. In addition, for the diagnosis of food allergy, blood and skin prick tests can be used, which detect IgE (allergen-specific immunoglobulin E) specific for the offending food. The presence of IgE antibodies is called sensitization. A distinction should be made between sensitization that is not clinically relevant (the presence of IgE without allergic symptoms) and allergy (the presence of IgE with allergic symptoms). There are to date no reliable diagnostic tests to diagnose anaphylaxis. The gold standard for the diagnosis of food allergy is a double-blind placebo-controlled food challenge (DBPCFC). During a DBPCFC the suspected food is hidden in another food and administered in gradually increasing doses and reactivity is compared with placebo administered in the same way on another day. During a DBPCFC neither the allergist nor the patient is aware of on which day the test food contains the suspected allergen or placebo. Although a DBPCFC is the gold standard, it is expensive, labor-intensive and can be time-consuming for patients. However, it is a safe diagnostic test for food allergy, but most importantly undergoing a DBPCFC improves health-related quality of life (HRQL) of food allergic patients irrespective the outcome of the DBPCFC.

To date, no curative therapy for food allergy exists and because of the life-threatening nature of anaphylaxis the cornerstone of therapy is prevention. Therefore, food avoidance is currently the only way for food allergic patients to prevent an allergic reaction. Despite taking precautions, accidental ingestion may happen. Consequently, food allergy and anaphylaxis has a significant impact on quality of life of food allergic patients.

The care for (high risk) food allergic patients may be subdivided into acute and long-term management. For food allergic patients at high risk of anaphylaxis in the community, epinephrine should preferably be prescribed in the form of an epinephrine auto-injector (EAI). An EAI is a single use, disposable, prefilled automatic injection device with a fixed dose of epinephrine. Epinephrine is the medication of choice in the emergency treatment of anaphylaxis in the community and there are no absolute contra-indications to treatment with epinephrine in a patient experiencing anaphylaxis. After using an EAI the patient should be transported to a hospital as soon as possible for possible further treatment. The time during which patients are observed following an (severe) allergic reaction varies in clinical practice. Recommendations vary from between two to twenty-four hours. All food allergic patients at high risk of anaphylaxis should carry an EAI at all times. However, many high risk food allergic patients have not been prescribed an EAI. Even when they have been prescribed an EAI, these high risk food allergic patients, adolescents in particular, do not always carry their EAI and often do not use their EAI in the event of emergency situations.

In this thesis several aspects of food allergy, anaphylaxis and epinephrine auto-injectors were investigated: the prevalence, the reasons for the under-prescription of auto-injectors in food allergic patients at high risk for anaphylaxis, the reasons for non-compliance and non-use of an EAI, the burden of treatment with having to carry an EAI at all times and the impact of food allergy, anaphylaxis and carrying an EAI at all times on the health-related quality of life in food allergic patients. Also, the prevalence, severity, clinical characteristics and predictors of late reactions in food-allergic children and adolescents after DBPCFC were investigated.

Chapter 1 is a general introduction, describing the definition, clinical manifestations, prevalence and diagnosis and treatment of food allergy and anaphylaxis and its impact on the quality of life of food allergic patients.

The first part of this thesis, **chapter 2** demonstrated that the prevalence of food allergy in high-risk food allergic adolescents, when compared to a previous study in 2009 by Flokstra-de Blok et al., has not increased appreciably in the last six years. In 2009 as well as in 2016 the calculated questionnaire-based prevalence of probable food allergy was 6.2%. **Chapter 2** also demonstrated that EAI ownership has improved marginally when compared to a previous study in 2009 by Flokstra-de Blok et al. This improvement was not statistically significant, and there is ultimately still a substantial under-prescription of EAIs in high-risk food allergic adolescents.

Since food allergy is one of leading causes of anaphylaxis, it is important that patients and health-care providers are capable of recognizing a severe food allergic reaction and treating it adequately. Given the important role of general practitioners (GPs) in acute and long-term care of food allergy and anaphylaxis, the EAI prescription practices by general practitioners to food allergic patients in primary care in the Netherlands was investigated. **Chapter 3** demonstrated that food allergic patients at high risk for anaphylaxis who visit their general practitioner (GP) are often not prescribed an EAI, including those with a previous severe anaphylactic reaction. It was shown that previously identified low rates of EAI ownership, described in **chapter 2**, may be partly due to general practitioners not prescribing this medication to patients for whom it would be appropriate to do so. These findings suggests that there is a need for improvement of the quality of care for high risk food-allergic patients in primary care.

In the second part of this thesis, **chapter 4** examined the relationship between self-reported compliance with carrying an EAI and the burden of treatment as perceived by food allergic adolescents and their parents. It was shown that the majority of food allergic adolescents prescribed an EAI and their parents were positive about the EAI which suggests that the perceived burden of treatment was low. However, the burden of treatment was higher in food allergic adolescents prescribed an EAI who reported not carrying the EAI at all times. Thus, although food allergic adolescents perceive a limited burden of having to carry an EAI, this burden does seem to influence the decision many adolescents make to do so on a daily basis. Remarkably, the burden of treatment of both food allergic adolescents and their parents were not associated with HRQL, perceived disease severity, illness perception, or trait anxiety. The burden of treatment measure thus measures a distinct concept related to compliance behavior. Further studies on factors influencing the burden of treatment of food allergic adolescents may be helpful in order to improve compliance.

In **chapter 5** factors other than self-perceived disease severity to predict health-related quality of life (HRQL) of food allergic-adults (≥ 18 years) and children (8-12 years) in Europe were investigated and identified. The prediction model for adults accounted for 65% of the variance in total food allergy quality of life (FAQLQ) scores. For adults having a fish or milk allergy, type of most severe symptoms, and gender were important predictors in addition to perceived disease severity. The prediction model for children accounted for only 28% of the variance in total FAQLQ scores. For children having a peanut or soy allergy and country of origin were important predictors in addition to perceived disease severity. Surprisingly, experiencing anaphylaxis or being prescribed an EAI did not seem to be related to HRQL of either food-allergic adults or children. Awareness of some of these predictors may be helpful to guide the development of interventions such as food labeling to minimize the impact of having a food allergy on HRQL.

Successful treatment of anaphylaxis in the community relies on early and correct use of EAIs. In the Netherlands pharmacists supply EAIs to food allergic patients and have a crucial role in instructing patients in how and when to use an EAI. In the last part of this thesis, in **chapter 6**, the knowledge, attitudes, and beliefs regarding food allergy and anaphylaxis among pharmacists in the Netherlands were investigated, but also how accurately pharmacists demonstrated how and when to use an EAI to patients. **Chapter 6** demonstrated that there were important knowledge gaps about food allergy and its management among pharmacists in the Netherlands. Importantly, food allergic patients at high risk for anaphylaxis who receive their EAI from a pharmacy in the Netherlands are often not or incorrectly instructed on how to use an EAI. Given the importance of timely and correct administration of epinephrine in case of (severe) food allergic reaction, these findings highlight that improvement of demonstration accuracy is urgently needed.

The gold standard in the diagnosis of food allergies is the double-blind, placebo-controlled food challenge (DBPCFC). A DBPCFC can result in immediate onset of symptoms, but late onset of symptoms has also been reported. The time during which children are observed following a DBPCFC varies in clinical practice. Recommendations vary from between 2 to 24 hours. In **chapter 7** the prevalence, severity and clinical characteristics of late reactions in food-allergic children and adolescents after DBPCFC were determined, and factors which are associated with and may predict late reactions (LRs) were ascertained. **Chapter 7** demonstrated that LRs in food-allergic children after DBPCFC are poorly predictable, and are generally not severe. Isolated LRs (LRs not preceded by an immediate reaction) occurred with comparable frequency after active and placebo challenges and are thus unlikely to be true allergic reactions. All LRs, including those on the placebo day, are more frequently reported in younger children. Children who do not experience severe immediate reactions may thus be safely discharged home 2 hours after a DBPCFC.

The following general conclusions can be drawn from this thesis:

- The prevalence of food allergy in Dutch high-risk food allergic adolescents has not increased appreciably in the last six years. The calculated questionnaire-based prevalence of probable food allergy was 6.2%.
- EAI ownership has improved marginally, however, there is still a substantial under-prescription of EAIs in high-risk food allergic adolescents in the Netherlands. The under-prescription of EAIs may be partly due to GPs not prescribing this medication to patients for whom it would be appropriate to do so.
- High-risk food allergic patients who visit their GP are often not prescribed an EAI, even those with a previous allergic reaction, partly due to GPs not prescribing this medication to patients for whom it would be appropriate to do so.
- The majority of food-allergic adolescents and their parents were positive about the epinephrine auto-injector: the burden of treatment was low. For food-allergic adolescents, a higher burden of treatment was associated with self-reported non-compliance with carrying an epinephrine auto-injector at all times.
- The burden of treatment was not associated with health related quality-of-life, illness severity and perception, or anxiety.
- Experiencing anaphylaxis or being prescribed an EAI did not seem to be related to HRQL of either food allergic adults (≥ 18 years) or children (8-12 years).
- Important predictors other than self-perceived disease severity for HRQL of food allergic adults in Europe were type of allergenic food, type of symptoms, and gender. For children important predictors were type of allergenic food and country of origin.
- Knowledge gaps about food allergy and its management exist among pharmacists in the Netherlands.
- Pharmacists in the Netherlands often give incorrect and incomplete demonstration of EAIs.
- Late reactions in food allergic children and adolescents after DBPCFC do occur, are poorly predictable and are generally not severe. Children who do not experience severe immediate reactions may be safely discharged home two hours after a DBPCFC.

SAMENVATTING

Voedselallergie is een abnormale immunologische reactie van het lichaam op, in andere opzichten, schadeloos voedsel. Allergische symptomen op voedsel variëren van milde gelokaliseerde symptomen tot ernstige, systemische zelfs levenbedreigende reacties (anafylaxie). Symptomen en tekenen van anafylaxie kunnen optreden binnen enkele minuten tot uren na het innemen van het allergene voedingsmiddel. De ernst van de reactie is afhankelijk van een complexe wisselwerking tussen verschillende factoren. Risicofactoren voor een voedselgeïnduceerde anafylactische reactie worden die erkend uit epidemiologische studies zijn een eerder ernstige anafylactische reactie op een voedingsmiddel die een acute behandeling of ziekenhuisopname tot gevolg had, astma of astmatische reactie op een allergeen voedingsmiddel, leeftijd (adolescenten/ jong volwassen), systemische reactie op sporen van allergene voedingsmiddelen, en het hebben van een pinda- of notenallergie . Ook co-factoren verhogen de kans op een allergische reactie of verhogen de ernst ervan. Co-factoren zijn levensstijlfactoren, medicatie, patiënt-specifieke factoren en al bestaande aandoeningen.

Voedingsmiddelen die de meest ernstige allergische reacties bij kinderen en adolescenten veroorzaken zijn koemelk , kippeneiwit , pinda's en noten, terwijl ze bij volwassenen meestal worden veroorzaakt door pinda's, noten, en fruit. Allergieën voor vis- en schaaldieren komen minder vaak voor, maar zijn meestal vrij ernstig.

Voedselallergie is een groeiend gezondheidsprobleem in landen met een westerse levensstijl. Voedselallergie treft ongeveer zes tot acht procent van de kinderen in het eerste levensjaar. De meeste kinderen ontgroeien hun overgevoeligheid voor bepaalde voedingsmiddelen, en ongeveer twee tot drie procent van de volwassen bevolking ontgroeit zijn voedselallergie niet. Over het algemeen wordt aangenomen dat de prevalentie van voedselallergie en anafylaxie toeneemt, hoewel betrouwbare populatie gebaseerd onderzoeken beperkt zijn en (op enkele uitzonderingen na) tijdreeksen ontbreken.

De diagnose van voedselallergie is primair gebaseerd op een zorgvuldige anamnese en kan door lichamelijk onderzoek worden ondersteund. Bovendien kan voor het diagnosticeren van voedselallergie gebruik gemaakt worden van bloed- en huidpriktesten, waarbij het specifiek IgE (immunoglobuline E, is een type proteïne en wordt ook wel een antilichaam genoemd) voor het desbetreffende voedingsmiddel wordt gedetecteerd. De aanwezigheid van IgE antistoffen wordt sensibilisatie genoemd. Er moet een onderscheid worden gemaakt tussen sensibilisatie dat niet klinisch relevant is (dit wil zeggen aanwezigheid van IgE zonder allergische symptomen) en allergie (de aanwezigheid van IgE met daarbij allergische symptomen). Tot op heden zijn er geen betrouwbare diagnostische tests voor het diagnosticeren van anafylaxie. De gouden standaard voor het diagnosticeren van een voedselallergie is een dubbelblinde, placebo-gecontroleerde

voedselprovocatie. Tijdens een dubbelblinde, placebo-gecontroleerde voedselprovocatie wordt het verdachte voedingsmiddel dat in een ander voedingsmiddel verborgen is in oplopende doseringen toegediend en deze reactie wordt vergeleken met de reactie bij toediening van de placebo die op een andere dag op een vergelijkbare wijze wordt gegeven. Tijdens een dubbelblinde, placebo-gecontroleerde voedselprovocatie weten zowel de allergoloog als de patiënt niet op welke dag het verdachte voedingsmiddel of placebo wordt gegeven. Hoewel een dubbelblinde, placebogecontroleerde voedselprovocatie de gouden standaard is, is het duur, arbeidsintensief en kan het tijdrovend voor patiënten zijn. Echter, is het een betrouwbare diagnostische test voor het diagnosticeren van een voedselallergie en verbetert het bovendien de kwaliteit van leven van voedselallergische patiënten ongeacht de uitkomst van deze test.

Tot op heden bestaat er geen curatieve therapie voor voedselallergie en vanwege het levensbedreigende karakter van anafylaxie is voorkomen beter dan genezen. Daarom is het vermijden van het voedingsmiddel momenteel de enige manier voor voedselallergische patiënten om een allergische reactie te voorkomen. Ondanks het nemen van voorzorgsmaatregelen bestaat er de kans dat iemand het voedingsmiddel waar hij of zij allergisch voor is binnenkrijgt met als mogelijk gevolg een ernstige allergische reactie. Logischerwijs kunnen voedselallergie en anafylaxie een aanzienlijke impact hebben op de kwaliteit van leven van voedselallergische patiënten.

De zorg voor (hoog risico) voedselallergische patiënten kan worden onderverdeeld in mangement op korte termijn (acute zorg) en lange termijn. Voor voedselallergische patiënten met een hoog risico op anafylaxie, moet epinephrine bij voorkeur worden voorgeschreven in de vorm van een epinefrine auto-injector (EAI). Een EAI is een voorgevulde, automatische injectie-spuit met een vaste dosis epinephrine voor eenmalig gebruik. Epinefrine is het middel van eerste keus bij acute behandeling van anafylaxie. Er zijn geen absolute contra-indicaties voor behandeling met epinephrine wanneer een patiënt anafylaxie doormaakt. Na het gebruik van een EAI moet de patiënt zo spoedig mogelijk worden vervoerd naar een ziekenhuis voor eventuele verdere behandeling. De tijd dat kinderen worden geobserveerd na een (ernstige) allergische reactie varieert in de praktijk. Aanbevelingen variëren van twee tot vierentwintig uur. Alle voedselallergische patiënten met een hoog risico op anafylaxie dienen een EAI bij zich te hebben. Echter, veel hoog risico voedselallergische patiënten hebben geen EAI voorgeschreven gekregen. En zelfs al hebben ze een EAI voorgeschreven gekregen, dan zijn deze voedselallergische patienten (adolescenten in het bijzonder) vaak therapieontrouw, dragen ze niet altijd hun EAI bij zich en gebruiken ze vaak hun EAI niet in geval van nood.

In dit proefschrift zijn verschillende aspecten van voedselallergie, anafylaxie en EAIs onderzocht: de prevalentie, de redenen voor onderprescriptie van auto-injectoren aan voedselallergische patiënten met een hoog risico op anafylaxie, de redenen voor ondergebruik en het niet ten alle tijden dragen van een EAI. Ook zijn de last die patiënten ervaren van een EAI en de impact van voedselallergie, anafylaxie en het te allen tijde dragen van een EAI op de kwaliteit van leven van voedselallergische patiënten onderzocht. Ook zijn de prevalentie, de ernst, de klinische kenmerken en mogelijke voorspellers van late reacties na dubbelblinde, placebo gecontroleerde voeselprovocaties bij voedselallergische kinderen en adolescenten onderzocht.

Hoofdstuk 1 is een algemene inleiding op dit proefschrift. Hierin wordt achtergrondinformatie gegeven over de definitie, de klinische verschijnselen, de prevalentie, de diagnose en behandeling van voedselallergie en anafylaxie, en de impact van voedselallergie en anafylaxie op de kwaliteit van leven van voedselallergische patiënten.

In het eerste deel van dit proefschrift liet **hoofdstuk 2** zien dat de prevalentie van voedselallergie bij hoog risico voedselallergische adolescenten in vergelijking met een eerdere studie in 2009 door Flokstra-de Blok e.a. de laatste zes jaar niet noemenswaardig is toegenomen. In 2009, evenals in 2016, bleek de op vragenlijstonderzoek gebaseerde prevalentie van voedselallergie 6,2% te zijn.

Hoofdstuk 2 liet ook zien dat EAI bezit in vergelijking met een eerdere studie in 2009 door Flokstra-de Blok e.a. marginaal is verbeterd. Hoewel deze verbetering niet statistisch significant was, is er uiteindelijk nog steeds een aanzienlijke onderprescriptie van EAIs aan hoog risico voedselallergische adolescenten.

Aangezien voedselallergie één van de belangrijkste oorzaken van anafylaxie is, is het belangrijk zowel patiënten als zorgverleners een ernstige allergische reactie kunnen herkennen en adequaat kunnen behandelen. Gezien de belangrijke rol van huisartsen bij de acute en langdurige zorg van voedselallergie en anafylaxie, hebben wij het EAI voorschrijfgedrag van huisartsen aan voedselallergische patiënten in Nederland onderzocht. **Hoofdstuk 3** liet zien dat voedselallergische patiënten met een hoog risico op anafylaxie, die hun huisarts bezoeken, vaak niet een EAI worden voorgeschreven. Het wordt zelfs niet voorgeschreven aan diegene die een eerdere ernstige anafylactische reactie hebben doorgemaakt. In **hoofdstuk 2** werd eerder al beschreven dat het bezit van een EAI bij voedselallergische adolescenten zeer laag is. Dit kan deels te wijten zijn aan het feit dat huisartsen geen EAIs voorschrijven aan patiënten die er wel één zouden moeten hebben. Deze bevinding suggereert dat er een behoefte is aan verbetering van de kwaliteit van zorg voor deze hoog risico voedselallergische patiënten in de eerste lijn.

In het tweede deel van dit proefschrift liet **hoofdstuk 4** de relatie zien tussen de zelf-gerapporteerde compliantie met het dragen van een EAI en de lasten van een EAI die door voedselallergische adolescenten en hun ouders worden ervaren. Het onderzoek liet zien dat de meerderheid van de voedselallergische adolescenten met een EAI én hun ouders positief waren over de EAI. Dit suggereert dat de ervaren last van de behandeling laag was. De last die voedselallergische adolescenten met een EAI ervaren was hoger bij voedselallergische adolescenten die meldden dat zij niet altijd hun EAI bij zich dragen. Ondanks het feit dat voedselallergische adolescenten een beperkte last ervaren van het altijd bij zich moeten dragen van een EAI, lijkt deze last invloed te hebben op beslissingen die vele jongeren dagelijks maken. Opvallend was dat de last van het altijd moeten dragen van een EAI ervaren door zowel voedselallergische adolescenten als hun ouders niet geassocieerd was met kwaliteit van leven, zelf-gepercipieerde ernst, ziekteperceptie of angst. Het meetinstrument (*Burden of Treatment (BoT) vragenlijst*) dat de last van een EAI meet, meet dus een afzonderlijk concept met betrekking tot de compliantie. Nader onderzoek naar factoren van de last van een EAI ervaren door voedselallergische adolescenten kan nuttig zijn om de compliantie te verbeteren.

In **hoofdstuk 5** werden factoren anders dan zelf-gepercipieerde ernst onderzocht om de voedselallergie-gerelateerde kwaliteit van leven te voorspellen van voedselallergische volwassenen (≥ 18 jaar) en kinderen (8-12 jaar) in Europa. Het predictiemodel voor volwassenen was in staat om 65% van de variantie in de totale *Food Allergy Quality of Life Questionnaire* (FAQLQ) scores te voorspellen. Naast zelf-gepercipieerde ernst waren het hebben van een vis- of melkallergie, de meest ernstige symptoom tijdens een reactie en geslacht belangrijke voorspellers bij volwassenen. Het predictiemodel voor kinderen was in staat om 28% van de variantie in de totale FAQLQ scores te voorspellen. Naast zelf-gepercipieerde ernst waren het hebben een pinda- of soja-allergie en het land van herkomst belangrijke voorspellers bij kinderen. Het doormaken van anafylaxie en het voorgeschreven krijgen van een EAI bleken verrassend genoeg bij zowel volwassenen als kinderen geen onafhankelijke voorspellers van voedselallergie-gerelateerde kwaliteit van leven. Bewustwording van deze voorspellers kan nuttig zijn bij de ontwikkeling van interventies zoals bijvoorbeeld allergeenetikettering van voedingsmiddelen. Dit kan bijdragen aan het minimaliseren van de impact dat een voedselallergie kan hebben op kwaliteit van leven.

Een succesvolle behandeling van anafylaxie buiten het ziekenhuis hangt af van een vroege en correcte toediening van een EAI. In Nederland verstrekken apothekers EAIs aan voedselallergische patiënten. Apothekers hebben daarom een cruciale rol in het instrueren van voedselallergische patiënten. Zij moeten vertellen hoe en wanneer een patiënt een EAI dient te gebruiken. In het laatste deel van dit proefschrift werd in **hoofdstuk 6** de kennis, attitudes en opvattingen ten aanzien van voedselallergie en anafylaxie onder

apothekers in Nederland onderzocht. Ook werd onderzocht hoe zorgvuldig apothekers instructies geven aan patiënten over het gebruik van de EAI. Uit **hoofdstuk 6** bleek dat er belangrijke kennislacunes bestaan onder apothekers in Nederland over voedselallergie en behandeling van voedselallergie. Een belangrijke bevinding was dat voedselallergische patiënten met een hoog risico op anafylaxie, die hun EAI van een apotheker in Nederland krijgen, vaak niet of onjuist geïnstrueerd zijn over hoe je een EAI dient te gebruiken. Deze bevinding benadrukt, gezien de noodzaak van een tijdige en correcte toediening van epinefrine in geval van een (ernstige) voedselallergische reactie, dat de instructies die apothekers geven verbetert moeten worden.

De gouden standaard voor de diagnose van voedselallergie is een dubbelblinde, placebo-gecontroleerde voedselprovocatie. Een dubbelblinde, placebo-gecontroleerde voedselprovocatie kan leiden tot het onmiddellijk optreden van allergische symptomen, maar de allergische symptomen kunnen ook later optreden. De tijd waarin kinderen worden geobserveerd na een voedselprococatie varieert in de kliniek. Aanbevelingen variëren tussen 2 tot 24 uur. In **hoofdstuk 7** werden de prevalentie, de ernst en de klinische kenmerken van de late reacties bij voedselallergische kinderen en adolescenten na dubbelblinde, placebo-gecontroleerde voedselprovocatie onderzocht. Ook werd onderzocht welke factoren geassocieerd zijn met late reacties en of deze factoren een late reactie kunnen voorspellen. **Hoofdstuk 7** liet zien dat late reacties bij voedselallergische kinderen na een voeddselprovocatie slecht voorspelbaar zijn, en dat deze reacties over het algemeen niet ernstig zijn. Geïsoleerde late reacties (late reacties die niet voorafgegaan worden door een onmiddellijke reactie) traden met vergelijkbare frequentie op na verum en placebo provocaties. Dit zijn zeer waarschijnlijk geen klinisch relevante allergische reacties. Alle late reacties, ook die op de placebo dag, komen vaker voor bij jongere kinderen. Kinderen die geen ernstige onmiddellijke reacties hebben ervaren tijdens een voedselprovocatie kunnen twee uur na een dubbelblinde, placebo-gecontroleerde voedselprovocatie veilig naar huis worden ontslagen.

De volgende algemene conclusies kunnen getrokken worden naar aanleiding van dit proefschrift:

- De prevalentie van voedselallergie bij Nederlandse hoog risico voedselallergische adolescenten is in de laatste zes jaar niet toegenomen. De op vragenlijstonderzoek gebaseerde prevalentie van voedselallergie was 6,2%.
- Het EAI bezit is marginaal verbeterd. Hoewel deze verbetering niet statistisch significant was, is er uiteindelijk nog steeds een aanzienlijke onderprescriptie van EAIs aan hoog risico voedselallergische adolescenten. Dit kan deels te wijten zijn aan het feit dat huisartsen geen EAIs voorschrijven aan patiënten die er wel één zouden moeten hebben.
- Voedselallergische patiënten met een hoog risico op anafylaxie, die hun huisarts bezoeken, krijgen vaak niet een EAI voorgeschreven. Het wordt zelfs niet voorgeschreven aan diegene die een eerdere ernstige anafylactische reactie hebben doorgemaakt.
- De meerderheid van de voedselallergische adolescenten met een EAI en hun ouders waren positief over de EAI: de ervaren last van de behandeling was laag. De last die voedselallergische adolescenten met een EAI ervaren was hoger bij voedselallergische adolescenten die meldden dat zij niet altijd hun EAI bij zich dragen.
- De last van het altijd moeten dragen van een EAI ervaren door zowel voedselallergische adolescenten als hun ouders was niet geassocieerd met kwaliteit van leven, zelf-gepercipieerde ernst, ziekteperceptie of angst.
- Het doormaken van anafylaxie of het voorgeschreven krijgen van een EAI bleken bij zowel volwassenen (≥18 jaar) en kinderen (8-12 jaar) geen onafhankelijke voorspellers van voedselallergie-gerelateerde kwaliteit van leven te zijn.
- Bij volwassenen waren naast zelf-gepercipieerde ernst het hebben van een vis- of melkallergie, meest ernstige symptoom tijdens een reactie en geslacht belangrijke voorspellers voor voedselallergie-gerelateerde kwaliteit van leven. Bij kinderen waren naast zelf-gepercipieerde ernst het hebben een pinda- of soja-allergie en het land van herkomst belangrijke voorspellers.
- Er bestaan belangrijke kennislacunes onder apothekers in Nederland over voedselallergie en de behandeling van voedselallergie.
- Apothekers in Nederland geven vaak onjuist of onvolledige instructies over hoe je een EAI dient te gebruiken.
- Late reacties bij voedselallergische kinderen na een dubbelblinde, placebo-gecontroleerde voedselprovocatie zijn slecht voorspelbaar en deze reacties zijn over het algemeen niet ernstig. Kinderen die geen ernstige onmiddellijke reacties hebben ervaren tijdens na een dubbelblinde, placebo-gecontroleerde voedselprovocatie kunnen twee uur na deze voedselprovocatie veilig naar huis worden ontslagen.

摘要

食物过敏是免疫系统导致的人体对本身无害食物的异常反应。过敏的症状从轻微的局部反应到全身的严重反应甚至可危及生命（全身过敏反应）。症状和过敏反应可以在进食致敏食物后数分钟至数小时内发生。过敏反应的严重程度取决于多种因素的相互作用。食物所导致全身过敏反应的危险因素包括：既往曾因严重的食物过敏反应而需要急诊治疗或住院、哮喘或对食物的哮喘反应、青少年或青年、对微量食物过敏原的全身反应及对花生或坚果过敏。而且，协同因素增加过敏反应的发生风险或其严重程度。协同因素包括生活方式因素、药物、患者本身的因素及先前的状况。

最常见导致儿童和青少年发生严重过敏反应的食物有牛奶、鸡蛋、花生及坚果，而成人最常见的过敏食物有花生、坚果、水果及蔬菜。鱼和贝类导致的过敏反应相对少见但常常非常严重。

在西方生活方式的国家，食物过敏是一个日渐常见的健康问题。食物过敏使百分之六到百分之八的一岁儿童受到影响。随着年龄的增长，大多数儿童对某种食物过敏反应的严重程度逐渐下降，但是仍有百分之二至百分之三的成年人存在食物过敏现象。尽管可靠的人群数据有限并且（除少数情况外）时间序列的数据更加缺乏，但是人们普遍认为食物过敏和全身过敏反应的发生率逐渐增加，

食物过敏的诊断主要依据患者的具体临床病史，同时查体的结果也作为诊断依据。另外，血液和皮肤点刺试验（为了检测可疑食物特异性IgE）也用于食物过敏的诊断。IgE抗体的存在成为致敏反应。应该区分临床不相关的致敏（存在IgE但没有过敏症状）和过敏（存在IgE同时有过敏症状）。目前尚没有诊断全身过敏反应的可靠诊断试验。诊断食物过敏的金标准是一个双盲随机对照食物激发(DBPCFC) 。实施DBPCFC时，给予可疑食物并逐渐增加剂量，并与安慰剂比较患者的反应。尽管DBPCFC是金标准，但是这项检查花费高、实施复杂而且可能会增加患者负担。然而，它是食物过敏一项安全的诊断试验，而最重要的是，不管结果如何，通过进行DBPCFC可以改善食物过敏患者健康相关的生活质量(HRQL)。

至今尚没有治疗食物过敏有效的治疗，而且由于全身过敏反应可危及生命，所以最根本的治疗是预防。所以，饮食限制是目前预防食物过敏患者发生过敏反应的唯一途径。即使采取防范措施，意外摄入仍可能发生。所以，食物过敏和全身过敏反应严重影响食物过敏患者的生活质量。

高危食物过敏患者的治疗可以分为紧急和长期的治疗。对于发生全身过敏反应的高危患者来说，应该给予装入肾上腺素自动注射器(EAI)的肾上腺素，以防万一。EAI是一个一次性、装入固定剂量肾上腺素的预充自动注射装置。肾上腺素是社区急诊治疗全身过敏反应的药物，　而且治疗发生全身过敏反应的患者时肾上腺素没有绝对禁忌症。应用EAI后，患者应尽快转入医院进一步治疗。临床实践中，儿童在发生严重的过敏反应后需留观的时间因人而异。推荐从两个小时至二十四小时不等。所有发生全身过敏反应的高危食物过敏患者均应随时携带EAI。然而，很多高危的食物过敏患者并没有处方给予EAI。即使他们有了EAI，这些高危的食物过敏患者，尤其是叛逆的青少年，并不总是携带EAI，而且在发生急性过敏时经常也不使用EAI。

在这篇论文中有关食物过敏的某些方面，全身过敏反应及肾上腺素自动注射器都有所研究：发生全身过敏反应的高危食物过敏患者应用自动注射器的的普及率及原因，不接受、不使用EAI的原因，随身携带EAI的治疗负担及食物过敏的影响，全身过敏反应与随身携带EAI对食物过敏患者健康相关生活质量的影响。另外，DBPCFC后食物过敏的儿童及青少年迟发反应的发生率、严重性、临床特点及预测因素也有涉及。

第一章 是概论部分，包括食物过敏和全身过敏反应的定义、临床表现、患病率、诊断与治疗，及其对食物过敏患者生活质量的影响。

本文的第一部分——**第二章**，描述了食物过敏在食物过敏易感青少年中的患病率，并与2009年Flokstra-de　Blok等人的研究相比较发现在过去六年中患病率并未增加。2009年和2016年基于计算问卷的大概食物过敏患病率都是6.2%。 **第二章** 还描述了EAI的使用者较2009 Flokstra-de Blok 等人的研究中略有增加。.尽管这一变化没有统计学差异，但是已有大量的高危食物过敏青少年患者应用了EAIs。

由于食物过敏是严重过敏反应最主要的原因，所以患者和卫生保健者能识别严重的食物过敏反应并第一时间做出处理就显得尤为重要。考虑到全科医师(GPs)　在食物过敏和全身过敏反应的紧急和长期治疗中的重要作用，我们调查研究了荷兰的社区医疗中全科医师对食物过敏患者EAI的处方情况。**第三章**描述了那些全身过敏反应的高危食物过敏患者就诊于全科医师（GP）后通常并没有拿到EAI，其中甚至包括那些曾有严重全身过敏反应的患者。这反映了**第二章**中提到的已证实的低EAI使用率，部分可能的原因是全科医师并没有向合适的患者开具该处方。这一结果表明需要改善社区医疗对于高危食物过敏患者的医疗质量。

在本论文的第二部分中，**第四章**研究了自我报告的携带EAI依从性与食物过敏青少年及其父母治疗负担的关系。研究结果表明，大部分应用EAI的食物过敏青少年对EAI持积极态度，这意味着他们反映的治疗负担也就偏低。然而，处方中有EAI但并未随身携带的食物过敏青少年反映的治疗负担就会高一些。所以，尽管食物过敏的青少年认为携带EAI的负担有限，但是这个负担确实会影响这些青少年在日常生活中能否随身携带EAI。需要注意的是，食物过敏青少年及其父母的治疗负担与HRQL、对疾病严重性的认知或焦虑状态并不相关。所以治疗负担测定的是与依从性相关的不同概念。今后对于影响食物过敏青少年治疗负担因素的研究可能对改善依从性有所帮助。

第五章研究了除了疾病严重性自我认知之外的因素，以预测欧洲食物过敏的成年人(≥18岁)和儿童(8-12岁)的健康相关生活质量(HRQL)。成年人的预测模型包含整体食物过敏生活质量(FAQLQ) 评分中的65%变量。对于鱼类或牛奶过敏的成年人来说，最严重的症状类型和性别是最重要的预测因素，还包括对疾病严重性的认知。儿童预测模型仅包含了FAQLQ总评分中28%的变量。花生或大豆过敏以及国籍是重要的预测因素，另外还有对疾病严重性的认知。令人惊讶的是，曾发生后全身过敏反应或使用EAI似乎与食物过敏成人或儿童的HRQL并不相关。认识到这些预测因素可能对指导干预措施的实施有所帮助，比如食物标示，从而把食物过敏对HRQL的影响降到最小。

社区中成功治疗全身过敏反应有赖于早期、正确使用EAIs。在荷兰，药剂师给食物过敏患者提供EAIs，并在指导患者如何、何时使用EAI中起了关键作用。 在本论文的最后部分，在**第六章**，对荷兰药剂师有关食物过敏、全身过敏反应的知识、态度和信念进行研究，但还包括药剂师如何向患者精确展示如何、何时使用EAI。**第六章**表明　荷兰的药剂师们对食物过敏的认识和管理方面参差不齐。　重要的是，在荷兰，发生全身过敏反应的高危食物过敏患者在从药剂师那里拿到EAI后通常得不到关于EAI使用方法的指导或被错误指导。由于及时、正确使用肾上腺素在（严重）食物过敏反应中的重要性，这些研究结果强调了改进示范的精确性迫在眉睫。 诊断食物过敏的金标准是双盲、随机、对照食物激发(DBPCFC)。DBPCFC可以导致即刻出现症状，但是迟发的症状也时有报道。在临床实践中，DBPCFC后儿童观察的时间有差异。推荐时间从2至24小时不等。　在**第七章**中，对食物过敏儿童和青少年在DBPCFC后迟发反应的发生率、严重性及临床特点进行描述，同时明确了与迟发反应（LRs）相关并可能预测迟发反应的因素。**第七章**表明，在食物过敏的儿童中DBPCFC后 LRs 的发生难以预测，而且通常并不严重。孤立LRs （之前没有速发反应的LRs）在激发剂和安慰剂组中发生的频率相当，所以不像是真正的过敏反应。所有的LRs，包括, 安慰剂诱导的LRs，在低龄儿童中更多见。所以，在DBPCFC后观察了两个小时仍为发生速发过敏反应的儿童回家应该是安全的。

从本论文总结出以下几点：

- 荷兰高危的食物过敏青少年发生的食物过敏患病率在过去六年没有增加。根据调查问卷调查的食物过敏患病率估测为6.2%。
- EAI所有权并没有多大改善，但是，荷兰仍有大量高危食物过敏青少年应用处方EAIs。处方使用EAIs的部分原因可能是科医师(GPs)没有给应该使用药物的病人开具处方。
- 即使是包括那些既往曾有严重过敏反应的患者在内，高危食物过敏患者在看过GP后通常并没有拿到EAI的处方，部分原因在于GPs没有给应该使用药物的病人开具处方。
- 大部分食物过敏的青少年及其父母对肾上腺素自动注射器持积极态度，原因在于治疗负担低。
- 对于食物过敏的青少年，治疗的负担更多与自我报告得随身携带肾上腺素自动注射器依从性差有关。
- 治疗负担与健康相关生活质量、疾病严重性、对疾病认知及焦虑无关。曾有过敏反应或处方使用EAI似乎与食物过敏成人(≥18岁)或儿童(8-12岁)的HRQL均不相关。
- 除了自我认知的疾病严重性，欧洲食物过敏成人HRQL的重要预测因素包括过敏食物类型、症状类型及性别。对儿童重要的预测因素使食物过敏类型和国籍。
- 在荷兰，药师关于食物过敏和治疗的认识存在差异。
- 在荷兰，药师关于EAIs的展示通常不正确也不完整
- DBPCFC后食物过敏儿童和青少年的确实会发生迟发反应，但是通常难以预测，且并不严重。在DBPCFC后观察两小时没有急性过敏反应发生的儿童回家后一般是安全的。

ACKNOWLEDGEMENTS

'In the world you may be just one person.
But to one person, you just might be the world'
- Author unknown -

My journey to medical school started with a visit to a small hospital in the Chinese countryside with a terribly sick orphan. My life has changed ever since. I remember, as if it were yesterday, being in that run-down hospital holding her. She had trouble breathing and her skin and lips started to turn blue. If I knew what I know now, I could have done more. Unfortunately, I could not help her and neither could the doctor in that hospital for a variety of reasons. Overwhelmed by helplessness I witnessed her dying and had to take her back to the orphanage by taxi. I can assure you that this story, even though I have written and told it many times, still brings tears to my eyes. Simultaneously, it also reminds me that it was back then that it fired up my passion for health care and taking care of those in need. It motivated me so much that I was sure to stick to my plan to become a medical doctor, however challenging life gets and regardless of how many obstacles get put in my way to get there. Once a funny, very old, American-Chinese lady told me if you cannot enter through the front door, maybe there is a window, it is called a *window of opportunity* for a reason. I still think about that. Getting into medical school was not easy, and it was a great feeling knowing that I had finally gotten into medical school. However, taking on another academic study after having finished two studies already, people told me that I was absolutely crazy. Let alone, if you told them you would do it in four years and combine it with writing a Ph.D. thesis. Of course sometimes I wished it was easier, but if it was, everyone else would do it. Overall, I am so happy that I did.

Though only my name appears on the cover of this thesis, during my journey I have met and worked with kind and wonderful people from whom I learned a lot, and a great many people have contributed to its production.

Firstly, I would like to express my special appreciation and thanks to my supervisor **Professor Dr. Anthony Dubois**. Anthony, you have been a tremendous mentor for me, you are one in a million. I have learned so much from you, and I have always appreciated your quick responses to my questions and that I could contact you at any time if I encountered problems or just wanted to brainstorm. I would like to thank you for encouraging my research, believing in my abilities and for allowing me to grow as a research scientist. Your (humorous) advice on both research as well as on my career have been very valuable.

And they say behind every great man there's a woman, in your case **Joyce**. *Oh boy*, **Joyce Dubois**, is something you say quite often. Indeed, *Oh boy* Joyce you are such fun-loving, caring and compassionate woman. I have enjoyed all the great time we spent together. Thank you for your warm welcome into the "research family" and I really do hope you keep on organizing those amazing Christmas get-togethers.

Another person that I would like to express my special appreciation and thanks to is my co-supervisor **Dr. Bertine Flokstra-de Blok**. You are such a great person. The joy and enthusiasm you have for research was contagious and motivational for me, even during tough times in the Ph.D. pursuit. I admire your involvement in and commitment with all sorts of projects and combining all this with being a wife and mother of two adorable kids. Thank you for always being there.

I would also like to thank my assessment committee members: Professor Dr. **Roy Gerth van Wijk**, Professor Dr. **Gerard Koppelman**, and Professor Dr. **Johanthan O'B Hourihane** for their time, interest and helpful comments. I would also like to thank the other members of my oral defense committee, Professor Dr. **Thys van der Molen**, Professor Dr. **Marike Boezen,** Professor Dr. **Suzanne Pasmans**, Dr. **Aline Sprikkelman**, and, Drs. **Yolanda Meijer** for their time and insightful questions.

Professor Dr. **Pieter-Jan Coenraads**, we met at the very beginning of my Ph.D. journey. We travelled to Tianjin (China) together which was really fun. Even though my scientific research project in Tianjin did not turn out the way we expected, it was during this time I became aware of my enthusiasm for scientific research. Thank you for teaching me about dermatology and your enthusiasm for scientific research.

I am deeply grateful to **Feikje Groenhof** for the long discussions that helped me sort out the details of my work on my general practitioners' project. Also thank you for helping me out with the technical part to create a database. I could not have done that project without you.

I am also hugely appreciative to **Boudewijn Kollen**, especially for sharing his epidemiological and statistical expertise so willingly and providing me with statistical advice at times of critical need. I have learned a lot from you. Also special thanks to **Hans Burgerhof** and **Marjan Kerkhof** for being willing to listen to my statistical questions and giving me helpful advice.

I would also like to thank all my **co-authors** for your input in the design of the study, inclusion of participants, analyses and interpretation of data and critically reviewing our manuscripts. I hope we will continue to collaborate in future research projects.

Tina van der Velde, **Joke Kemna**, **Sven Poortman**, **Nahlah AlAgla**, **Jeske Neutel**, **Dorien van Ginkel**, **Elske Bak**, **Sanne de Vries** and **Margriet Bootsma** all of you have contributed to this thesis in your own special and hardworking way. Thank you!

Jeanette Kukler and **Anne-Marie Oomkes**, there would not have been a food challenge unit without you two. Thanks for helping me with the inclusion of participants and letting me learn more about how things work at the food challenge unit.

Aad van Mourik, Janny Tjassing, Jannette Tienkamp, Joke van der Mark, Reint Huizinga, Jans van Aalst-Ubels, Joke van der Mark, Maaike Bansema, Gerard Terwischa van Scheltinga, Hanna van Poppelen, and Lampkje Bulstra, thank you for your administrative and office support activities, and your efforts to ensure a smooth progress of combining and planning my Ph.D. thesis with my clinical rotations and trips abroad.

I gratefully acknowledge the funding sources that made my Ph.D. work possible. I was funded by the **Guide Research Institute**. I was also supported by **ALK-Abelló B.V**., **Meda Pharma**, and **Nutricia Nederland B.V.**.

I would also like to thank the food allergy support organizations, the Dutch Foundation for Food Allergy (**Stichting Voedselallergie**) and the Dutch Anaphylaxis Network (**Nederlands Anaphylaxis Netwerk**) for their support and help. I really appreciate your commitment in providing support to food allergic people at risk and their families and raising awareness about food allergy and anaphylaxis in the community. I really do hope that you stay involved in helping and supporting scientific research.

A major obstacle in research is the difficulty in recruiting patients, because without patients there can be no research. I am very thankful for all the **patients** who voluntarily participated in my research.

My **colleagues of GRIAC**, I did not have much time to attend many research meetings, however, those meetings that I did attend I really enjoyed the lively and insightful discussions that always took place.

My **roommates of KZ00.27**, although I have been mostly working from my office at home, thank you very much for making the atmosphere of our room as friendly, inspiring and fun as possible when I was around.

Anneke Amir, thank you for encouraging me to finish my *China studies* while I was distracted and focused on getting into medical school. You are the sweetest and best student counselor I have ever met.

Combining clinical research, doing clinical rotations and being a mom was not always easy. However, I have met some great people who understood this and were flexible enough to give me the space to sometimes work on my Ph.D. thesis or just be at home when needed. I would like to thank in particular **Henk Los** and **Jaap Strijbos**, both pulmonologists at Nij Smellinge, Drachten, the Netherlands. It was because of you both that I chose to do my pulmonology internships again at your department. It was such a great pleasure to be an intern at your department. Thank you for all that you have taught me about pulmonology, but also about what is important in life.

Another department that I would like to sincerely thank is the **Department of Surgery** and in particular the **Department of Pediatric Surgery** at University Medical Center Groningen (UMCG), Groningen, the Netherlands. My last clinical rotations I did at these departments. To the whole team, thanks for making me feel at home in your department. I want to thank you all for taking the time out of your (undoubtedly) busy schedules to allow me to observe your practice. I cherish the knowledge that you have shared with me and I hope to be part of your team soon.

While writing my manuscripts, this thesis and doing my clinical rotations, I did teach Mandarin-Chinese to many wonderful and talented students at my home, the Language Centre of the University Groningen, Groningen Confucius Institute, and RSG de Borgen (Lindenborg). You are too numerous to name, but thank you for taking my mind off my thesis and studies and making teaching such an enjoyable moment. I would also like to thank my colleagues from the above mentioned schools, thank for your support, kindness and interest in my research and studies. A special thanks to my colleague teacher and coach **Jildau Vrieswijk**. Thank you for being such a great colleague and my coach this school year at RSG de Borgen (Lindenborg). I am very grateful that I could turn to you for any advice. Many thanks for the grammatical editing of my Dutch summary. **Peter Frans**, thank you for being such a great boss, thanks for being so flexible, understanding and letting me combine teaching Mandarin-Chinese at (y)our school with all my other work. I am looking forward to keep working with you to make Mandarin-Chinese the greatest and most interesting subject there is at (y)our school.

Getting a Ph.D. is not easy. It needs passion and patience. Good guidance and advice. But also, love, encouragement, and support from your family and friends. Many friends have helped me stay sane through these last years. I greatly value your friendship. Special thanks to **Sarah & Drew, Pascal & Helene, Sophie & David, Andrea & Veronique, Neily & Auliya, Pascal & Lian, Daan & Renske, Astrid, Amanuel, Biniam, Ping & John, Terese, Rong Rong (aka Lily), Merèl, Nadia, Lisa, Doreen, Anne, Roderick, Louise, Suzanne, and Françoise Clijssen**. **Mark & Linda, Dennis & Femke**, thank you for the great winter

holiday weekend getaways. Despite the fact that we haven't seen any snow so far, we and our kids did have lots of fun.

Nicole Goossens, a 1,000 flower off to you! Thank you for being such an inspiring person and being my paranymf. Without you my Ph.D. journey would not have been such a great learning experience and fun. I have enjoyed our trips to several meetings abroad. I still remember having fun running down the harbor of Boston on an early morning before going to a conference. Also my sincere thanks for taking care of our project and manuscript when I was not able to do so.

Ping He, my sweetest Chinese sister, gosh we go way back! I still remember the day you came to the Netherlands for the first time. You seemed a bit lost at the beginning and had a hard time, but what I admire so much about you is how you see the opportunity in every difficulty. It always makes me think of the word 'crisis' in Chinese, 危机, it is a combination of the word for 'danger' and 'opportunity'. I feel as if in every difficult situation you are put in, you are aware of the 'danger', but you still see the opportunity. Thank you for always being there, also thanks for being my paranymf today, and helping me to be all that I can be. I look forward to sharing many more of life's lovely moments with you.

Min Chen, 非常感谢, a special thanks to you for helping me with my Mandarin-Chinese summary and for being such an inspiring professor and great friend. I owe you lots of *Douwe Egberts* cups of coffee.

Brian Downey, thank you for being such an inspiring person and teacher. We go way back, and I still remember having fun with all those Chinese students while studying at Hogeschool Holland. Many thanks for the grammatical editing of some parts of my thesis. I look forward to visiting you and your wife Susan in Shanghai with my family one day.

Robin Soemopawiro, our house would be a mess without you. I really appreciate the wonderful care you give our home and family. Thank you for making my life easier, and letting me focus on other things than our housekeeping. Thank you for being such a great maid, and above all a great friend and 'aunty' for our family.

I am also extremely thankful for our wonderful au-pairs we welcomed into our home the last couple of years. It is great to be completely at ease while my husband and I work and to know everything is taken care of and my children are loved, is such a blessing! Thank you **Erica Persson, Amanda Gomez-Aragón, Alessia Roggeri** (aka Bibi) and **Carolina Formenti.**

Und jetzt kommen die Kamele.....mit die grosse Bulte, **Opa Bruintje**, *Gossiemuppie*, I miss talking to you a lot. I miss spending time with you in Germany. I wish you were here today, as I cannot think of anyone who would have been prouder. You taught me that no matter how old you are now you are never too young or too old for success or going after what you want.

Another person I deeply miss is **Oma de Boer**. Some days memories still knock the wind out of me. You were so proud when you read my columns about my adventures in China in the *Flevopost*. Everybody in your village knew about me because of you. I always really enjoyed our early morning phone calls. You were the only one who, just like me, also liked waking up very early. Unfortunately, you are no longer here. I miss your laugh, your smile, the way you always made me feel like everything was going to be ok.

Of course no acknowledgments would be complete without giving thanks to my **mom Wilma** and her husband **Arjan**, and also my **Dad Gerard** and his wife **Anne**. I love you all! **Mom** and **Dad**, thank you both for showing faith in me and giving me liberty to choose what I desired. You both taught me about hard work and self-respect, about persistence and about how to be independent. Without each of you, I would be nowhere near the person I am, and the person I am still working on becoming. I salute you all for the selfless love, care, pain and sacrifice you did to shape my life. Although you sometimes hardly understood what I was researching, you were willing to support any decision I made. **Arjan**, especially you and mom have had a rough time with the loss of **Ellemieke**. We all wished she was still here and she is deeply missed. I admire your strengths, and also that you were always cheerful when we were around. Thank you for being part of my life. **Anne**, thank you for all the lovely meals that you cooked. I wish I had such a talent of creating such beautiful and tasty meals.

I also would like to thank my parents-in-law, **Rob en Yvonne**, and also **Bas, Birgit, Tom** and **Eva**. Thank you for supporting me through all those years. **Rob**, thank you for helping with photographing my cover. I would also like to thank uncle **Frans** and aunt **Wendy**, uncle **Hans** and aunt **Marion**, uncle **Klaus** and aunt **Merilyn**, **Philip**, **Matthias**, **Brenda, Daan**, **Dennis, Christy** and all the **Saleh family** in Indonesia for their support, kindness and interest in my research and studies.

Last, but certainly not least, thank you to you, **Bart Saleh**. I love you more than anyone. Ever. Times a hundred million billion. You are my best friend. You are my true love. You are my happily ever after. Through your love, patience, support and unwavering belief in me, I have been able to complete this dissertation journey. Over the years you have patiently endured many long hours alone while I was abroad, studied or worked on my dissertation.

At the same time we have laughed and cried, traveled and played, built and settled, and planned and discussed our lives. Who would have thought that after 18 years of being together we are where we are now, and have two beautiful children who sometimes are really testing our patience. Thank you with all my heart and soul. Finally, to my two sweet children, **Brian** and **Izzy**, thank you for the happiness you brought into my life and for reminding me the important things in life.

Phinally.**D**one! Thank you for taking the time to read this thesis.

Don't forget to enjoy the little things in life!

With lots of love,

Jacquelien Saleh-Langenberg
Groningen, October 2016

LIST OF PUBLICATIONS

Saleh-Langenberg J, de Vries S, Bak E, Kollen BJ, Flokstra-de Blok BMJ, Dubois AEJ. Knowledge, attitudes and beliefs regarding food allergy among pharmacists in the Netherlands. *(revision submitted at Pediatric Allergy and Immunology (PAI), October 2016)*

Saleh-Langenberg J, Bootstra GM, van Ginkel CD, Kollen BJ, Flokstra-de Blok BMJ, Dubois AEJ. Changes in the prevalence of food allergy and epinephrine auto-injectors in high-risk food-allergic adolescents in Dutch high schools between 2009 and 2016. *Pediatr Allergy Immunol. 2016 Jul 5*.

Saleh-Langenberg J, Flokstra-de Blok BM, Goossens N, Kemna JC, van der Velde JL, Dubois AE. The Editor recommends this issue's articles to the reader: summary and comments on 'The compliance and burden of treatment with the epinephrine auto-injector in food allergic patients: focus on adolescents'. *Pediatr Allergy Immunol. 2016 Feb 2016 27;5*.

Saleh-Langenberg J, Flokstra-de Blok BM, AlAgla N, Kollen BJ, Dubois AEJ. Late systemic reactions in food allergic children after double blind, placebo-controlled food challenges. *Allergy. 2016 Apr 27*.

Saleh-Langenberg J, Dubois AE, Groenhof F, Kocks JW, van der Molen T, Flokstra-de Blok BM. The epinephrine auto-injector prescription attitudes of general practitioners to food-allergic patients at high risk for anaphylaxis. *Allergy Asthma Clin Immunol. 2015 Oct 15;11:28*.

Saleh-Langenberg J, Goossens NJ, Flokstra-de Blok BM, Kollen BJ, van der Meulen GN, Le TM, et al. Predictors of health-related quality-of-life of food-allergic patients in eight European countries. *Allergy 2015 Jun;70(6):616-24.*

Saleh-Langenberg J, Flokstra-de Blok BM, Goossens N, Kemna JC, van der Velde JL, Dubois AE. The compliance and burden of treatment with the epinephrine auto-injector in food allergic patients: focus on adolescents. *Pediatr Allergy Immunol. 2015 Aug 13*

Saleh-Langenberg, J; Flokstra-de Blok, BMJ; Dubois, AEJ. De ernstige allergische reactie, risicofactoren voor een ernstiger beloop en de indicaties voor een epinephrine auto-injector. *Allergie Actueel 1-2013*.

Saleh-Langenberg, J. Pediatric Allergy Expert Day. *PraatjesMaker Nutricia Nederland B.V. July 2012*.

ABOUT THE AUTHOR

Jacquelien Saleh-Langenberg always thought that one day she would become business woman of the year. Therefore, after graduating from high school, she decided to study a Bachelor degree in International Business and Languages. During this study she lived abroad for quite some time. First she moved to Zaragoza (Spain) and thereafter to Hong Kong (China). During her time in Hong Kong, she travelled to many different places in China, including Guangzhou, where she worked for an international company for a while. Inevitably, she was bitten by the 'China bug' and decided that she wanted to learn all about the Chinese language and culture.

From 2003 till 2009 she studied a Bachelor degree in Sinology (nowadays called China Studies) at the University of Leiden in the Netherlands. During this time she studied for two years at the University of Beijing. While working as a volunteer in an orphanage in China during her studies in Beijing, her heart was broken in a beautiful way. Her interest in the human body, health care and people's health started to grow from then on. She became highly motivated to devote herself to helping others, especially those in need.

To pursue this dream, she decided to undertake another academic study - Medicine. In 2009 she started a pre-master in Medicine, before starting the Master program in 2010 at the University of Groningen in the Netherlands. Before starting with her clinical rotations, she first did a scientific research project in Tianjin, China. During her time in Tianjin, she became aware of her enthusiasm for scientific, medical research, and the importance and relevance of doing such research.

In 2011 she applied for the MD/PhD program in Groningen. This program allows medical students to obtain a PhD during their Master studies. During the course of this MD/PhD program, she combined clinical research and doing clinical rotations with another of her passions: teaching Mandarin-Chinese.

Besides being a wife and mother of two children, Jacquelien would love to pursue her career in (pediatric) surgery and devote herself to helping those in need around the world.