

From Department of Clinical Science and Education, Södersjukhuset

Karolinska Institutet, Stockholm, Sweden

Severe reactions to foods in childhood

- clinical perspectives, epidemiology and risk management

Mirja Vetander



**Karolinska
Institutet**

Stockholm 2014

All previously published papers were reproduced with permission from the publisher.

Published by Karolinska Institutet. Printed by E-print

© Mirja Vetander, 2014
ISBN 978-91-7549-420-3

ABSTRACT

Food allergy is a public health issue, particularly among children, and seems to be increasing worldwide. Allergic reactions to foods vary in terms of symptoms and severity. Anaphylaxis, the most severe allergic reaction, can be fatal. Food allergy has significant negative impact in the daily lives of allergic children and their families.

The overall aim of this thesis was to gain knowledge about severe reactions to foods among Swedish children with regard to epidemiology, clinical perspectives (study I and II respectively), and risk management (study III). Study I (paper I and II) is an emergency department (ED) medical record study based on a retrospective chart review performed at three hospitals in Stockholm targeting children with anaphylaxis and allergic reactions to foods during 2007. Study II (paper III) is a cohort study where children identified in study I were investigated in relation to new ED visits during the follow-up period 1 January 2007 – 30 June 2010. Study III (paper IV) is a qualitative study where 10 focus group discussions were conducted with 31 parents of food-allergic children to explore strategies of risk management.

The main findings in relation to the three study areas in this thesis are:

Epidemiology: The incidence of anaphylaxis managed at paediatric EDs in Stockholm during 2007 was 32 per 100 000 person-years and food was involved in 92% (paper II). The incidence of subsequent ED visits for reactions to foods among children with a prior ED visit due to reactions to foods was 92 per 1000 person-years. Previously known food allergy was a risk factor for subsequent ED visits (paper III).

Clinical perspectives: The current guidelines presented in the European Academy of Allergology and Clinical Immunology position paper on anaphylaxis in children were not entirely easy to apply when classifying and grading the severity of anaphylaxis in our study population. We attribute this difficulty to lack of description of some respiratory and neurological symptoms and use of subjective wordings (paper I). Among 371 children who visited the EDs due to acute reactions to foods, tree nuts and peanuts were the most common eliciting foods. Among children under three years these allergens were actually as common triggers as milk and egg (paper II). Most children prescribed with adrenaline auto-injectors did not use their device when they experienced anaphylaxis (paper II and III). The severity of previous reactions to foods could not accurately predict the severity of subsequent reactions. However, treatment with adrenaline often hampered the classification of change in severity (paper III).

Risk management: The management of food allergy risk permeates many aspects of everyday life according to the parents in study III. Although most followed the norm of constant risk avoidance and vigilance, some took calculated risks in specific situations where the parent could observe and manage the danger. Parents did this to counterbalance the burden of the food-allergic condition, not only for the child but also for the family as a whole (paper IV).

In summary: This thesis provides novel data on the epidemiology and clinical characteristics of anaphylaxis and severe reactions to foods among Swedish children. In addition, it provides information about the unpredictability of the food allergic condition and the difficulties associated with studying the disease. Finally, it demonstrates the impact of risk management on parents and family life, and also how risk avoidance and calculated risk-taking are intertwined and can be seen as two sides of the same coin: parent responsibility.

LIST OF PUBLICATIONS

- I. **Vetander M**, Helander D, Lindquist C, Hedlin G, Alfvén T, Östblom E, Nilsson C, Lilja G, Wickman M. Classification of anaphylaxis and utility of the EAACI Taskforce position paper on Anaphylaxis in Children. *Paediatric Allergy and Immunology*, June 2011;22(4):369-73
- II. **Vetander M**, Helander D, Flodström C, Östblom E, Alfvén T, Ly D H, Hedlin G, Lilja G, Nilsson C, Wickman M. Anaphylaxis and reactions to foods in children - a population-based case study of emergency department visits. *Clinical and Experimental Allergy*, April 2012; 42(4):568-77
- III. **Vetander M**, Ly D H, Håkansson N, Lilja G, Nilsson C, Östblom E, Wickman M, Bergström A. Recurrent reactions to food among children at paediatric emergency departments. *Clinical and Experimental Allergy*, January 2014;44(1):113-20
- IV. Stjerna M-L, **Vetander M**, Wickman M, Olin Lauritzen S. The management of situated risk: A parental perspective on child food allergy. *Health: An Interdisciplinary Journal for the Social Study of Health, Illness and Medicine* (London). Published online ahead of print April 2013

CONTENTS

1	INTRODUCTION.....	1
2	BACKGROUND.....	3
2.1	Allergic diseases.....	3
2.2	Food allergy and anaphylaxis.....	4
2.2.1	Definitions.....	4
2.2.2	Pathogenesis.....	6
2.2.3	Epidemiology.....	7
2.2.4	Provoking allergens.....	8
2.2.5	Symptoms.....	9
2.2.6	Diagnosis.....	9
2.2.7	Management.....	10
2.2.8	Comorbidity and heredity.....	11
2.2.9	Prognosis.....	12
2.2.10	Primary prevention.....	12
2.2.11	Effect on everyday life.....	13
3	AIM AND RESEARCH QUESTIONS.....	15
4	MATERIAL AND METHODS.....	17
4.1	Study design and study populations.....	17
4.1.1	Study I: An ED medical record study.....	17
4.1.2	Study II: A cohort study.....	18
4.1.3	Study III: A focus group study.....	18
4.2	Methods.....	18
4.2.1	Study I and II.....	18
4.2.2	Study III.....	19
4.3	Definitions and objectives.....	20
4.3.1	Classification of reactions in study I and II.....	20
4.3.2	Objectives.....	20
4.4	Ethical approval.....	21
4.5	Analysis.....	21
4.5.1	Statistical analysis (Paper I–III).....	21
4.5.2	Qualitative analysis (Paper IV).....	22
5	RESULTS.....	23
5.1	Utility of the EAACI position paper on anaphylaxis in children (Paper I).....	23
5.1.1	Encountered difficulties and proposed modifications.....	23
5.1.2	Classification of severity.....	24
5.2	Anaphylaxis and reactions to foods in the ED (Paper II).....	25
5.2.1	Incidence of anaphylaxis.....	25
5.2.2	Additional results.....	25
5.3	Recurrent reactions to foods in the ED (Paper III).....	27
5.3.1	Incidence of and risk factors for revisits.....	28
5.3.2	Change in severity of the reactions.....	29
5.3.3	Additional results.....	30

5.4	Parents' experiences of managing risk related to food allergy (Paper IV)	30
5.4.1	Risk avoidance	31
5.4.2	Risk taking	32
6	DISCUSSION	34
6.1	Clinical perspectives	34
6.1.1	Factors that hamper classification of anaphylaxis	34
6.1.2	Provoking allergens	35
6.1.3	Food allergy – an unpredictable disease	36
6.2	Epidemiology	37
6.2.1	Anaphylaxis	37
6.2.2	Recurrent reactions	38
6.3	Risk management	39
6.3.1	Underuse of adrenaline auto-injectors	39
6.3.2	Balancing risk and burden	40
6.4	Strengths and limitations	42
6.5	Ethical considerations	45
6.6	Clinical implications and future perspectives	46
7	CONCLUSIONS	48
8	SAMMANFATTNING PÅ SVENSKA	49
9	ACKNOWLEDGEMENTS	51
10	REFERENCES	53

LIST OF ABBREVIATIONS

AAI	Adrenaline auto-injector
APC	Antigen-presenting cell
CI	Confidence interval
EAACI	European Academy of Allergology and Clinical Immunology
ED	Emergency department
FAAN	Food Allergy and Anaphylaxis Network
FcεRI	The high-affinity receptor
Fg	Focus group
ICD	International Classification of Disease
IgE	Immunoglobulin E
IL	Interleukin
MHC	Major histocompatibility complex
NIAID	National Institute of Allergy and Infectious Disease
RR	Relative risk
sIgE	Allergen-specific immunoglobulin E
Th	T-helper cell

1 INTRODUCTION

Food allergy is an increasing paediatric public health problem affecting nearly 8% of all children (1). Allergic reactions to food can vary substantially in terms of both manifested symptoms and severity. Anaphylaxis, the most severe food allergic reaction, can be fatal.

The true incidence of anaphylaxis among children on a population basis has not yet been established. This is partly due to the fact that until recently there has been a lack of agreement on the definition and criteria for diagnosis of anaphylaxis. According to current criteria – which are widely accepted internationally – anaphylaxis is an acute allergic reaction involving two or more organ systems after exposure to a likely allergen, or hypotension alone after exposure to a known allergen for that patient (2).

To date, it has not been possible to predict the severity of reactions in individuals allergic to food (3). Since there is neither a cure nor preventive treatment for food allergy at present, management is restricted to careful avoidance of the offending food and constant preparedness to respond to accidental exposure. However, despite the best efforts, complete avoidance is difficult and the fear of a fatal reaction often causes considerable anxiety in families of food-allergic children. In fact, food allergy has been shown to have a significant detrimental impact on quality of life (4).

When this doctoral project was initiated, the incidence of anaphylaxis among Swedish children was unknown. Very few paediatric studies had investigated acute allergic reactions to foods in relation to sex and age, eliciting foods, clinical characteristics and management. Furthermore, the utility of the newly proposed criteria for classification and severity grading of anaphylaxis had not been evaluated. In addition, knowledge about recurrent allergic reactions to foods in the paediatric population was scarce, especially with regard to risk factors for re-reactions and the risk of subsequent reactions being more severe. Finally, little was known concerning how parents perceived management of food allergy.

2 BACKGROUND

2.1 ALLERGIC DISEASES

Food allergy and anaphylaxis belong to the group termed allergic diseases, as do asthma, rhinitis, drug allergy, insect allergy, eczema, urticaria and angioedema. Allergic diseases are increasing worldwide and are estimated to affect 30-40% of the world population, thus representing a major health problem (5). Although there are large geographical differences in the prevalence of allergic diseases, with the highest frequencies in countries with a Western lifestyle (6, 7), children bear the greatest burden worldwide (5). A study done in Sweden reported that over half of all children were affected with an allergy-related disease at some time during their first 12 years of life (8). There is significant co-morbidity between allergic diseases, with allergic symptoms often showing a progression throughout childhood, referred to as the atopic march (9). The first manifestations are often eczema and food allergy in infancy followed by development of rhinoconjunctivitis and allergic asthma at school-age.

The onset of allergic disease is a result of the immune system interpreting normally harmless substances (i.e. allergens or antigens) as foreign, leading to an imbalanced and harmful immune response (10). Usually allergic reactions are caused by allergen-specific immunoglobulin E (sIgE) antibodies. A personal and/or familial tendency to produce IgE antibodies at a high rate in response to exposure to supposedly harmless substances is referred to as atopy (10). The term sensitisation is used to describe elevated levels of sIgE antibodies in serum. In allergic individuals, exposure to an allergen against which the individual is sensitised may lead to allergic symptoms which can be acute or delayed. However, it is far from always the case that clinical symptoms correspond to the presence or the levels of sIgE. Hence, sensitisation does not equal allergy (11).

The determinants of allergic diseases include interplay between genetic and environmental factors as well as the timing of these exposures (12). Indeed, the influence of genetics is strong, with a positive family history of allergic disease being a significant risk factor for development of allergic conditions (13, 14). However, genetic factors cannot explain the rapid increase in the prevalence of allergic diseases in the last decades. Hence, environmental factors must be central to the development of allergic disease, although their effects may partly be mediated through epigenetic mechanisms (15).

In fact, there appear to be many environmental factors associated with the development process that may have contributed to the worldwide increase of allergic diseases, including loss of protective factors and addition of risk factors. Such factors include aspects of lifestyle, dietary habits, exposure to microbes, indoor and outdoor environment (exposure to smoking, traffic-related air pollution) and climatic variation (7). For example, it has been hypothesised that increased cleanliness and reduced family size, both leading to decreased microbial exposure, could explain the global increase in allergic diseases; this theory is often referred to as the hygiene hypothesis (16, 17). Lifestyle factors associated with the anthroposophic way of life and living on a farm have also been reported to decrease the risk of allergic diseases in childhood

(18, 19). Although the recent increase in allergic disease most likely reflects changes in the interactions between the external environment and genes, the aetiologic mechanisms involved are currently unclear (11).

2.2 FOOD ALLERGY AND ANAPHYLAXIS

2.2.1 Definitions

Food allergy

Food allergy was recently defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given antigen (20). This definition encompasses immune responses that are (1) IgE-mediated, (2) non-IgE-mediated, (3) mixed IgE-mediated and non-IgE-mediated and (4) cell-mediated (Figure 1). The absolute majority of acute allergic reactions to food are IgE-mediated; thus IgE-mediated food allergy is the focus in this thesis. However, food protein-induced enterocolitis syndrome, which is a non-IgE-mediated disorder, can also present with acute symptoms such as repetitive emesis and dehydration a few hours after exposure to the offending foods (20).

Non-immunological adverse food reactions are more common than true food allergy and are caused by food intolerance, which is an effect of pharmacological properties of the food (21). Examples include tyramine-induced nausea and headache, metabolic disorders like lactose intolerance, and bacterial food poisoning.

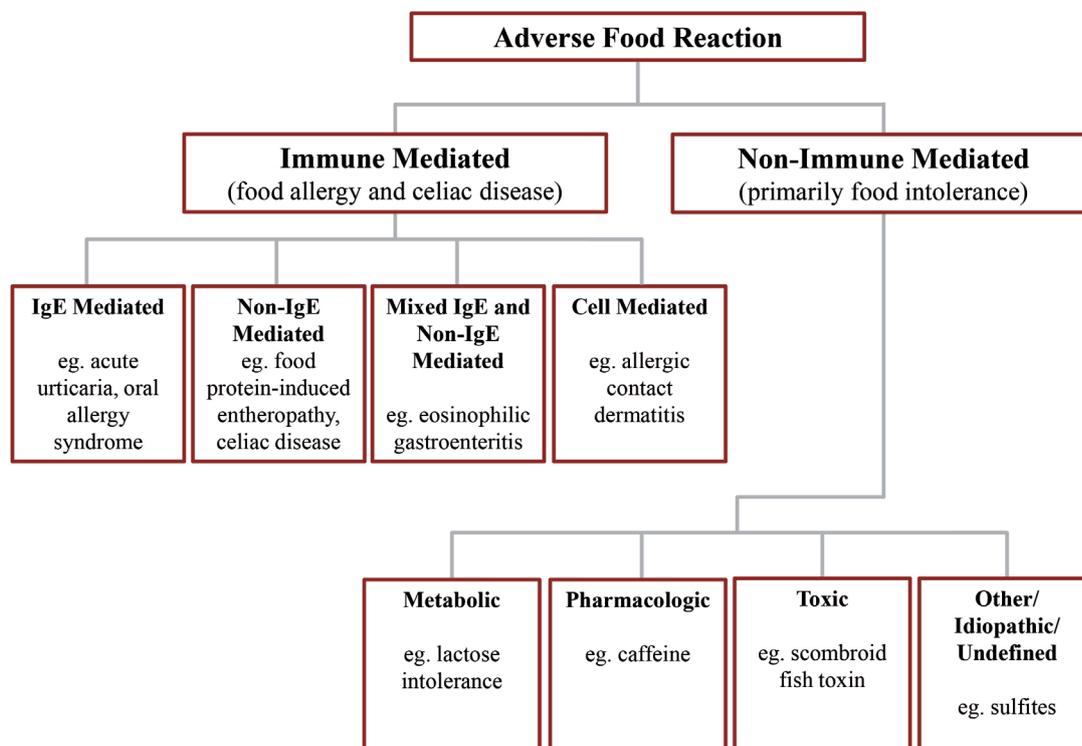


Figure 1. Classification of adverse food reactions from Boyce et al (20).

Anaphylaxis – definition and grading of severity

Anaphylaxis was first described in 1902 by Richet and Portier: they injected dogs with toxins from sea anemones with the intention of demonstrating the development of immune resistance. However, instead of developing immunological protection, the dogs had severe allergic reactions and died after receiving the second injection. Richet and Portier called this reaction ‘against’ phylaxis (protection) or anaphylaxis (22). In humans, anaphylaxis can have both underlying immunological (IgE-mediated or non-IgE-mediated) and non-immunological mechanisms (23). However, the vast majority of cases are mediated through an immunological IgE-dependent mechanism as described below.

Until recently there has been a lack of widely accepted criteria for anaphylaxis. However, the 2006 symposium of the National Institute of Allergy and Infectious Disease (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) proposed a consensus definition of and criteria for anaphylaxis to satisfy epidemiological, research and clinical needs (2). According to this definition, anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. The proposed diagnostic criteria for anaphylaxis are presented in Table 1. In brief, anaphylaxis is a probable diagnosis in presence of symptoms from two or more organ systems after exposure to a likely allergen, or hypotension alone after exposure to a known allergen for that patient.

Table 1. Clinical Criteria for Diagnosing Anaphylaxis*

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 (eg, generalised urticaria, itching or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:
A) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
B) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence) **OR**
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 (eg, generalised urticaria, itch-flush, swollen lips-tongue-uvula)
B) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
C) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
D) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) **OR**
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 of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

* Ref: Sampson et al 2006 (2)

PEF: peak expiratory flow

**Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

The NIAID-FAAN criteria for anaphylaxis correspond fully to the criteria presented by the European Academy of Allergology and Clinical Immunology (EAACI) Taskforce on Anaphylaxis in Children in 2007 (24) and by the World Allergy Organization in 2011 (25). So far, the NIAID-FAAN criteria have turned out to be highly sensitive but less specific (26). To date, there is no world-wide agreement on how anaphylaxis should be graded in terms of severity, although a proposal was presented by the EAACI Taskforce on Anaphylaxis in Children in 2007 (24).

2.2.2 Pathogenesis

Although the immune systems of all individuals recognise food antigens as foreign most people do not develop food allergies. The process of developing oral tolerance to foods is brought about mainly by the action of regulatory T cells and dendritic cells as well as local immune responses. In addition, commensal microbes in the gastrointestinal tract seem to play an important role in driving the immune responses by inhibiting the development of allergic responses to food antigens (27, 28).

However, individuals with food allergy develop pathological immune responses when they encounter food allergens (Figure 2). In the initial phase of the development of IgE-mediated food allergy the allergen passes epithelial barriers and is taken up by an antigen-presenting cell (APC) such as the dendritic cell (11). Fragments of the ingested antigen are then presented on the major histocompatibility complex (MHC) molecule which together with other co-stimulatory molecules bind the naive T-helper cell. At this point the antigen-presenting cell will decide whether the naive T-helper cells will develop into Th1, Th2 or Th17 effector cells or regulatory T cells (11). In the food allergic individual, naive T-helper cells will differentiate into Th2 cells producing the cytokines IL-4 and IL-13. These cytokines stimulate B-cells to produce allergen-specific IgE (sIgE) antibodies. These secreted sIgE antibodies circulate in serum and bind to high-affinity receptors (FcεRI) on mast cells in the connective tissue and on basophil leukocytes in the circulation. The individual is now sensitised to that specific food allergen (11).

At a subsequent exposure the allergen will cross bind to allergen-specific IgEs on the mast cell and basophil, thereby activating the cells. This results in a degranulation process with release of inflammatory mediators such as histamines, leukotrienes and proteases. These inflammatory mediators lead to vasodilatation, increased vascular permeability, smooth muscle contraction, inflammatory cell recruitment and tissue damage, thus causing the allergic reaction (11, 29, 30). The mast cells of non-allergic individuals are also coated with IgE but since these are polyclonal, cross-linking does not occur (31).

Sensitisation to foods can occur through the gastrointestinal tract: most of these food allergens are heat stable, resistant to acid degradation, and resistant to proteolysis (28). Sensitization can also occur to inhaled plant and tree pollens through the respiratory tract after which IgE-mediated allergic reactions to foods containing cross-reacting epitopes may develop. These allergens are usually labile proteins that are easily degraded. Extra-intestinal sensitisation through the skin may also occur. Food allergens derived from plants are classified based on their structural and biological properties with different levels of allergenicity depending on their resistance to processing such as heating and enzymatic actions (28).

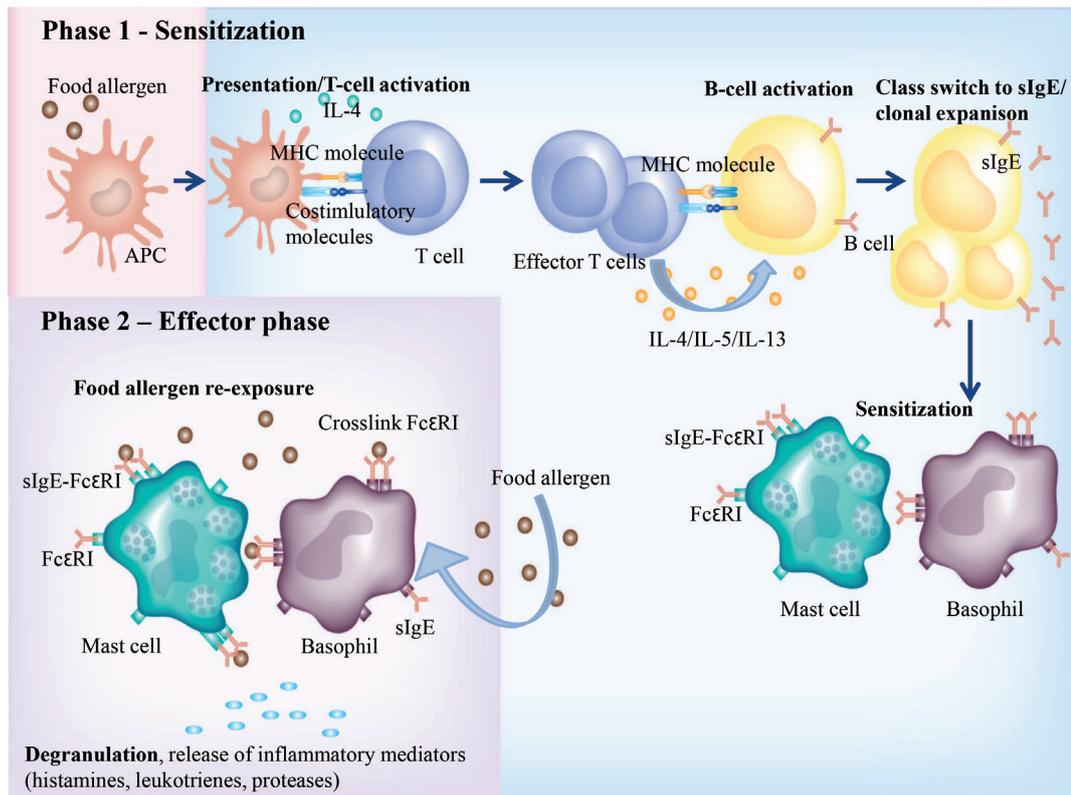


Figure 2. Mechanisms involved in the development of IgE-mediated food allergy. Adapted from Gomez et al (29).

2.2.3 Epidemiology

Estimates of the actual incidence and prevalence of food allergy and anaphylaxis are uncertain. Comparisons of epidemiologic data are often complicated due to differences in allergy definitions, methodologies, and characteristics of the study populations with regard to ages and exposures. In addition, few studies investigating the epidemiology of food allergy have used the gold standard of diagnosis: the double-blind placebo-controlled food challenge (32). As to anaphylaxis, the study of its epidemiology has until recently been hindered by the lack of widely accepted criteria for anaphylaxis. Notwithstanding these challenges, several systematic reviews on the epidemiology of anaphylaxis and food allergy have been published in recent years (32-36). True for food allergy as well as anaphylaxis, self-reported rates are generally higher than those determined on the basis of medical history and clinical testing (3, 34, 37, 38).

The occurrence of food allergy and anaphylaxis appears to have increased in recent decades (3, 39-45). However, regarding the prevalence of food allergy there have been occasional reports on a levelling off in the last ten years (46, 47).

Anaphylaxis

In 2006 the Working Group of the American College of Allergy, Asthma, and Immunology published a comprehensive review of studies written in English (34). There, the authors estimate the lifetime prevalence of anaphylaxis to be between 0.05 and 2%, with the highest number of incident cases among children and adolescents. In a review on the epidemiology of anaphylaxis in Europe the authors report the life-time

prevalence to be 0.3% (95% CI 0.1-0.5) and the incidence rates for all-cause anaphylaxis range from 1.5 to 7.9 per 100 000 person-years (35). Population-based estimates of anaphylaxis incidence rates among children are scarce (48-52) and vary widely: from 5 (51) to 314 (52) episodes per 100 000 person-years. Varying populations, different study designs and diverse classifications of anaphylaxis contribute to the divergent estimates.

Fatalities due to anaphylaxis are extremely rare. In the UK the rate of fatal anaphylaxis irrespective of cause is documented to be 0.33 deaths per years per million inhabitants (53) while the rate of deaths due to food-induced anaphylaxis was 0.06 per year per million children younger than 16 years during the period 1990 to 2000 (54). In Sweden there have been two fatalities among children due to food-induced anaphylaxis in the last six years according to professional allergologists.

Food allergy

Food allergy affects more than 1% but less than 10% of the population according to a recent systematic review performed by Chafen et al (33). However, the authors conclude that the evidence for the prevalence of food allergy is severely limited by the lack of uniform criteria for making a diagnosis. According to a meta-analysis by Rona et al the prevalence of allergy to any foods is 12% in children and 13% in adults when assessed by self-reported symptoms (based on 23 studies) and 3% for all ages when assessed by clinical testing and medical history or double-blind placebo controlled food challenge (6 studies)(36). In a recent large population-based study from Australia, more than 10% of one-year-old children had challenge-proven IgE-mediated food allergy to raw egg (8.9%), peanut (3.0%) or sesame (0.8%) (55). However, the majority (80%) of the infants with raw egg allergy actually tolerated baked egg. In Sweden the prevalence of doctor-diagnosed food allergy among 12-year-old children of a large national population based survey is 8% according to parental report (56), a figure which conforms with the findings in several recent studies on the prevalence of self-reported food allergy among children (57-59).

2.2.4 Provoking allergens

Food allergens

Food allergens are usually proteins, but sometimes haptens (i.e. a small molecule that can elicit an immune response only when attached to a large carrier such as a protein) and occasionally carbohydrates. Any food can trigger an allergic response, and more than 170 foods have been reported to cause IgE-mediated reactions (3). However, a limited number of foods cause the majority of food allergic reactions worldwide with milk, egg, soy, wheat, peanut and tree nuts accounting for over 80% of the reactions in children (28). The distribution of allergens depends on dietary practices and thus varies from country to country. For example, fish and shellfish commonly elicit allergy among children in the Mediterranean countries (60, 61) while sesame seed allergy is frequent in Israel (62). In Scandinavia the most prevalent childhood food allergies have been reported to be to egg, milk and peanut in young children and to fruit and vegetables in older children (63). Where allergies to fresh fruits and vegetables are concerned, there is often a link to pollen allergy. This is called pollen-associated food allergy syndrome or oral allergy syndrome; up to half of all pollen allergic individuals experience mild oropharyngeal symptoms after eating certain raw fruits and vegetables (64, 65). Food triggers also include additives such as spices, parasites such as the

nematode *Anisakis simplex* which can be found in fresh fish, and carbohydrates contained in fresh red meat (23).

Other triggers

Although foods are by far the most common cause of anaphylaxis in children, other triggers like insect stings and medications also cause anaphylaxis in the paediatric population (23). Medication-triggered anaphylaxis can for example be caused by antibiotics, nonsteroidal anti-inflammatory drugs and allergens used in immunotherapy. Other less common triggers include latex, exercise, underlying mast cell disorders and inhaled allergens such as animal dander and grass pollen (23). In some cases, no trigger can be identified and the anaphylaxis is classed as idiopathic (23).

2.2.5 Symptoms

Food allergies cause a wide spectrum of clinical signs and symptoms depending on the nature of the reaction. The onset of symptoms of acute IgE-mediated reactions to foods ranges from within seconds to a few hours after exposure to the allergen. IgE-mediated food allergic reactions vary substantially in severity with anaphylaxis being the most severe form. Several organ systems can be affected: the skin (e.g. flush, urticaria, angio-oedema), the respiratory tract (e.g. wheeze, cough, stridor, cyanosis, rhinitis, conjunctivitis,), the gastrointestinal tract (e.g. nausea, vomiting, diarrhoea, abdominal pain), the central nervous system (e.g. anxiety, headache) and the cardiovascular system (e.g. syncope, hypotension, arrhythmia). The most common manifestations of anaphylaxis are urticaria and angio-oedema, which occur in 90% of patients (66). Children are more likely to experience respiratory compromise than hypotension or cardiovascular shock (23, 67). Isolated respiratory symptoms are rare (68). Oral symptoms such as tingling and pruritus are common among patients with pollen-associated food allergy syndrome; this mild localised reaction often subsides within minutes of ingestion although some patients may experience more systemic symptoms which occasionally progress to anaphylaxis (69).

Many signs and symptoms of allergic reactions overlap with other diseases and conditions. Differential diagnoses to consider include asthma exacerbations, aspiration of foreign objects, acute generalised urticaria and/or angio-oedema, anxiety, food poisoning, systemic mast cell disorders, hypoglycaemia and septic shock (70). However, the multisystem involvement that is a hallmark of anaphylaxis makes it easy to recognise in most cases.

2.2.6 Diagnosis

The diagnosis of food allergy as well as anaphylaxis is primarily based on a detailed medical history and careful physical examination. As for anaphylaxis, it remains a clinical diagnosis and there is to date no reliable diagnostic test although elevated levels of histamine (in plasma or in urine) or serum tryptase sometimes can be useful in confirming an acute episode of anaphylaxis. However, serum tryptase levels are often normal among patients with food-induced anaphylaxis (23). The assessment of anaphylaxis triggered by insects is quite straightforward since the trigger often is obvious and methods for measuring venom-specific IgE-levels are commercially available. Conversely, assessment of medication-triggered anaphylaxis is often

hampered by the lack of appropriate reagents for use in skin tests or for measurement of medication-specific IgE levels (23). Since the focus in this thesis is allergic reactions to foods, the assessment of anaphylaxis from other triggers will not be discussed further.

When assessing a patient with suspected allergic reactions to foods, history-taking should focus on the elicited symptoms and their severity, the relationship between the intake of the food and the onset of symptoms and the amounts that triggered the reaction. Dietary details are crucial, especially when the trigger is not obvious. For example, if the reaction occurs after ingesting a meal prepared outside the home, speaking to people who prepared the food is the only way to identify hidden ingredients. In addition, possible cofactors such as exercise, ingestion of medications, acute infections and emotional stress should be asked for (25). However, medical history has limited positive predictive value and further tests are needed (3). To diagnose IgE-mediated food allergy, skin-prick tests, sIgE measurements and oral food challenges are recommended, whereas intradermal testing and measurement of total serum IgE are not (71).

Skin-prick tests and sIgE tests are certainly useful for diagnosis and can also be used to prospectively follow up the sensitivity of a patient. These methods are highly sensitive and it has been recognised that the probability of a clinically relevant allergy is associated with the wheal sizes elicited by a skin prick test and the concentration of sIgE-antibodies in the serum. However, studies correlating skin test wheal size or sIgE to the clinical outcome food allergy report varying diagnostic cut-off levels (1). In addition, these tests have rather low specificity and false negative results occur (1, 72).

Component-resolved diagnostics, the next generation of sIgE tests, enables the quantification of IgE-antibodies against individual allergen components at a molecular level within an allergen extract (73). Component-resolved diagnostics might differentiate clinical reactivity (IgE binding to 'potent' stable allergens) from less clinically relevant sensitisation (binding to labile proteins), but severe reactions can occur despite lack of noted binding to the allergens being measured (1).

Oral food challenges might be required for final diagnosis when tests are inconclusive or if they are negative and the initial reaction was severe. This procedure should be done by qualified personnel and in facilities that are prepared to handle anaphylaxis (28). The gold standard is the double-blind placebo-controlled food challenge, but this is an expensive, protracted procedure. Therefore most units perform open challenges.

2.2.7 Management

Acute management

Acute management of anaphylaxis include rapid assessment of the patient's airways, breathing, circulation, mentation and skin, and prompt intramuscular administration of adrenaline at a first aid dose of 0.01 mg/kg to a maximum adult dose of 0.5 mg (25). The dose can be repeated every 5-15 minutes if needed. Adrenaline is the first line treatment for anaphylaxis; it reduces morbidity and mortality via its alpha- and beta-adrenergic properties, which increase blood pressure and decrease upper airway obstruction, urticaria, angio-oedema and wheeze. The patient should be placed on the back or in a comfortable position with the legs elevated. Supplemental oxygen, nebulised beta-2 adrenergic antagonist and intravenous infusion of (for example) 0.9%

saline should quickly be given if needed. Second-line medications include antihistamines and glucocorticoids, which are recommended in most anaphylaxis guidelines although the evidence base for these medications in the initial management of anaphylaxis is poor. Up to 11% of children with anaphylaxis may experience a second phase of symptoms 1-78 hours after the initial symptoms have resolved, so called biphasic reactions. Thus, monitoring in a medically supervised setting after resolution of symptoms should be considered with the duration of monitoring being individualised based on the severity of the reaction (25).

Long term management

To date there are no recommended preventive medications for food allergy, hence management relies on allergen avoidance and readiness to treat allergic reaction promptly if they occur (1, 20). Comprehensive education about avoidance includes information about the importance of reading labels, the potential for cross-contamination and high-risk scenarios such as eating at restaurants and travelling. Sometimes avoidance of entire food groups should be recommended because of cross-reactivity between certain foods (1). Care should be taken to ensure that the diet provides adequate nutrition, especially for children with multiple allergies. Many food allergies are outgrown, so regular re-evaluations are needed.

In addition to food avoidance, the patient should be taught to recognise the signs and symptoms of allergic reactions and be prescribed medications to use in case of future reactions. Exactly what makes a patient suitable to be prescribed adrenaline auto-injectors (AAIs) is debated and current prescription practices vary widely (74, 75). However, a previous episode of anaphylaxis is certainly an indication for prescription. Again, education is a crucial: the child and his/her caregivers should be told how and when to use the AAI. They should also be supplied with a personal management plan, preferably one that emphasises the key symptoms and signs that should lead to adrenaline injection (25). Since up to 20% of patients with anaphylaxis require repeated adrenaline dosing, patients should be advised to carry two AAIs (76). All patients with IgE-mediated food allergies should be prescribed antihistamines to be used for mild symptoms and never in place of adrenaline (77). Children with asthma should also be advised to use inhaled bronchodilators liberally if experiencing an allergic reaction.

Although there is no cure for food-induced allergic reactions to date, there is effective treatment for patients with anaphylaxis triggered by insect stings: subcutaneous immunotherapy with relevant insect venom will achieve protection in up to 98% of children (25).

2.2.8 Comorbidity and heredity

Children with food allergy have been reported to be 2-4 times more likely to have other allergic diseases such as asthma, eczema and respiratory allergies compared to children without food allergy (39). In particular, eczema and food allergy are highly associated (20, 78): up to 37% of children under 5 years of age who have moderate to severe atopic dermatitis are reported also to have IgE-mediated food allergy (79). In patients with asthma, the coexistence of food allergy may be a risk factor for severe asthma exacerbations (71). Children who develop allergy to one foodstuff are at higher risk of developing more food allergies (80). As to heredity, having a biological parent

or sibling with a history of allergic rhinitis, asthma, eczema or food allergy is a strong risk factor for development of food allergy (71, 81).

2.2.9 Prognosis

Development of tolerance

Spontaneous clinical tolerance develops in some food-allergic individuals, and resolution tends to occur in allergen-specific patterns. For example, allergy to egg, milk, wheat, and soy is generally outgrown during childhood, whereas allergies to peanut, nuts, and seafood are usually lifelong. However, if the first episode of an allergic reaction is accompanied by a high level of specific IgE against the triggering food, the allergy tends to persist over time (3, 20). Patients who have developed tolerance can sometimes suffer a 'relapse' of their allergy. Research has indicated that once tolerance is established, the likelihood of recurrence may be decreased if the patient eats the food frequently (77). However, there are many uncertainties in this field.

Risk factors for severe allergic reactions

The severity of a reaction depends on multiple factors, related both to the host and the event (82). The dose of the allergen, the allergenicity, the form in which the foodstuff is ingested (raw or cooked, e.g. if the allergen is sensitive to heat or gastric juice) are all of importance for the risk and severity of a reaction (83). However, the amount of food that elicits a reaction, i.e. the threshold levels, varies considerably, not only between different individuals (84-86), but also in the same individual at different times (87). This variability is probably explained by other factors that affect reaction severity, so called co-factors. Examples of co-factors are alcohol, medication (for example aspirin), physical exercise, concurrent infections, other ongoing allergic disease such as asthma, and pollen allergy (82, 83). Ingestion on empty or full stomach might be taken into account as well (3). Co-factors that amplify anaphylaxis have been described in up to 20% of paediatric patients (88).

Since multiple factors contribute to the severity of an allergic reaction, it is hardly surprising that many studies to date report difficulties predicting the severity of the next reaction on an individual basis (87, 89-92). For example, Pumphrey et al found that more than half of the deaths due to food-induced anaphylaxis in the UK 1999-2006 occurred in patients whose previous reactions had been mild (93). However, there are some known risk factors for fatal food-induced anaphylaxis such as a previous life-threatening anaphylactic episode, delayed administration of adrenaline, and active asthma (23, 53, 94, 95). Severe reactions have also been reported to be more likely in adolescents (96) and in youths with multiple food allergies (57).

2.2.10 Primary prevention

Until recently it was assumed that allergen exposure early in infancy was a risk factor for food allergy but today there is a shift towards the opposite notion that prolonged allergen avoidance might instead be a risk factor (15). It is proposed that prolonged allergen avoidance bypasses induction of oral tolerance, while still allowing food sensitisation through alternative routes, particularly through the skin (1). According to this hypothesis, which has so far been supported by most epidemiologic studies, it is the

timing and balance of cutaneous and oral exposure that determine whether the child develops an allergy or tolerance (97).

In a recent comprehensive review by Sicherer and Sampson (1) the recommendations for primary prevention of food allergy are: *Healthy diet during pregnancy and no maternal allergen avoidance during pregnancy or while breast-feeding. Exclusive breast-feeding for at least four months if at risk for allergy and when unable to do so, hydrolyzed infant formula should be considered. Not to delay introduction of solid foods beyond 4-6 months, including allowing allergenic food although not necessarily as weaning foods.* However, it should be noted that studies on these topics show conflicting results. As for studies investigating whether prebiotics or probiotics can have a protective effect, the findings have so far been contradictory and inconclusive (1, 15).

2.2.11 Effect on everyday life

Food-allergic patients and their families are continually confronted with the necessity of dietary vigilance and the possibility of sudden onset of severe reactions. Thus, it is hardly surprising that food allergy has been repeatedly shown to impair quality of life in the affected families (98-104). In fact, children with peanut allergy have been reported to have a poorer quality of life than children with insulin-dependent diabetes mellitus (105). Furthermore, parents of peanut-allergic children report more disruption of daily activities than parents of children with rheumatologic diseases (106). Food-allergic children and their parents are burdened with a variety of tasks in everyday life, such as checking every step in the process of purchasing and preparing food and educating extended family members, child care providers and teachers to ensure the child's safety (4, 107, 108). Getting accurate information about ingredients when eating away from home is associated with difficulties, which influences decisions such as which restaurant to go to and where to go on vacation (104, 109). Regarding potential limitations on social activities, parents of food-allergic children have been reported to avoid letting their children participate in age-appropriate activities such as playing at friends' houses or attending birthday parties (104, 110).

Since total allergen avoidance often is difficult despite the best of efforts, there is always a risk of unexpected and potentially life-threatening reactions. The burden in the affected families appears to be related to this element of living with risk (4). The defining elements of risk are uncertainty and possible negative outcome (111). In fact, food allergy has been described as an important example of risk (112) as life with this condition involves uncertainties, danger and constant risk management (113). Eating is a fundamental human need, but among allergic individuals, food can be regarded as dangerous. Consequently, children with food allergy can be seen as 'children at risk'. However, relatively little is known about the experiences of living with the risk associated with this condition and even less has been done to explore risk management in everyday situations in depth.

When exploring the experiences of those living with long-term conditions, qualitative research can provide insights that quantitative studies cannot (114). In recent years a handful of qualitative papers have been published exploring experiences of food allergy management among affected children and adolescents (115-119) their parents (100, 108, 120) or both parties (121, 122). These studies confirm that crucial parts of the experience of living with food allergy are being at risk of, and living in fear of, adverse

reactions as well as the never-ending task of constant vigilance and decision-making. For example, Gillespie et al found feelings of living with risk and fear to be predominant among mothers of food-allergic children (120). 'Living with risk' was also identified as a major theme in a recent qualitative investigation into the maternal experience of having a child with severe food allergy (108).

3 AIM AND RESEARCH QUESTIONS

In this thesis, the overarching aim was to gain knowledge about the epidemiology and clinical characteristics of severe reactions to foods among Swedish children and furthermore to explore risk management among parents with food-allergic children.

The specific research questions were:

Are the widely accepted criteria for anaphylaxis and the severity grading presented in the EAACI position paper on anaphylaxis in children (24) applicable on Swedish children? (Paper I)

What is the incidence of anaphylaxis requiring emergency department care in the paediatric population? Among children who visit the emergency department due to reactions to food: what are the clinical characteristics? Which foods elicit reactions and how are the children managed? (Paper II)

Among children who have visited the emergency department due to reactions to food, what is the incidence and what are the risk factors for subsequent emergency department visits due to reactions to foods? Can the severity of previous reactions be used to predict the severity of subsequent reactions? (Paper III)

How do parents understand and manage the risks posed by food allergy in the context of everyday life? (Paper IV)

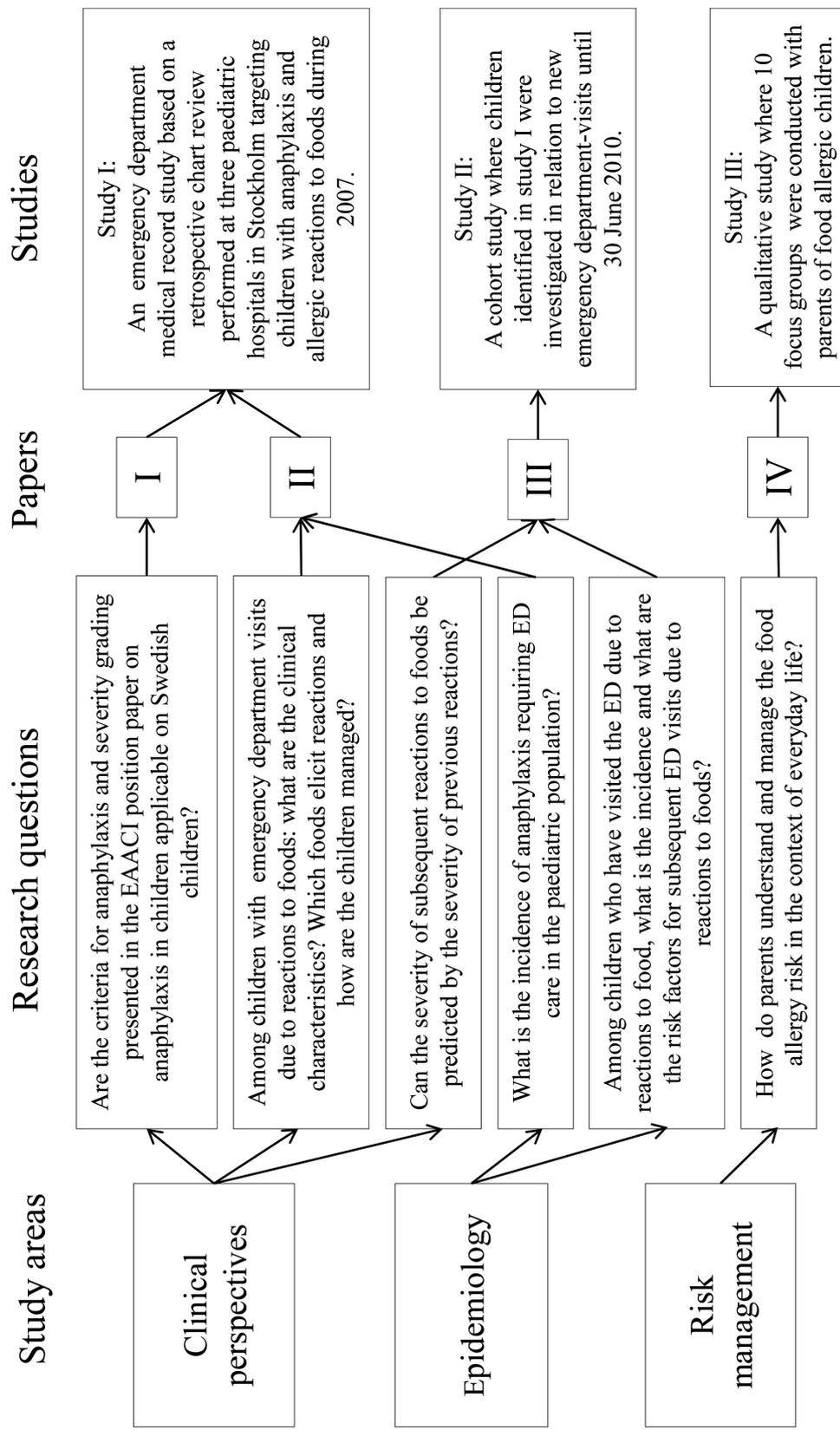


Figure 3. Overview of the study areas, research questions, papers and studies in the thesis.

4 MATERIAL AND METHODS

Figure 3 illustrates how the study areas, research questions, papers and studies in this thesis relate to each other. Study I (papers I and II) and study II (paper III) are quantitative studies while study III (paper IV) has a qualitative approach.

4.1 STUDY DESIGN AND STUDY POPULATIONS

4.1.1 Study I: An ED medical record study

This population-based case study was done on children 0 to 18 years old who had visited the ED of any of the three paediatric hospitals in Stockholm County. Inclusion criteria were any acute reaction to foods or anaphylaxis irrespective of cause. The study period was from 1 January through 31 December 2007. The hospitals were Sachs' Children and Youth Hospital, and the two branches of Astrid Lindgren's Children's Hospital in Solna and Huddinge. The catchment area of these hospitals was Stockholm County.

To identify eligible patients we searched for 19 possible discharge codes selected from the International Classification of Disease, tenth revision (ICD-10) (Table 2). A pre-review was performed of children admitted to Sachs' Children and Youth Hospital January to March 2007 or during another randomly selected three months the same year (May, June and August) with ICD codes J45, L20, L24.6, L27 and K52.2 as the only diagnosis. Since we did not identify any child with anaphylaxis among these children, records with these ICD codes as the only diagnosis were not reviewed further.

Table 2. The discharge codes initially used for retrieval of clinical emergency department records (*ICD-10*)

Code	Diagnosis
J45	Asthma
K52.2	Allergic and dietetic gastroenteritis and colitis
L20	Atopic dermatitis
L27	Dermatitis due to substances taken internally
L24.6	Irritant contact dermatitis due to food in contact with skin
L50.0	Allergic urticaria
L50.9	Urticaria, unspecified
T63	Toxic effect of contact with venomous animals
T78.0	Anaphylactic shock due to adverse food reaction
T78.1	Other adverse food reactions, not elsewhere classified
T78.2	Anaphylactic shock, unspecified
T78.3	Angioneurotic oedema
T78.4	Allergy, unspecified
T78.8	Other adverse effects, not elsewhere classified
T78.9	Adverse effect, unspecified
T80.5	Anaphylactic shock due to serum
T88.1	Other complications following immunisation, not elsewhere classified
T88.6	Anaphylactic shock due to adverse effect of correct drug or medicament properly administered
T88.7	Unspecified adverse effect of drug or medicament

4.1.2 Study II: A cohort study

In this cohort survey, children identified in study I with ED visits due to allergic reactions to foods during 2007 (the index reaction) were reinvestigated in relation to new ED visits due to reactions to foods. The follow-up period was between 1 January 2007 and 30 June 2010. Children not resident in Stockholm County at the time of the index reaction were excluded since they were rather unlikely to have visited any of the paediatric EDs in Stockholm at a new allergic reaction to foods.

4.1.3 Study III: A focus group study

In this qualitative study we conducted focus group discussions with parents of children with food allergy with the aim of exploring the parents' understanding and management of food allergy. Participants were recruited consecutively among parents of the children identified in study I who in 2007 had attended the EDs at either Sachs' Children and Youth Hospital or Astrid Lindgren's Children's Hospital in Solna due to acute reactions to foods. In spring 2008 we sent a letter to the identified families inviting the parents to participate in an online survey about their child's food allergy. This letter included brief information about our plans for a subsequent interview study. To be able to answer the web-site survey the parents had to have sufficient knowledge of Swedish.

The parents invited to participate in the study were those who had confirmed in the online survey that their child's ED visit in 2007 was due to an allergic reaction to foods and that their child had current food allergies. The parents of children with ED visits to Sachs' Children and Youth Hospital were invited to participate in 2009 by letter and were contacted by phone a few weeks later and asked if they wished to participate. The parents of children with ED visits to Astrid Lindgren's Children's Hospital in Solna were instead invited by e-mail in 2010. In the letter and the e-mail we explained the purpose of the study and that declining participation in the study would not affect their contacts with the clinic. The parents were encouraged to participate regardless of their perception of the degree of severity of their child's food allergy.

4.2 METHODS

4.2.1 Study I and II

Review procedure

In study I all medical records at the three paediatric hospitals that pertained to children identified according to the selected ICD codes were reviewed in detail. Two trained paediatric allergologists took the decision on inclusion or not for all uncertain cases. Among children with repeated ED visits during 2007 we included only the first record in study I unless the child had reacted to different foods on different occasions, in which case we included one record per eliciting food. This was done to avoid oversampling of symptoms to a specific food. The only exception was during calculation of the incidence of anaphylaxis in paper II.

In study II the medical records of all children in the cohort were reviewed to identify any visits to the EDs at Sachs' Children and Youth Hospital, Astrid Lindgren's Children's Hospital in Solna and in Huddinge during the time for follow-up. We also reviewed medical records from two new local emergency units affiliated with Astrid

Lindgren's Children's Hospital in Solna and in Huddinge that opened during the follow-up period, since children with milder reactions to foods could have been admitted there when they visited the EDs. Concerning children for whom there was any uncertainty as to whether the ED revisit was caused by an allergic reaction to foods, a trained paediatric allergologist was consulted.

Data collection

Information regarding each ED visit was recorded with the same procedure in study I and II. We had access to complete medical records from the ED visits including notes taken during ambulance transport as well as by the nurse in charge at admission. Furthermore, we had access to referral letters written at discharge from the EDs and medical records from in- and out-patient visits at the three paediatric hospitals prior to and after the ED visits.

Recorded symptoms and signs were entered in an online database designed for this purpose. Clinical data were extracted using a predefined protocol. Symptoms and signs entered in the database were those objectively registered by health care staff as well as subjective symptoms reported by the patients and described in the clinical records. Vomiting and diarrhoea were entered in the database even when only reported by the patient or parents, provided these symptoms had occurred shortly before admittance. Signs and symptoms were assumed absent if they were not reported or reported as not present. Information about current allergic diseases, probable eliciting agent, prescription of self-injectable adrenaline, pharmacological treatment and referral for follow-up was also collected. The eliciting food was recorded as 'mixed food' in study I and as 'unknown' in study II if the patient had eaten foods containing many different and sometimes unknown components or meals with several foods where it was not possible to discover the culprit allergen. When two triggers were observed they were also included in this category.

4.2.2 Study III

The parents that accepted the invitation to participate in the focus group discussions were allocated to groups according to the age of their child (above/ below 9 years of age) as parenting a younger or older child can involve different experiences of risk management. We aimed for each group to include four to six parents. The focus group sessions were carried out in neutral rooms (not located at the emergency departments) at the Sachs' Children and Youth Hospital and Astrid Lindgren's Children's Hospital in Solna. The discussions were moderated by M-L Stjerna, the social scientist on the research team. She had previous experience of carrying out both focus group discussions and individual interviews with grown-ups and young people in studies concerning food and eating and tobacco consumption. M Vetander attended all interviews acting as a silent observer until at the end of the interviews, when she answered medical questions that had been raised by the parents during the interviews. The observer was attentive to the interaction between participants and after each focus-group session the interviewer and the observer shared their perceptions of the group interaction.

Each focus group session started with an introduction: the moderator and the observer introduced themselves and the moderator introduced the overall topic for the group discussion. The moderator then opened up for the participants to share experiences as parents of food-allergic children, with a first question about how they had experienced

the hospital emergency visit, and then followed up with questions about how life with the food allergic child had evolved thereafter. The notion of risk was not introduced to the parents as part of the introduction. The discussions were monitored according to a topic guide used in all sessions, covering everyday management of the allergy at home, in nursery, school and other arenas such as restaurants and during vacations. To encourage discussion between parents an adrenaline auto-injector was shown. All focus group discussions were digitally recorded with the parents' permission and transcribed verbatim by M-L Stjerna.

4.3 DEFINITIONS AND OBJECTIVES

4.3.1 Classification of reactions in study I and II

To classify anaphylaxis and grade its severity we used the EAACI position paper on anaphylaxis in children (24). As already stated, these criteria correspond to the NIAID-FAAN criteria for anaphylaxis (2). However, both identification of anaphylaxis and severity grading according to the EAACI position paper were associated with some difficulties, which are presented in detail in the result section. To be able to classify anaphylaxis and grade severity we used a slightly modified version of the EAACI position paper, presented in Table 3, page 24. Severity of reactions was ultimately classified into: 1) No anaphylaxis, no adrenaline given, 2) No anaphylaxis, adrenaline given, 3) Anaphylaxis. Anaphylaxis was further classified into mild, moderate and severe.

4.3.2 Objectives

Study I – Paper I and II

Both papers I and II are based on study I and have a descriptive approach. In paper I we evaluated whether the classification of anaphylaxis proposed by the EAACI Taskforce on Anaphylaxis in Children in 2007 was applicable on Swedish children who had visited an ED due to reactions to foods during 2007.

The objective in paper II was to describe the overall incidence of anaphylaxis, irrespective of cause, in a paediatric ED setting and to describe reactions to foods in relation to sex, age, triggers, clinical characteristics and management.

Study II – Paper III

In paper III the objectives were to investigate the incidence and potential risk factors for subsequent ED visits for food allergic reactions among children with a prior ED visits due to reactions to foods. In addition, we also set out to determine the risk of impairment at re-reactions in this group of children.

Study III – Paper IV

In paper IV the aim was to explore the way parents understand and manage the food allergy risk in the context of everyday life, as 'situated risk'. The notion of situated risk refers to how different situations in everyday life can be framed as risky by the individual (123).

4.4 ETHICAL APPROVAL

Ethical permission for all studies was granted by the regional ethics review board at Karolinska Institutet, Stockholm, Sweden. Register numbers for the permits were:

Study I: 2008/569-31, 2012/1051/32

Study II: 2008/569-31, 2010/1040-32, 2012/1051/32

Study III: 2008/569-31, 2012/1051/32

4.5 ANALYSIS

4.5.1 Statistical analysis (Paper I–III)

All statistical analyses were carried out with the statistical program SPSS (version 18 and 20, SPSS, Inc, Chicago, USA).

Paper I and II

Prevalence rates were expressed as percentages in paper I and II. In paper II the continuous variable age was expressed as mean, median and range. The incidence of anaphylaxis per 100 000 person years was calculated from the population of all children 0-18 years of age living in Stockholm during 2007, in total 447 739 (124). For statistical comparison, dichotomous variables were analysed with either the Chi-square test or Fisher's exact test. The One-Sample Kolmogorov-Smirnov test was used for comparisons of distribution between variables. Due to the multiple comparisons performed in this paper, we considered a p-value of ≤ 0.01 to be significant.

Paper III

Prevalence rates were presented as percentages. Means, range and standard deviation were compiled for the continuous variable age. Dichotomous variables were compared with the Chi-square test and the independent t-test was used to compare means. A p-value of <0.05 was considered to be significant. The incidence rate of ED revisits was computed as the number of events divided by the sum of the patient-years at risk and expressed as the rate of ED revisits/100 patient-years.

Cox proportional hazards regression was used to estimate relative risks (RRs) and the corresponding 95% confidence intervals (CIs) for possible risk factors for ED revisits. Person-time of follow-up was computed for each child from the date of the index reaction in 2007 to the date of the first ED revisit, date of 18th birthday, date when the child moved away from Stockholm county, or end of follow-up (30 June 2010), whichever occurred first. To examine the proportionality assumption, cumulative hazard functions for all covariates were plotted.

Patient characteristics evaluated as possible risk factors for ED revisits included sex, age group, hospital of initial recruitment, season of the first ED visit, severity of the index reaction, eliciting foods at the index reaction, history of specific atopic diseases prior to the index reaction (i.e. food allergy, asthma, eczema and allergy to inhalant allergens), and prescription of adrenaline auto-injector before the index reaction. The same covariates were assessed for the possibility of confounding and included in the final model if they changed the estimate of the crude RRs by more than 10%. These factors were age, eliciting food, food allergy, asthma, allergy to inhalant allergens and prescription of adrenaline. Sex was a priori kept in the final adjusted cox proportional

hazard model. Since food allergy is highly correlated with asthma, allergy to inhalant allergens and prescription of adrenaline, the last three covariates were not included in the final model.

4.5.2 Qualitative analysis (Paper IV)

In study III (paper IV) the focus group discussions were analysed qualitatively with the aim of exploring parents' understanding and management of food allergy. In the analysis we adopted a dialogical perspective on the interaction that takes place in focus groups. As described by Marková et al, each contribution in a focus group discussion is interdependent on previous and future contributions (125). Consequently, the unit of analysis is not the individual, but rather the interaction and tensions between different thoughts, ideas and arguments as they appear in the discussions.

The transcribed focus group discussions were first analysed by drawing boundaries between topical episodes, that is, when participants discussed or accounted for a certain topic during a sequence of time. Topical episodes that dealt with the same topic were joined together, labelled and categorised as a topic, in this case with a focus on different aspects of allergy management. The recurrent topics were then grouped into a smaller number of major themes. Attention was also given to topics that were treated as taken for granted and topics that led to debate or were questioned during the group discussions. The initial identification of topical episodes in the transcripts and emerging topics was performed by M-L Stjerna, and the subsequent analysis and discussion of the patterns of topics and major themes was done within the research group.

5 RESULTS

5.1 UTILITY OF THE EAACI POSITION PAPER ON ANAPHYLAXIS IN CHILDREN (PAPER I)

Five hundred thirty-one (531) medical records were identified and manually reviewed (Figure 4). Two children were excluded due to incomplete documentation in the medical records. In all, 371 children were found to have had ED visits due to acute reactions to foods during 2007. Among these 371 children, 10 had more than one ED visit caused by reactions to different foods on different occasions, yielding 381 records for final analysis.

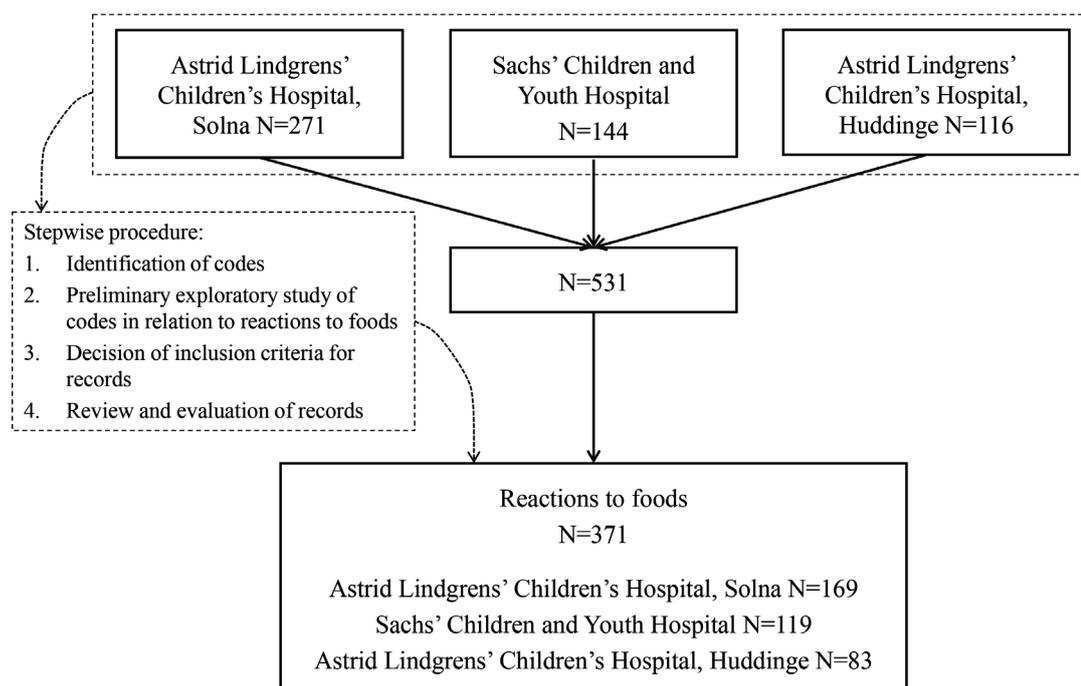


Figure 4. Flowchart of the review of clinical records of children who visited the ED at any of the three paediatric hospitals in Stockholm, Sweden, 1 Jan – 31 Dec 2007

5.1.1 Encountered difficulties and proposed modifications

Among the 371 children with ED visits due to acute reactions to foods, 46 different symptoms or clinical signs were retrieved from the medical records of which 37 were described in the EAACI position paper on anaphylaxis in children. However, when attempting to use the criteria for identification and severity grading of anaphylaxis proposed in the EAACI position paper (24), we encountered some difficulties.

In the EAACI position paper abdominal pain is classified as mild or crampy and is only considered to be indicative of anaphylaxis if crampy and persistent. In addition wheezing is classified into mild or moderate. However, in our retrospective analysis of medical records the extent of wheeze and abdominal pain could seldom be retrieved. For example, in some medical records the only description of respiratory compromise was the term 'affected breathing pattern' which we considered to be indicative of respiratory compromise when classifying anaphylaxis. We considered abdominal pain

irrespective of severity as a sub-criterion for anaphylaxis. Among children fulfilling the criteria for anaphylaxis, we considered abdominal pain and wheeze to be indicative of moderate anaphylaxis while affected breathing pattern was considered to be indicative of mild anaphylaxis.

Furthermore, we found six symptoms in the medical records that were not mentioned or defined in the EAACI position paper: chest tightness, non-barky cough, speaking difficulties, muffled voice, tiredness and somnolence. We considered the first four symptoms to be indicative of respiratory compromise when classifying anaphylaxis. As to severity grading of anaphylaxis, we considered chest tightness and tiredness to be indicative of mild anaphylaxis while cough, speaking difficulties, muffled voice and somnolence were considered to be indicative of moderate anaphylaxis.

According to these findings we suggested some modifications of the EAACI Taskforce position paper on anaphylaxis in children table ‘Grading the severity of anaphylactic reactions’ marked in bold in Table 3. We used our slightly modified criteria for anaphylaxis and severity grading when classifying anaphylaxis in paper I, II and III.

5.1.2 Classification of severity

After we had modified the criteria for anaphylaxis and severity grading suggested in the EAACI paper, 128 children fulfilled the criteria and 243 did not. Among children who did not fulfil the criteria for anaphylaxis, 70 had been given intramuscular adrenaline at home, in the ambulance or at arrival at the hospital, which might have prevented anaphylaxis. In the anaphylaxis group, 4% (n=5) were classified as having mild, 81% (n=104) as having moderate and 15% (n=19) as having severe anaphylaxis.

Table 3. Suggested modification (marked in bold) of the EAACI position paper table ‘Grading the severity of anaphylactic reactions’ (24).

Grade	Skin	Gastrointestinal	Respiratory	Cardiovascular	Neurological
1 Mild	Sudden itching of eyes and nose, generalised pruritus, flushing, urticaria, angio-oedema	Oral pruritus, oral ‘tingling’, mild lip swelling, nausea or emesis, mild abdominal pain	Nasal congestion and/or sneezing, rhinorrhoea, throat pruritus, mild wheezing, chest tightness	Tachycardia (increase >15 beats/min)	Change in activity level, anxiety, tiredness
2 Moderate	Any of the above	Any of the above, crampy abdominal pain, diarrhoea, recurrent vomiting	Any of the above, hoarseness, cough , barky cough, swallowing or speaking difficulties , muffled voice , stridor, dyspnoea, moderate wheezing	As above	‘Light-headedness’, feeling of ‘impending doom’, somnolence
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.

* Hypotension defined as systolic blood pressure: age 1 month to 1 year <70 mmHg, age 1-10 years < [70 mmHg + (2 × age)]; age 11-17 years <90 mmHg

5.2 ANAPHYLAXIS AND REACTIONS TO FOODS IN THE ED (PAPER II)

As described in paper I, 371 children were found to have had 381 unique reactions to certain foods that led to visits at the ED of any of the three paediatric hospitals in Stockholm County during 2007. These children were subdivided into three groups: group A/ anaphylaxis (n = 128), group B/ no anaphylaxis, but adrenaline administered (n = 70) and group C/ no anaphylaxis, no adrenaline administered (n = 173). An additional 12 children with anaphylaxis that was probably not caused by foods were identified, among whom the triggers were specific immunotherapy (n = 2), insect sting (n = 1), exposure to furred animals (n = 4), exercise (n = 1) and idiopathic (n = 4).

5.2.1 Incidence of anaphylaxis

Anaphylaxis irrespective of cause was found among 140 children, of whom 128 reacted to foods. Another three children had repeated ED visits during 2007 caused by the same food and were classified as having had a mild allergic reaction at their first visit to the ED but anaphylaxis at the second visit. Accordingly, 143 children had anaphylaxis and food was the trigger for 92%. With a population of 447 739 children 0-18 years of age, the incidence of anaphylaxis in Stockholm County in 2007 was 32 per 100 000 person years irrespective of trigger. The corresponding incidence of food-related anaphylaxis was 29 per 100 000 person years.

5.2.2 Additional results

Demographic data and allergic co-morbidity

Table 4 presents demographic data and allergic co-morbidity among the 371 children with acute reactions to foods. The majority of the children had a history of allergic disease (73%) at admission and 60% a history of food allergy. Children without anaphylaxis that had not been given adrenaline were significantly younger, were less likely to have allergic diseases and had been prescribed adrenaline in an adrenaline auto-injector (AAI) significantly less frequently (all P-values < 0.01) compared with anaphylactic children. These differences were not seen when comparing anaphylactic children with children without anaphylaxis that had been given adrenaline.

Table 4. Anthropometric data and co-morbidity among 371 children prior to visits due to reactions to foods to the paediatric EDs during 2007.

	Anaphylaxis N=128 n (%)	No anaphylaxis	
		Adrenaline administered N=70 n (%)	No adrenaline administered N=173 n (%)
Girls n=176 (47%)	57 (45)	31 (44)	88 (51)
Age in years (mean/median), 6/4	6/6	7/6	5/2
Any allergic disease co-morbidity, n=270 (73%)	103 (80)	56 (80)	111 (64)
Asthma, n=109 (29%)	47 (37)	26 (37)	36 (21)
Eczema, n=94 (25%)	39 (31)	18 (26)	37 (21)
Urticaria, n=10 (3%)	4 (3)	2 (3)	4 (2)
Allergy to inhalant allergens, n=107 (29%)	46 (36)	28 (40)	33 (19)
Previously known food allergy, n=222 (60%)	87 (68)	52 (74)	83 (48)
Adrenaline auto-injector prescribed before ED visit, n=77 (21%)	38 (30)	25 (36)	14 (8)

Among the 371 children with reactions to foods, 183 (49%) were in the age group 0-3 years. In this age group only 28% had anaphylaxis compared with 40% among the 188 children that were 4 years or older (P-value < 0.001). However, in absolute numbers, anaphylaxis was most prevalent among the youngest children.

Eliciting foods

Peanuts and tree nuts, particular cashew, were the dominating eliciting food types, followed by milk and egg (Table 5). Other foods causing anaphylaxis not listed in Table 5 were kiwi, banana and cucumber (n = 1 for each foodstuff). In 26% of the children, no specific eliciting food could be identified since the ingested meal had contained several food items that could have triggered the reaction.

Among children with anaphylaxis and reported allergy to pollen (n=35), admission due to anaphylaxis tended to be more common during the deciduous tree pollen season March-May compared with the rest of the year (P-value 0.015).

Reactions to milk and egg were common in infants but uncommon, or even nonexistent, among teenagers. Meanwhile, reactions to peanuts and tree nuts showed an increasing prevalence with increase of age (Figure 5). Interestingly, reactions to peanut or tree nuts were just as common as reactions to milk or egg in children below 3 years of age (P-value 0.38).

Table 5. Eliciting foods among 371 children with 381 ED visits due to reactions to foods. Only eliciting foods associated with reactions to foods in at least five children are presented.

	Not anaphylaxis N=252 n (%)	Anaphylaxis N=129 n (%)
Tree nuts and/or peanut, n=148 (39%)	86 (34)	62 (48)
Tree nuts, n=58 (15%)	34 (13)	24 (19)
Cashew nut, n=19 (5%)	9 (4)	10 (8)
Hazelnut, n=11 (3%)	8 (3)	3 (2)
Almond, n=8 (2%)	5 (2)	3 (2)
Walnut, n=7 (2%)	5 (2)	2 (2)
Pistachio, n=6 (2%)	3 (1)	3 (2)
Other tree nuts, n=5 (1%)	2 (0.8)	3 (2)
Peanut, n=53 (14%)	29 (12)	24 (19)
Nuts unspecified, n=37(10%)	23 (9)	14 (11)
Egg, n=43 (11%)	28 (11)	15 (12)
Milk, n=34 (9%)	26 (10)	8 (6)
Fish, n=12 (3%)	11 (4)	1 (0.8)
Seeds, n=7 (2%)	4 (2)	3 (2)
Sesame seeds, n=5 (1%)	2 (0.8)	3 (2)
Wheat, n=6 (2%)	3 (1)	3 (2)
Shellfish, n=6 (2%)	5 (2)	1 (0.8)
Apple, n=6 (2%)	4 (2)	2 (2)
Mixed foods*, n=99 (26%)	69 (27)	30 (23)

* Intake of several foods at the same time

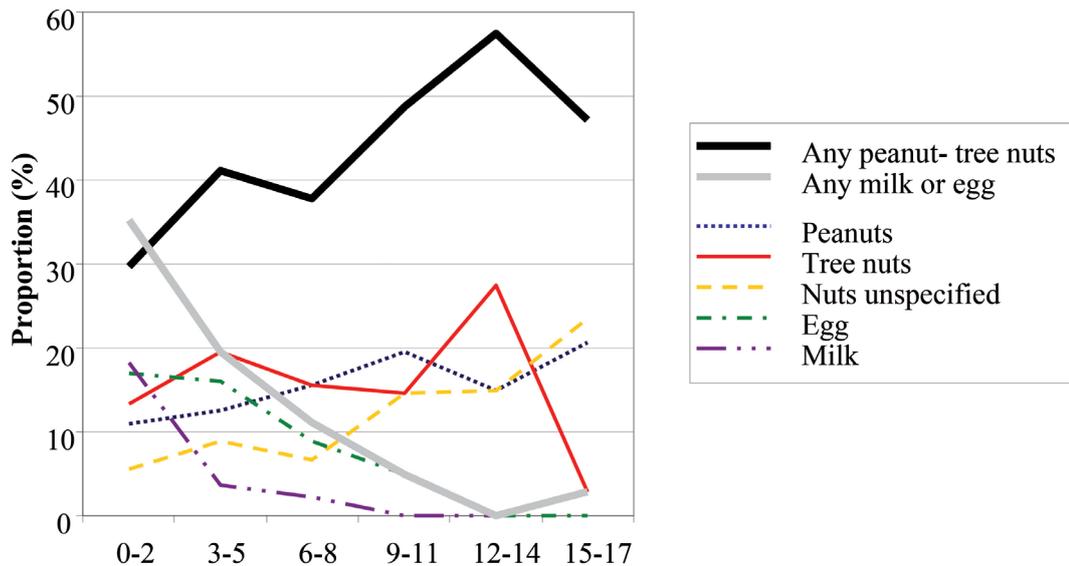


Figure 5. Eliciting foods in relation to age among 371 children with 381 ED visits due to acute reactions to foods.

Symptoms and management

Irrespective of severity grading, cutaneous signs and symptoms were most common, occurring in 74% of all cases. Symptoms from the oral cavity, gastrointestinal tract and lower airways were more frequent than symptoms of cardiovascular or neurological origin (34%, 29% and 28% versus 4% and 7%, respectively). There were no fatal cases or any child with cardiac arrest during the study period. However, three children lost consciousness, one of whom also had respiratory arrest. This was a 4-year-old boy with known food allergy (milk, egg and hazelnut), asthma and eczema who had been prescribed an AAI. After a meal at his day-care centre, where he had eaten pancakes claimed to be milk and egg free, he vomited and then developed generalised urticaria and breathing difficulties. During ambulance transport he had a short respiratory arrest. Adrenaline was not administered until arrival at the ED.

Seventy-one per cent of the children with anaphylaxis were administered adrenaline either before arrival at the hospital or at the ED, of whom 22% were given repeated doses. Among children with anaphylaxis who had been prescribed an AAI before the ED visit, 55% (21/38) did not use it. Children with anaphylaxis and underlying asthma tended to present with acute wheeze more often than anaphylactic children without underlying asthma (P-value = 0.01). Follow-up was arranged for 71% of the children who came to the ED with acute reactions to food, regardless of severity.

5.3 RECURRENT REACTIONS TO FOODS IN THE ED (PAPER III)

Among the 371 children with ED visits owing to allergic reactions to foods during 2007 identified in study I, 13 children were not resident in Stockholm County, leaving 358 children for inclusion in the cohort. During the follow-up period (1 January 2007 – 30 June 2010) 80 of 358 children (22%) visited the ED again due to recurrent reactions to foods. Nineteen children revisited the ED more than once during follow-up (Figure 6).

At the time of the index reaction, children who later came back to the ED were similar to children who did not in terms of proportion of girls, age, sex, severity of the reaction and eliciting foods. However, allergic co-morbidity tended to be more common in children with ED revisits, and the link between ED revisits and either food allergy or prescription of an AAI before the index reaction was significant ($p < 0.01$).

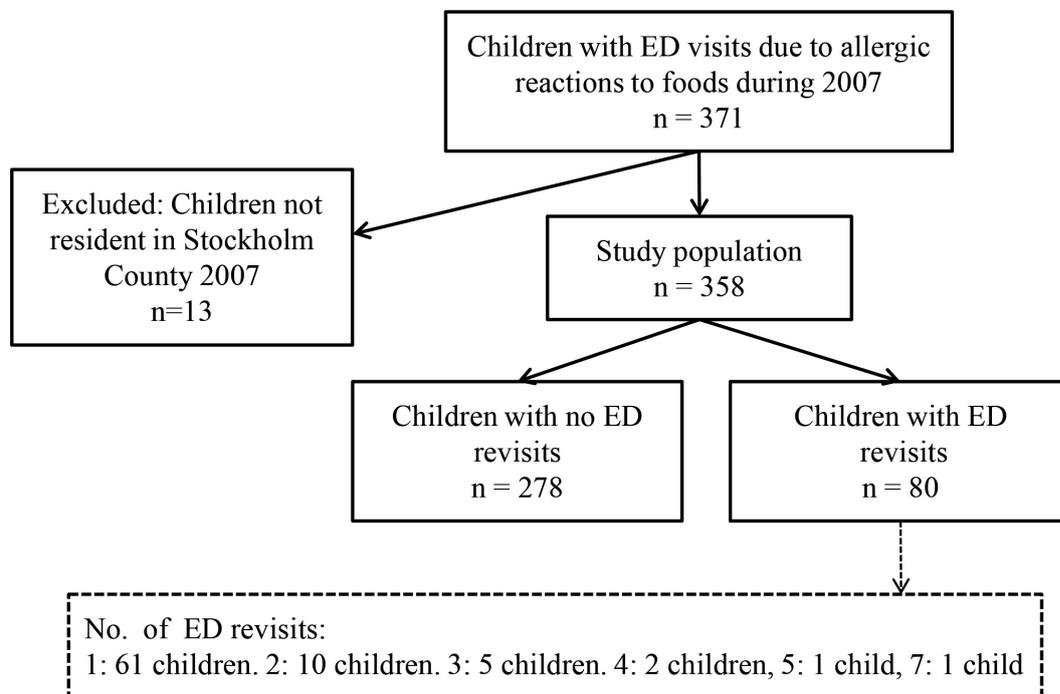


Figure 6. Description of the cohort of children with index visits to an ED during 2007 due to reactions to foods and final allocation into two groups: children with ED revisits versus children with no ED revisits due to reactions to foods during follow-up.

5.3.1 Incidence of and risk factors for revisits

Incidence

In the cohort consisting of 358 children, 80 children had at least one ED revisits due to recurrent reactions to foods over a period of 873 patient-years. This yields an incidence rate of 9 ED revisits per 100 patient-years.

Risk factors

Known food allergy before the index ED visit in 2007 was identified as a risk factor for ED revisits (adjusted RR = 2.30, 95% CI 1.35-3.94) and for children with two or more food allergies the adjusted relative risk was 2.79 (95% CI: 1.56-5.00). Furthermore, prescription of an AAI before the index reaction was also significantly related to the risk of ED revisits (adjusted RR = 2.02, 95% CI 1.17-3.49). We observed no statistically significant associations with other potential risk factors such as sex, age, other atopic diseases, eliciting food at the index reaction or severity of the index reaction. However, allergy to inhalant allergens before the index reaction was associated with a tendency towards increased risk of ED revisits (adjusted RR = 1.73, 95% CI 0.97-3.10). The more severe the index reaction, the more the relative risk for ED revisits increased, although it did not reach statistical significance.

5.3.2 Change in severity of the reactions

As to severity of the reactions at the ED revisit among the 80 children with recurrent reactions, 16 (20%) of the children had mild-to-moderate anaphylaxis and 4 (5%) had severe anaphylaxis. The remaining 60 (75%) children did not fulfil the criteria for anaphylaxis, though it should be kept in mind that 27 had been given adrenaline that may have prevented anaphylaxis.

Compared with the index reaction, 21% were having a more severe reaction at the time of the ED revisit, 38% a less severe reaction and the remaining 41% a reaction of comparable severity. Three children (4%) with mild index reactions (no anaphylaxis, no adrenaline given) had severe anaphylaxis at the ED revisit. However, as illustrated in Figure 7, treatment with adrenaline either at the index reaction or at ED revisit often hampered our classification of change in severity. For example, among 28 (44%) of the 63 children who were having a comparable or less severe reaction at the ED revisits, treatment with adrenaline may have influenced the change in severity.

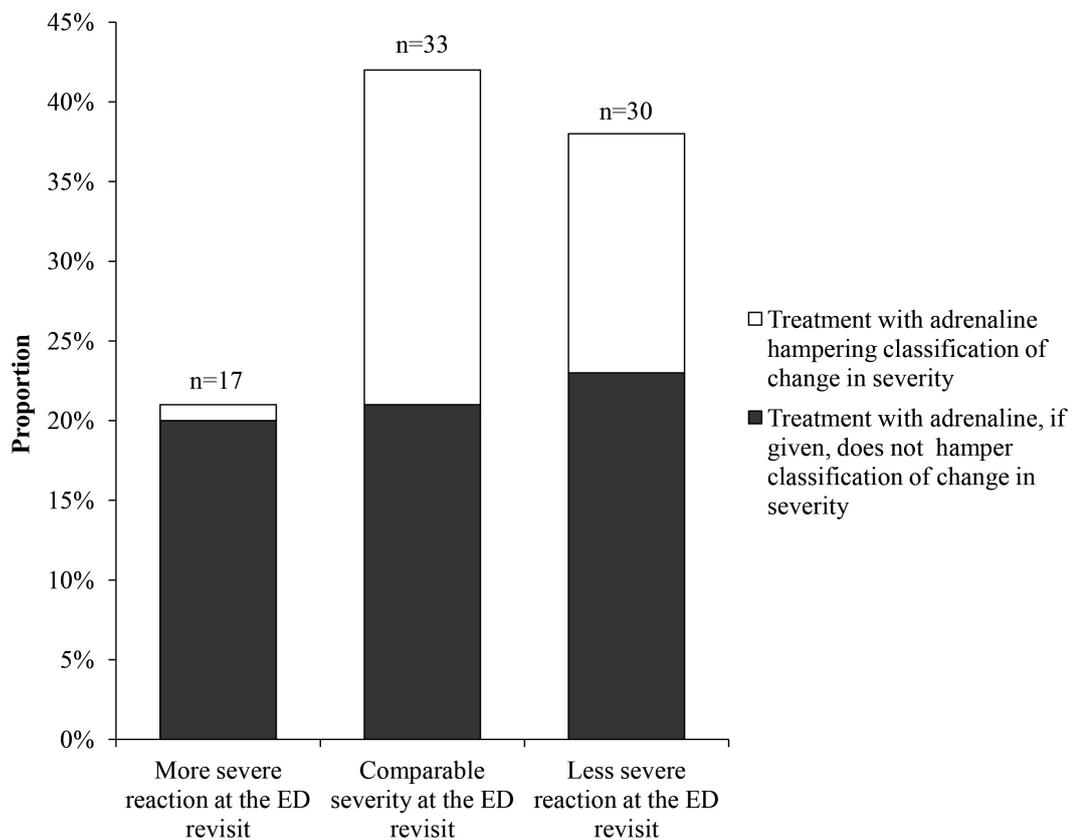


Figure 7. Change in severity of the reactions among 80 children with repeated ED visits due to allergic reactions to foods. The total height of each bar represents the percentage of children in a given stratum of change in severity of the reaction (ED revisit compared to the index reaction). The white area of the bar represents the percentage of children in a given stratum of change in severity in which treatment with adrenaline could have influenced the severity of the reaction, thereby hampering classification of change in severity.

5.3.3 Additional results

Eliciting foods

Tree nuts or peanuts caused 35% of the reactions at the ED revisits, egg and milk 13% of the reactions respectively, and other specified foods 19% of the reactions. For 21% of the children the eliciting food was unknown. When comparing the eliciting foods at the ED revisits and at the index reactions, we found that 19 (24%) children had reacted to the same food and 14 (18%) to a different food. For the remaining 47 children (59%) it was not clear from the medical records whether they had reacted to the same food item or not.

Compliance with adrenaline auto-injectors

Fifty-seven (71%) of the 80 children who revisited the ED had been prescribed an AAI before the ED revisit, of whom 23 (40%) used it at the time of the ED revisit. However, among the 17 children who experienced anaphylaxis at the ED revisit and had been prescribed an AAI, only 4 (24%) had used the device.

Children with multiple ED revisits

Nine children had three or more ED revisits during follow-up. At the time of their second ED revisit all nine children had an established contact with the health care system and the majority were being treated by a paediatric allergy specialist. Six (67%) of these nine children had known allergy to egg or milk at the index reaction. These six egg- or milk-allergic children had a total of 26 ED revisits and the eliciting food was egg or milk at ten of the 26 ED revisits, other specified foods at seven and unknown at nine of the ED revisits.

5.4 PARENTS' EXPERIENCES OF MANAGING RISK RELATED TO FOOD ALLERGY (PAPER IV)

Among the 95 parents invited to participate in the focus group sessions (44 by letter and 51 by e-mail), 40 accepted the invitation. However, due to late cancellations, 31 parents finally participated in the study: 25 mothers and 6 fathers of children aged one to 17 years (Table 6). The 31 parents were all native Swedish-speaking, with a level of education ranging from upper-secondary school to university. All children had been diagnosed with a food allergy, either single food or multiple, and most of them had been prescribed an AAI. Ten focus group sessions were scheduled, to make it possible for all parents to find time to participate. This meant that the number of participants in each group was fairly small. Eight groups included three or four participants and two groups had just two participants due to late cancellations. Focus group sessions 1-7 were performed at Sachs' Children and Youth Hospital and sessions 8-10 at Astrid Lindgren's Children's Hospital in Solna.

During the focus group sessions the parents clearly recognised the similarity in their experiences and all participants took part in the discussions. Qualitative analysis of the material revealed risk as a prominent subject during the group discussions. We identified four recurrent topics related to how risk is managed in everyday life and in different social contexts: 'Constantly being one step ahead', 'Making unsafe zones safe', 'Calculated risk taking' and 'Sometimes you have no choice'. These recurrent topics were grouped into two major themes, risk avoidance and risk taking.

Table 6. Information about the participants in the focus group sessions

Focus group session number	Number of participants*	The sex and ages** of the participating parents' children
1	2 (1 M, 1 F)	2 boys (5 years (n=2))
2	2 (2 M)	1 girl (3 years), 1 boy (3 years)
3	4 (3 M, 1F)	4 girls (3 years (n=2), 6 years (n=2))
4	4 (2 M, 2 F)	3 girls (3 years (n=2), 5 years), 1 boy (8 years)
5	3 (3 M)	3 boys (14 years, 17 years (n=2))
6	3 (2 M, 1F)	2 girls (9 years, 12 years), 1 boy (17 years)
7	3 (3 M)	1 girl (4 years), 2 boys (4 years, 5 years)
8	3 (3 M)	1 girl (8 years), 2 boys (4 years, 7 years)
9	4 (3 M, 1F)	1 girl (8 years), 3 boys (3 years, 5 years, 8 years)
10	3 (3 M)	1 girl (10 years), 2 boys (10 years, 14 years)

* M: Mother, F: Father. ** Ages at the time of the focus group sessions

5.4.1 Risk avoidance

Constantly being one step ahead

In every focus group session, the parents talked in detail about all the precautions they take to protect their children from coming into contact with the foods the child is allergic to. Lurking in the background is the risk of a severe allergic reaction; a threat of what *could* happen if not enough attention is paid *or* if one does not act correctly in the case of a severe reaction. They described the ways they try to manage this risk by planning ahead and by maintaining routines to 'check' every step in the process of purchasing and preparing food (parents are given a number within each focus group (Fg):

Mother 1: I think we spend a good twenty minutes more than anybody else in the grocery shop because we read *everything* (on the labels), even on things we think we know one hundred per cent, we still have to read it, because suddenly it has changed and can contain traces of nuts (...) and that's the only lifeline we have, to read everything. (Fg 5)

The parents also question the trustworthiness of the information from the food companies and they gave examples of contradictory food labelling. To identify the allergen in the child's meal or snack is often difficult since it can be disguised in foods not immediately associated with the allergen:

Mother 3 I am so pleased she is not allergic to milk protein any longer, I thought that was hard because there are so many products containing milk, you can't imagine, you know, like spices, I can understand that people don't think about milk in mixed spices or margarine or bread crumbs. (Fg 3)

The parents spoke about how they have to be constantly alert *in case* something were to happen: 'always having the cell phone at hand' or always bringing the child's allergy medications:

Mother 1: What I am most afraid of is that her throat is going to swell, anything else you can cope with, it could be unpleasant, but if your throat swells, you

cannot breathe and then you die, so to speak, and this is when it (the auto-injector) helps. (Fg 2)

It is obvious that the AAI has a unique position in terms of being a lifesaver and safeguard. However, as one father explained, the AAI is not the first choice rather the last resort if nothing else works, the ‘heavy artillery’.

Making unsafe zones safe

Another recurrent issue in the focus group discussions concerned risk and safety in different social arenas where the child spends time such as the family home, nursery, school, the playground, the houses of friends or grandparents, restaurants, airplanes and social events such as children’s parties or holiday trips. Most parents talked about their home as a safe zone where they can ensure that the child will not be exposed to the food allergen/allergens in question. However, even at home it can be difficult to be in control of everything, and this safe zone could suddenly become unsafe. When the parents discussed areas outside the home, they continuously assessed them as safe or unsafe. For example, the nursery can be safe when you can trust the staff but suddenly become unsafe when there are deviations from the ordinary routine:

Father 1: A new assistant at the day-care centre gave her (allergic to milk protein) a sandwich with cheese, believing that she was lactose-intolerant, there is no lactose in this cheese, and when this happened, it was my wife who picked her up, she was completely swollen and had difficulties breathing. (Fg 3)

The parents described how they strive to make unsafe zones safe, for example by letting the child have his or her own glass and plate at the nursery, by educating others to make them understand how the allergy ‘works’, by asking the neighbours never to offer the child anything to eat at the playground or by bringing their own food to children’s parties or restaurants. The parents also talk about how they have to impel others, even close relatives, to take the necessary precautions. They reasoned that this necessity could be due to the ‘disguised’ character of food allergy, invisible until the moment when the child has a reaction: ‘they don’t really understand it until it happens’.

5.4.2 Risk taking

Taking calculated risks

Against the norm of constant risk avoidance, a counter discourse of taking calculated risks emerged: some of the parents described how the efforts to prevent their children from getting into contact with the food allergens lead to undue restrictions in family social life. To become less circumscribed, they take calculated risks by introducing and testing products that may contain the food allergens, in order to find out whether the child can tolerate the product. The rights and wrongs of taking such calculated risks were discussed in greater detail in one of the focus groups:

Mother 2: I think you should always be paying attention, but all this reading (of labels) and all these traces of nuts everywhere nowadays, it’s...

Father 1: Yeah, we have decided, well of course you should be concerned, but somehow in the end you get so caught in a bubble. It’s not that you should be taking risks or be careless, but we have tested some products with that kind of label (Mother 2: oh, how scary) with traces of nuts, this is not what she is most allergic to, that’s milk and eggs and then

nuts, certain nuts, but then we tested just a very small amount, gave her just a mouthful to see what the reaction would be.

Mother 3: We are just like you (Father 1: yes) usually we try to test the stuff, even if it says, because otherwise you get so incredibly restricted (Father 1: yes) it's not that, I understand both, but we have valued the social aspects more, so we have the medicine at home and let her test the new stuff at home and just small pieces at the time and we talk (Father 1: you recognise the symptoms) exactly, we talk about how it feels, tickling on the tongue, in the throat, and observe her, because it has happened that she goes away when she has a reaction. (Fg 3)

When this risk taking is discussed among the parents, it is accompanied by accounts of how you always try to do this in a very controlled way: within certain limits, testing small amounts of food, observing the child closely, having medicine at hand or being close to the hospital.

Calculated risk-taking was also discussed in relation to the AAI. Although most parents stress that the device should go with their children wherever they go, some say they have decided to bring the AAI in certain situations only:

Mother 3: So, the first half year I was so extremely cautious, we had one at the nursery and one that was always in my bag, but I mean, I have thousands of bags and in the end I did not know which one the adrenaline injector was in, so it ended up with us keeping it in the front hall and bringing it if she was sleeping at a friend's or travelling. (Fg 7)

In addition, some parents of adolescents expressed worries during the sessions about their children not taking along the AAI when they leave home. For example, one mother says that although her son recently had a severe reaction that rendered him unconscious and he had to be taken to the hospital by ambulance, he still leaves the AAI at home when he goes to friend's parties, 'he doesn't want anybody else to know about it'.

Sometimes you have no choice

Another recurrent topic in the discussions was that sometimes *you actually have no choice*. If your child is multi-allergic it is nearly impossible to avoid exposure at all times, and you then have to learn to live with the allergic reactions. For example, a mother says that her daughter (allergic to egg, pistachio, cashew, hazelnuts, soy, sesame) has had so many allergic reactions, and that they sometimes haven't even been sure what she has reacted to, and that it is therefore almost impossible to completely avoid the allergens:

Mother 3: It is more important that she knows about her symptoms (Father 1: yes) than trying to avoid everything, I think that is probably impossible and then it almost feels as if it's okay that she has had her reactions and that we have had a social life somehow. (Fg 3)

Hence, the norm of risk avoidance is challenged both in active risk taking and in a more passive acceptance of the impossibility of complete avoidance.

6 DISCUSSION

The aim of this thesis is to increase the knowledge about severe reactions to foods among Swedish children and more specifically with regard to clinical perspectives, epidemiology and risk management. In this section the main findings in each paper are discussed in relation to these three study areas with risk management being discussed both from a parental and a clinical point of view.

6.1 CLINICAL PERSPECTIVES

6.1.1 Factors that hamper classification of anaphylaxis

Missing symptoms and subjective wording in current guidelines

In study I we found that the possibility of classifying and assigning a severity to anaphylaxis according to current guidelines presented in the EAACI position-paper (24) was hampered by a lack of description of some respiratory and neurological symptoms. In the guidelines, for example, the symptoms speaking difficulties, speaking with a muffled voice, non-barky cough, chest tightness and affected breathing pattern were not listed, but we considered them indicative of respiratory compromise. However, it could be argued that affected breathing pattern is a rather unspecific sign and that the subjective symptom chest tightness could indicate anxiety rather than true respiratory compromise. As to the missing neurological symptoms tiredness and somnolence, these can be caused by medication if sedative anti-histamines have been administered or be a sign of reduced brain perfusion indicating a severe reaction.

Conversely, information was sometimes missing in the medical records. According to the EAACI position paper the severity of anaphylaxis will depend on whether wheeze is mild or moderate and whether abdominal pain is mild or crampy (24). However, information about the extent of wheeze and abdominal pain could seldom be retrieved from the ED records, which also hampered our classification of anaphylaxis. Since the classification into mild and moderate/crampy is rather subjective, this would be a concern even in a prospective study.

Our classification of wheeze, abdominal pain and of the symptoms not mentioned in the EAACI position paper will influence our results. For example, in study I we found that very few children had mild anaphylaxis (N=5) in comparison to the number of children with moderate anaphylaxis (N=104), which is in contrast to the finding of others (89, 126, 127). Considering that we had made several modifications in order to be able to grade severity of anaphylaxis, this disparity was not unexpected. Since our possibility of distinguishing between mild and moderate anaphylaxis was limited, we chose to classify anaphylaxis into the two groups mild-to-moderate and severe in study II. The difficulties researchers encounter when attempting to classify and grade anaphylaxis into severity according to current guidelines, although briefly mentioned in some previous studies (127-130), have not been discussed in depth before.

Low age

Another factor that may have hampered correct classification of anaphylaxis is low age, thus being of importance particularly in study I, where 49% of the 371 children were in the age group 0-3 years. Among infants, symptoms of anaphylaxis can be difficult to recognise since subjective symptoms such as abdominal pain, general itching and dyspnoea cannot be communicated. In addition, some signs of anaphylaxis can be difficult to interpret since they also occur in healthy infants (for example vomiting and drowsiness after feeding) or in children with viral infections (vomiting, rash, conjunctivitis, rhinitis, cough) (131). A recent study performed in a paediatric ED-setting in the US supports the notion that many of the signs or symptoms of food-induced anaphylaxis are more difficult to recognise in infants (132). Our finding that the proportion of severe reactions was significantly lower among the youngest children (0-3 years) compared to older children, although in agreement with others (133), could partly be due to these age-related difficulties and hence introduce a misclassification of outcome.

Treatment with adrenaline

Adrenaline, the first choice drug in anaphylaxis according to guidelines worldwide, was administered to 71% of the children in study I with anaphylaxis. This proportion is considerable higher than in other European studies (60, 88, 134), although similar to estimates from the United States (127, 130). In addition, a large proportion of the children in study I and II who did not fulfil the criteria for anaphylaxis had been given treatment with adrenaline (29% and 45%, respectively), thereby possibly preventing anaphylaxis. The high rate of adrenaline treatment in our study population, although satisfying from a clinical point of view, also led to some difficulties when we attempted to grade change in severity in study II: among 44% of the children who paid a second visit to the ED and then showed reactions comparable to or less severe than those during the first visit, treatment with adrenaline actually hampered classification of change in severity. Interestingly, the effect of early treatment with adrenaline on the severity of the allergic reaction has seldom been discussed in previous studies in this field.

6.1.2 Provoking allergens

Anaphylactic triggers in general

Food was the underlying cause of anaphylaxis in 92% of the cases. Such a high proportion has not been described before (60, 88, 126-128, 130, 134-137), which might have several explanations. Percentages of the causes of anaphylaxis are determined by allergen exposure in the geographical area studied. In other paediatric studies in this research field, all performed outside Scandinavia, insect venom is often the second most common eliciting agent after foods, causing 4-24% of anaphylaxis (48, 88, 126, 130, 135, 137). In contrast only one child (0.7%) in our series had anaphylaxis due to insect sting, which can probably be attributed to our study population's limited exposure to insect stings: Swedish summers are short, and the study was done in an urban area where there are relatively few stinging insects. The importance of the study site is illustrated by the fact that only 1 of 333 cases of anaphylaxis was caused by insect sting in a Spanish study performed in an urban setting (52).

In addition, the proportion of triggers will depend on the classification and definitions used. In our survey, echoing the findings of others (127-129), no specific eliciting food

could be identified among 30 children with anaphylaxis who had ingested a meal containing multiple food items shortly prior to the reaction. We classified these children as having had a reaction to foods. However, if we had classified them as having anaphylaxis to an ‘unknown’ trigger instead of to foods, as done in most previous studies in this field, the proportion of children with anaphylaxis to foods would have been 70.6% in our study population, a rate that would conform with previous reports.

Culprit foods in particular

Among foods involved in anaphylactic reactions in study I, peanut and tree nuts were the dominating eliciting triggers, followed by egg and milk. These findings confirm those of others (88, 126-129, 133, 138). Interestingly, reactions to peanut or tree nuts were as common as reactions to milk or egg among children aged 0-2 years. In agreement with our finding, Rudders et al report peanut-tree nuts to cause 40% of anaphylactic reactions among infants, and egg-milk 49% of the reactions (133). In addition, Ferrari et al found peanut and hazelnut to be common allergen triggers already in the first 12 months of life among Swiss infants (139).

The fact that peanut and tree nuts, among tree nuts especially cashew, stand out as the most common cause of anaphylaxis in study I may have several explanations. First, parents whose children have reacted to peanut or tree nuts may be more prone to seek medical care, since these foods are recognised as potentially life-threatening allergens by society. Second, exposure to peanut and tree nuts is currently common in the Swedish population, as peanuts and tree nuts in food and in snacks have become increasingly popular during recent years. Third, peanut and tree nuts has been demonstrated to be potent allergens in comparison with other major food allergens (85, 86). For example, peanut has been reported to cause fatal reactions at a lower dose than other foods (53), and cashew nut has been identified as an even more potent allergen than peanut (140).

Based on the discussion above, and since nut allergy is more likely to be lifelong (unlike allergies to milk and egg), we expected reactions elicited by tree nuts or peanuts to show a stronger association with repeat visits to EDs than reactions elicited by milk and egg. However, this was not the case in our study II. One may speculate that accidental intake of food items such as milk and egg might be more likely than accidental consumption of nuts since the former may be hidden in many products and lack strong smell and flavour compared to nuts. Moreover, plates with pre-prepared dishes for allergic children may be mixed up. Our finding that the majority of children with multiple ED revisits were allergic to egg or milk supports this argumentation, as do other reports on high rates of accidental reactions among children with milk and egg allergy (126, 141-143). Most reactions to milk treated and with adrenaline have been reported to occur at home (138), also indicating the difficulty of avoiding this allergen. The difficulties associated with avoiding milk and egg due to their presence in multiple products was also discussed in the focus group discussions in study III.

6.1.3 Food allergy – an unpredictable disease

Subsequent reaction severity – hard to predict

In study II 38% of the children had less severe reactions and 21% more severe reactions at the ED revisit. The finding that the severity of the re-reaction could not be accurately predicted by the severity of the index reaction has also been reported in recent publications (89-92, 144, 145) The unpredictability of the food allergic condition is also

illustrated by the finding of Glaumann et al that neither threshold dose, nor severity scoring was reproducible among 27 peanut sensitised children undergoing a double-blind placebo-controlled food challenge followed by a single-blind oral food challenge (87).

As previously described, allergen dose and co-factors influence the severity of reactions. For example Hompes et al report that aggravating factors such as physical exercise were noted among 18% of children and adolescents with anaphylaxis (88). Pollen allergy is sometimes mentioned as a co-factor in food-induced anaphylaxis (83). Our data support this idea since pollen-allergic children in study I were at increased risk of being admitted with food-related anaphylaxis during the pollen season. Unfortunately, information about other intrinsic and extrinsic co-factors such as dose, recent exercise and current infections was rarely available in the medical records and could consequently not be addressed.

6.2 EPIDEMIOLOGY

6.2.1 Anaphylaxis

The incidence of anaphylaxis irrespective of cause was 32 per 100 000 person years in study I. As already stated, there is only limited data about the incidence of anaphylaxis in the paediatric population against which to compare our finding. Reported incidence rates range between 5 and 314 per 100 000 person-years (51, 52) with the lowest rate being reported from a retrospective study investigating the epidemiology of anaphylaxis presenting to EDs in Florida (51). Meanwhile Decker et al found an incidence rate of 70 per 100 000 person-years in the age group 0-19 years in their retrospective report on all providers of medical care to residents of Olmsted County in Minnesota (50). However, comparison of results is hampered by inconsistent criteria for anaphylaxis as well as differences in study design.

The highest rate of anaphylaxis among children so far was reported by Tejedor et al (52), who investigated the incidence of anaphylaxis among the general population of the city of Alcorcon, Spain. Cases were recovered by reviewing electronic clinical records from different public health settings (primary care, emergency department, hospitalised patients and outpatient allergy clinic). This study is of special interest, as it is one of few studies reporting the incidence rate of anaphylaxis among children that has used the current criteria for anaphylaxis (2). The incidence rate of anaphylaxis among children and adolescents ranged between 74 and 314 per 100 000 person-years according to age group with the peak incidence rate among children in the age group 0-4 years. Thus, the cited study's estimates were higher than ours, probably mostly due to the fact that they examined all health provider-diagnosed anaphylaxis, as further discussed below.

There are reasons to believe that our estimate of the incidence rate of anaphylaxis among children in our catchment area is lower than the true incidence of anaphylaxis in the underlying population. Our study was designed to catch all cases of anaphylaxis treated at the paediatric EDs in Stockholm County. Hence, our incidence rate does not take into account that anaphylaxis is sometimes not severe enough to prompt a visit to the ED. For example, some cases of anaphylaxis may have been treated by local health care providers. Only half of the patients with anaphylaxis have been reported to be treated at the ED in studies that collect data on cases from different public health

settings (48, 52, 88). Due to the differences in health care systems and access to health care, reports from other countries cannot be used to calculate missing episodes in our study population. In addition, some cases may have resolved spontaneously or, among patients prescribed with AAIs, have responded to self-administered adrenaline, therefore not prompting the patients to seek medical attention at all; this phenomenon has been described elsewhere (91).

Furthermore, as previously mentioned, the incidence rate of anaphylaxis may be affected by our classification of symptoms. For example, with the exceptions of vomiting and diarrhoea, we included only objective symptoms and signs registered by the health care staff. Hence, objective signs that were reported by the parent or the patient, but that had subsided before arrival to the ED were not included when classifying anaphylaxis in our series, even in the cases where AAIs had been used before arrival to the ED. This decision was taken due to the imprecise and vague information in the medical records concerning parental and patient reports of objective signs. In addition, the 70 children in study I who were treated with adrenaline at home, during transportation with ambulance or on arrival at hospital, and who did not fulfil the criteria for anaphylaxis, were not considered to have had anaphylaxis in our series. Through this approach we have probably missed some cases of anaphylaxis.

6.2.2 Recurrent reactions

Incidence rate of ED revisits

In study II, 80 of the 358 children in our cohort were found to have had ED re-visits due to reactions to foods during the follow-up period (1 January 2007-30 June 2010) yielding an incidence rate of 9 ED revisits per 100 patient-years. Since this study is unique in investigating recurrent reactions to foods in a paediatric ED-setting, there are no other studies to directly compare our findings against. Overall, there are few reports on re-reactions to foods among children. Most of the previous studies that have been published have investigated reactions to single foods and nuts (90, 91, 141, 146, 147) and only occasional surveys report on re-reactions to multiple foods (75, 142). In studies of accidental allergic reactions to single foods based on patient-parental reports, the annual incidence rate of accidental allergic reactions was 40 per 100 patients among 84 milk-allergic children (141) and 12.5 per 100 patients among 1411 children with peanut allergy (91). Fleischer et al, reporting on accidental reactions to multiple foods, found a substantially higher annual incidence rate of 81 per 100 patients among 512 preschool children with documented or likely allergy to milk and egg followed prospectively (142). Among 969 food-allergic children prescribed AAIs and managed by paediatric allergy clinics throughout the UK, the annual incidence of subsequent reactions was 48 per 100 patients (75).

All the above-mentioned studies report incidence rates of subsequent reactions irrespective of whether medical attention had been sought or not. Besides the fact that our study addressed emergency department presentations only, our rather low incidence rate of recurrent reactions to foods might have several explanations. Some patients in our cohort might have outgrown their food allergy during the follow-up period, in particular those with less severe reactions in our study group. In addition, we might have included some children who were not actually food-allergic since the diagnosis of food allergy was not definitively confirmed for all patients after the index reaction in 2007. Our low incidence rate could also, at least in part, be attributed to the

fact that a majority of the children in the cohort had medical follow-up after the index reaction: adequate secondary strategies after reactions to foods have been shown to reduce the risk of subsequent reactions (90, 143).

Risk factors for recurrent reactions

In study II, the only statistically significant risk factors for ED revisits within our multivariable model were known food allergy before the index ED visit, with a more pronounced risk among children with two or more food allergies, and prescription of AAI before the index reaction. Factors associated with subsequent reactions among food-allergic children reported by others are: more frequent and severe reactions (91, 146), higher number of baseline food allergies (142, 143) and higher number of baseline allergen specific IgE (142). These findings are not surprising since all the above-mentioned factors – including the risk factors identified by us – could be seen as a proxy for more severe allergic disease, as well as markers for true food allergy. Unfortunately, the possibility to predict subsequent reactions on an individual basis based on these risk factors is poor.

6.3 RISK MANAGEMENT

6.3.1 Underuse of adrenaline auto-injectors

Delay in the administration of adrenaline is a consistent risk factor for fatal food-induced anaphylaxis (93, 148-150). Therefore the low rate of use of AAIs among children with anaphylaxis (45% in study I and 24% in study II) is of great concern. Unfortunately this finding is in line with other reports (75, 93, 136, 142, 151-153). Due to the retrospective design in study I and II, with the data being collected from clinical records, we were not able to determine the reason for the limited use of AAIs. However, in the focus group sessions in study III, some parents talked about how they, or their adolescents, only bring the AAIs with them in certain situations, such as when travelling. This confirms previous reports on limited carriage of prescribed AAIs among food-allergic children and their caregivers, despite medical advice (118, 142, 154-156). Other reasons for underuse of AAIs pointed out in previous studies are lack of knowledge on how to use the device (157), fear regarding its use (118, 126, 151, 158), being unsure whether the symptoms are severe enough to require anaphylaxis treatment (75, 151, 159) or thinking it unnecessary to use the device (75, 159). The perception that the AAI should only be used when facing severe, potentially life-threatening symptoms is illustrated in our study III, in which parents talked about the AAI being the last resort if nothing else works.

It is currently recommended that AAIs should be prescribed along with written emergency reaction plans listing symptomatic indications for AAI administration (160). However, the formal evidence in support of management plans improving outcomes in cases of anaphylaxis is limited (161, 162). In the most recent systematic review investigating management plans, the authors conclude that the available evidence to support use of self-management plans is encouraging but weak (163). The questionable effectiveness of management plans is illustrated by the findings of a recent survey of 969 patients at paediatric allergy clinics in the UK prescribed with AAIs (75). All patients had been verbally informed and given written information by an allergy doctor and/or nurse as well as an allergy management plan for indications when adrenaline should be administered. They were also trained in administration

with a trainer device. Still, only a minority (17%) of the 245 participants who had experienced anaphylaxis in the previous year had used their AAI. The most common reason for nonuse was patient's inability to recognise situations in which use of the AAI was appropriate.

6.3.2 Balancing risk and burden

The analysis of the focus group material in study III reveals how the management of allergy risk permeates most aspects of daily life. The constant vigilance parents in our study adopted to avoid allergy risk echoes previous reports (100, 108, 120). Since circumstances around the child can change suddenly, for example when there is new personnel at the day-care centre, parents have the responsibility of preventing reactions in the unpredictable environment of their child's everyday life. Management strategies vary, as do the degrees of fear and uncertainty, but ultimately the risk of a severe reaction seems to remain a fundamental condition in parents' lives. Constantly dealing with the knowledge that something could happen seemed to be a vital aspect of child food allergy management, as also described by others (100, 108, 120).

Interestingly, we found that the principle of constant vigilance is challenged in discussions about taking calculated risks. Testing if, or to what degree, the child is 'really' allergic to certain food items was presented by some of the parents as a way to avoid undue limitations in family social life. This risk-taking did not emerge as an overall strategy but only in specific situations where the 'danger' can be observed and managed by the parent. The phenomenon of balancing the burden of the food-allergic condition by taking risks is well described among food-allergic adolescents (116, 118, 122, 164). Teenagers have been reported to take risks in order to fit in among peers, for example not carrying their AAI due to its bulky design, and to knowingly eat food they are allergic to (115-118, 121, 122, 164). A relationship between safety and burden among food-allergic teenagers has been described by MacKenzie et al, who found that the teenagers who were strictest at managing their food allergy also experienced the highest burden and those who were least strict experienced the least burden (116).

However, reports on risk-taking among parents are scarce (108, 142). Rouf et al found that mothers of food-allergic children accept the importance of the balance between completely avoiding risk and maintaining a relatively normal life: taking calculated risks was identified as necessary to achieve this balance (108). In addition, Fleischer et al report 11% of the recurrent reactions among pre-school children allergic to milk and egg could be attributed to purposeful exposure to known food allergens (142). The authors argue that this calls for improved education of parents and others on the importance of persistent vigilance. Notably, in our study, risk-taking did not emerge as a lack of knowledge about vigilance: taking calculated risks certainly amounted to actively risking an allergic reaction. However, when taking these risks, the parents still draw on knowledge about allergen avoidance but the knowledge is evaluated in a different context: the benefits of vigilance and food avoidance are weighed against the benefits of a better social life, not only for the child but also for the family as a whole. Hence, the constant vigilance and efforts to avoid allergens and talk about taking calculated risks can be seen as two sides of the same coin: parental responsibility. And being a 'good' parent may involve risk-taking.

Although the parental risk-taking in our study did not seem to be caused by unawareness about the importance of vigilance, it was often linked to uncertainty. Uncertainty as to what foods the child actually is allergic to, if the child tolerates traces

of the allergen and if products with advisory labelling really contain the allergen. Parental risk-taking by giving the child products with precautionary 'may contain allergens' statements has also been described by others (108, 165, 166). The use of voluntary allergen precautionary statements is increasingly common (167, 168); it represents a non-quantitative approach for warning of potential cross-contamination with food allergens (169) and patients and their parents tend to question whether there truly is a risk of cross-contact (116, 121). The observation that parents of food-allergic children have unmet information needs, leaving them uncertain how to manage safety, has been reported previously (100, 120, 170).

6.4 STRENGTHS AND LIMITATIONS

Epidemiological studies such as study I and II are potentially subject to two broad categories of errors that may affect their precision and validity: random error (caused by chance) and systematic error (caused by bias). High precision (sometimes called reliability) depends on the absence of random errors while high validity depends on the absence of systematic errors. The different sources of systematic errors are information bias, selection bias and confounding. In qualitative research the findings are evaluated in terms of trustworthiness instead of the conventional criteria of validity and reliability used in quantitative research. The assessment of the trustworthiness in qualitative health care research is often based on four criteria proposed by Gupta in 1981: credibility, transferability, dependability and conformability (171, 172). These terms are further discussed below. In this section the strengths and limitations of the present investigations are discussed based on the above presented concepts.

Study I and II

A considerable strength is that we used criteria for anaphylaxis that are now widely accepted internationally; this will allow our results to be compared with the findings of current as well as future studies on the epidemiology and clinical characteristics of anaphylaxis. Another strength is our extensive collection of data, where we retrieved information not only from the medical records from the ED, but also from ambulance reports, referral letters at discharge and the complete medical record of each child on a regional level before and after the ED visit. In addition we used specific ICD-codes for anaphylaxis as well as non-specific codes for allergic symptoms, combined with chart review to identify children with allergic reactions. This type of approach is likely to provide the most complete and representative group of patients, as demonstrated by others (173, 174). A strength specific of study I is its size and population-based approach within a defined catchment area. As to study II, a major strength is that we used Cox proportional hazard regression to estimate relative risks: using longitudinal models we could account for differences in time of exposure, for example, that the children contributed differently in relation to exposures and other factors since observation time was not equal.

The primary limitations are the retrospective design and our reliance on the documentation in the medical records for our data collection, since there is no guarantee that information about all symptoms and signs at reaction and underlying allergies was requested and noted down. It could be speculated that inclusion of some signs and symptoms, especially mild ones, will depend on the physician's competence as well as the work load on the ED. This limitation was partly compensated by the fact that we retrieved information from the complete medical records of each patient including ambulance reports, referral letters and outpatient visits after the ED visits. It should also be noted that although data collection from medical records has its limitations due to the risk of missing information, the information is highly reliable compared to parents' or children's retrospective recall of clinical features collected from questionnaires. Consequently, memory bias or recall bias should be modest.

However, due to our study design, information bias is likely to be present, and this must be considered when interpreting our results. First, and as already mentioned, subjective signs such as the extent of abdominal pain could seldom be retrieved from the medical records. According to the criteria for anaphylaxis, abdominal pain should

be persistent and crampy to be considered indicative of anaphylaxis (2). We considered abdominal pain regardless of severity as a sub-criterion for anaphylaxis, which may in some cases have caused misclassification of anaphylaxis. Second, our reports on allergic co-morbidity in the study population could be affected by information bias. A larger proportion of children with anaphylaxis as compared to those without anaphylaxis were seen and evaluated in outpatient clinics before or after the ED visit. Investigation of allergic co-morbidity probably is more extensive in outpatient clinics than in the ED, and thus the misclassification bias could be differential. Third, since the individual aetiological agent was evaluated using only medical records, we might have misclassified some of the children as having had reactions to food when the reaction was actually caused by another agent. However, it would not have been feasible to perform food challenges to confirm the trigger in all the children in the study population. In addition, it would have been unethical to perform food challenges on children with anaphylaxis, since the vast majority had suffered moderate or severe anaphylactic reactions.

Limitations specific to study II are the potential for residual confounding and confounding by severity in the analysis of risk factors for ED revisits. In addition, the precision is affected by the fairly limited sample size, as indicated by the rather wide confidence intervals in paper 3. Consequently, our non-significant associations should be interpreted with caution since they may be inconclusive rather than truly negative.

Study III

In study III a qualitative design was used to explore parents' experiences of allergy management. A strength in the study design was the use of focus group discussions, known to be particularly suited for the study of shared knowledge, opinions and attitudes (175). Focus groups are described in the literature as a carefully planned discussion designed to obtain perceptions on a defined area of interest in a permissive, non-threatening environment (176). Some of the core elements are that the groups should be relatively homogenous and small (6-12 members, even fewer when the addressed topic is sensitive) and the moderator should be skilled and trained in leading focus group discussions (177). These criteria were fulfilled in our study. However, it should be noted that due to late cancellations, two groups had just two participants. Since these dyads contributed rich narratives, they were included in the material. We conducted several focus group sessions in two slightly different sites, both at children's hospital, thereby enhancing our confidence in our findings. Also, after ten focus group sessions at two different sites, we argue that we reached a reasonable saturation of data.

Credibility deals with the quality of the research process and refers to how well data collection and the analysis process address the research objective. In study III we as researchers had different background and experiences: triangulation by researchers is a strategy to enhance the credibility. Credibility was also enhanced by the use of frequent citations in paper IV as well as by peer-review, where our interpretations were discussed with researchers at Stockholm University who were not directly involved in the study. However, we have not performed any member check as this is difficult to carry out and, more importantly, not relevant to the research approach in this study of experiences, knowledge and opinions as they emerge in conversations between parents.

Transferability concerns the question of whether our results are applicable to other subjects and other contexts. The recruitment through the health care system with all participants having experienced an ED visit quite recently, as well as the fact that

most of the families had been prescribed AAIs, suggests that the sample covered parental experiences of managing *severe* food allergy and not food allergy in general. Supporting this reasoning, many parents who declined to participate motivated their decision by their child's allergy not being a 'big deal' in everyday life since it was not severe. In addition, our sample included only Swedish-speaking parents and most were mothers. Hence, the transferability is limited to fairly well-educated Swedish parents who responded to an invitation from the allergy physician. It is clearly possible that other patterns of risk avoidance and risk-taking could be found in other groups of parents, which calls for additional studies of parents from other backgrounds, to be carried out in different sites.

Dependability refers to whether our findings would be replicated if the study was repeated in the same context, with the same methods and with the same participants. The fact that we used a topic guide that was decided on in advance and that the moderator was very experienced in using the method increases the dependability of our findings. Confirmability is a measure of how well the findings are supported by the data collected and refers to whether the findings are affected by personal interests and biases. We minimised the risk of bias introduced by my own and Dr Wickman's preconceptions (being physicians working with food-allergic children as our patients) by leaving the initial data analysis to M-L Stjerna, who does not possess such preconceptions.

6.5 ETHICAL CONSIDERATIONS

In study I and II we had permission from the ethic committee at Karolinska Institutet to review the medical charts without obtaining informed consent from the parents of the children. In the process of identifying children who had visited the ED due to anaphylaxis or allergic reactions to foods, we reviewed more than 500 medical records of which 383 met our inclusion criteria. It is possible that some children and parents would find this chart review an intrusion on their integrity.

In study III the participating parents gave their informed consent to participate in the study. They had received written information where we explained the purpose of the study and emphasised that their participation was completely voluntary and that declining to participate would not affect their contact with the clinic. The parents also had the opportunity to ask me questions regarding the study before deciding on participating.

Focus group discussions raise two ethical issues of special importance: the fact that the participant's experiences are shared with all group members and not just the researcher, and that the group discussion may give rise to stress and anxiety in some of the participants (175). The first issue was addressed in our study by explaining the need for confidentiality in the introduction to the focus group sessions. We also explained what would be done with our notes and tape recordings and that all names would be fictitious in the coming publications. As to the second issue, it is impossible to guarantee that participants will not be upset by comments from others, given the group context. However, we used small groups which is a recommended strategy when performing focus-group sessions on sensitive topics (178, 179). In addition, I observed the parents' reactions during the discussions and addressed the questions that appeared to have caused distress among the participants at the end of each session. Also important from an ethical perspective, I answered any medical questions that had been raised or disputed during the discussions at the end of each session, and offered parents who seemed to have unmet information needs a referral to a paediatric out-patient clinic. Notably, most of the participants expressed that they were glad to have been given this opportunity to discuss their experiences with other parents.

6.6 CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Classification of anaphylaxis

Unambiguous diagnostic criteria for defining anaphylaxis are desirable not only in research but also in the clinical setting, since accurate management depends on proper identification of patients with anaphylaxis as well as adequate severity grading. In study I and II we used the newly proposed and widely accepted criteria for anaphylaxis (2) and we graded the severity according to the proposal in the EAACI position paper on anaphylaxis in children (24). However, we found the possibility of classifying and severity grading anaphylaxis according to these guidelines to be hampered by a lack of description of some symptoms and by subjective wordings.

Based on our findings (paper I) I would like to suggest that the symptoms non-barking cough, chest tightness, speaking difficulties, speaking with a muffled voice, tiredness and somnolence are included in future proposals for severity grading of anaphylaxis. Furthermore, it would be desirable, although perhaps not feasible, if subjective descriptions as mild and moderate could be changed to more concrete wordings. However, such changes need to be validated.

Underuse of adrenaline auto-injectors

In study I and II (paper II and III) we showed that the majority of children with anaphylaxis prescribed an AAI did not use their device when needed. This is of particular concern since delayed administration of adrenaline is a consistent risk factor for severe or even fatal anaphylaxis. Clearly there is a need for further research to elucidate how best to encourage and motivate appropriate AAI usage. For example, it would be interesting to explore why children and their caregivers are reluctant to use the AAIs when experiencing anaphylaxis using a qualitative study design.

There is also a need for development and evaluation of standardised educational programs with the aim of changing attitudes towards using the AAI to treat ongoing reactions and to evaluate the benefit of management plans. Perhaps patient training and support can be improved by the use of internet, apps and real-time simulation.

Food allergy – an unpredictable disease

Our finding in study II (paper 3) that the severity of subsequent reactions cannot be accurately predicted from the severity of the index reaction adds to the picture of food allergy as an unpredictable disease. Further research to find novel biomarkers and improve diagnostic techniques to allow identification of those at particularly high risk of severe reactions is clearly warranted.

However, as long as we are unable to predict the severity of subsequent reactions on an individual basis, one could consider whether all children with a history of IgE-mediated reactions to foods should be prescribed an AAI, an argumentation supported by recently published guidelines sponsored by the National Institute of Allergy in the United States (71). But before considering implementation of such an approach there is a need for research on what effect providing children with AAIs has on their quality of life, as the few studies published so far investigating this issue show conflicting results (98, 180). In addition, the effect on adherence as well as on health economy must be studied. There is certainly a trade-off between over- and under-prescription of AAIs:

although some food-allergic children may experience severe life-threatening reactions in the future, the majority will not.

Ultimately, since finding an effective treatment is the only way to eliminate the risk of severe reactions, allergen-specific immunotherapeutic approaches such as oral immunotherapy and non-specific therapies such as omalizumab need to be further studied as to their safety and efficacy.

Handling uncertainty and worries

In study III (paper IV) we found that the norm of complete risk avoidance was challenged by some of the parents in order to achieve balance between the burden and the risk associated with food allergy. To live a life without taking any risks at all is not an achievable goal, nor is it desirable. With that said, and based on the knowledge that food allergic reactions can be fatal, risk-taking can hardly be encouraged in clinical practice. However, as a clinician caring for food-allergic children and their families it is important to be aware that calculated risk-taking occurs and to evaluate whether these families have unmet information needs. Although the risk-taking in our study did not emerge as a lack of knowledge about the importance of vigilance, it was often linked to uncertainty: uncertainties regarding products with advisory labellings and sometimes also regarding the child's current allergies. Hence, I believe that decreasing uncertainty among children with food allergies and their families is of utmost importance.

Different approaches and research needs can be considered in this context. First, a thorough allergological work-up is necessary to provide the individual with complete information about his or her food allergies, as are regular follow-ups to evaluate whether the food allergies have resolved. Since an overly restrictive diet must be avoided, food challenges should be performed liberally in case of uncertainty. Second, uncertainty related to products with precautionary labels, or rather 'may contain' labels, should be minimised. Third, the information on allergen thresholds that is currently being developed through use of data from clinical challenges (168, 181) could be used to guide low dose food challenges to evaluate an individual's sensitivity, thereby helping clinicians decide whether the patient should be advised to avoid foods with precautionary labelling or not (168).

Finally, since unpredictability and uncertainty will remain cornerstones of the food-allergic condition until cure is found, an important task for health care providers is to help families cope with burdens and worries. Although a high level of anxiety certainly create needs of special support, I would argue that parental worry should not be regarded entirely as a problem to be minimised. Worry should rather be recognised as an inherent aspect of managing a child's food allergy, one that should be taken into account and 'given space' in clinical practice. This is supported by the observation that the parents in study III, who already had access to medical expertise and advice, still clearly benefited from discussing the challenges of allergy management with other parents. To make it possible for parents to share experiences in other contexts than the traditional medical consultation, medical providers caring for food-allergic children and their families should facilitate contact between parents, with support groups and with allergy-related organisations.

7 CONCLUSIONS

The separate studies in this thesis suggest the following conclusions:

The criteria presented in the EAACI position paper on anaphylaxis in children are not quite applicable for classification and severity grading of anaphylaxis, in particular due to lack of description of some respiratory and neurological symptoms, and use of subjective wording.

The incidence of anaphylaxis managed at paediatric emergency departments in Stockholm during 2007 was 32 per 100 000 person-years and food was the trigger in 92% of the cases. Although this rate lies within the range of previous reports on the incidence of anaphylaxis among children, it is likely an underestimation of the true incidence in the underlying population.

The majority of children prescribed AAI do not use their device when they experience anaphylaxis to foods.

The incidence of subsequent reactions to foods requiring emergency department care among children who had previously visited the emergency department due to reactions to foods was 92 per 1000 person-years. This rate cannot be directly compared to the findings of others due to differences in study design. Previously known food allergy and prior prescription of adrenaline were risk factors for subsequent emergency department revisits. Unfortunately, the possibility of predicting subsequent reactions on an individual basis based on these risk factors is poor.

The severity of previous reactions to foods does not appear to be an accurate predictor of the severity of subsequent reactions.

The management of allergy risk permeates many aspects of everyday life in families with food-allergic children. Although most parents follow the norm of constant risk avoidance, some take calculated risks to have a less restricted social life. However, constant risk avoidance and calculated risk-taking are intertwined and can be seen as two sides of the same coin, i.e. parental responsibility. Being a 'good' parent may also involve risk-taking.

8 SAMMANFATTNING PÅ SVENSKA

Bakgrund

Födoämnesallergi är ett ökande folkhälsoproblem och drabbar upp till 8% av alla barn. Reaktionen vid födoämnesallergi varierar i svårighetsgrad; från lindrig klåda i munnen till anafylaxi. Det sistnämnda är en snabbt insättande reaktion från flera organsystem som är potentiellt livshotande. Individer som haft anafylaxi bör därför bära med sig en adrenalinspruta eftersom skyndsamt behandling med adrenalin intramuskulärt i dagsläget är den enda effektiva behandlingen. Med dagens diagnostiska metoder är möjligheten att urskilja vilka individer med födoämnesallergi som löper risk för svårare reaktioner begränsad. Eftersom det hittills inte finns någon botande behandling är den enda strategin att noggrant undvika födoämnet i fråga samt att vara konstant beredd att behandla eventuella reaktioner. Tyvärr är reaktioner på grund av oavsiktligt intag inte ovanliga. Sjukdomens oförutsägbara och potentiellt allvarliga karaktär leder ofta till en negativ inverkan på livskvaliteten hos de drabbade barnen och deras familjer.

När detta doktorandprojekt inleddes saknades kunskap om svåra reaktioner mot födoämnen bland svenska barn avseende förekomst, orsakande födoämnen, akut behandling, risken för förnyade reaktioner samt skillnader i svårighetsgrad över tid. Dessutom hade inte användbarheten av de då nyligen föreslagna kriterierna för klassificering och svårighetsgradering av anafylaxi utvärderats. Slutligen var lite känt om hur föräldrar upplever vardagen med ett barn som är födoämnesallergiskt och deras resonemang kring riskhantering.

Syfte

Det övergripande syftet med denna avhandling var att öka kunskapen om svåra reaktioner mot födoämnen bland svenska barn vad gäller såväl epidemiologi och klinik (studie I och II) samt riskhantering (studie III). Kunskap som kan ge ökad insikt inom sjukvården och därigenom ett förbättrat omhändertagande av barn med födoämnesallergi.

Metoder

Studie I (delarbete I och II) är en journalgranskningsstudie på Stockholms barnsjukhus där vi kartlagt akutbesök orsakade av reaktioner mot födoämnen samt av anafylaxi oavsett utlösande orsak under 2007.

I studie II (delarbete III) har vi utfört en kompletterande journalgenomgång bland de barn som identifierats i studie I för att kartlägga förnyade akutbesök på grund av reaktioner mot födoämnen under perioden 1 januari 2007 till och med 30 juni 2010.

Studie III (delarbete IV) är en kvalitativ studie där vi utfört 10 fokusgruppsintervjuer med 31 föräldrar till födoämnesallergiska barn för att utforska deras upplevelser av riskhantering.

Resultat

De huvudsakliga resultaten i detta avhandlingsarbete uppdelat på de studerade områdena är som följer:

Epidemiologi: Förekomsten av anafylaxi hos barn omhändertagna på Stockholms barnsjukhus akutmottagningar under 2007 var 32 per 100 000 personår och födoämnen orsakade 92% av reaktionerna (delarbete II). Återinsjuknande på grund av reaktioner mot födoämnen som ledde till akutbesök bland de ovan nämnda barnen var 92 per 1000 personår under uppföljningsperioden, det vill säga nästan en på tio under ett års tid (delarbete III).

Kliniska perspektiv: Våra försök att klassificera och svårighetsgradera anafylaxi baserat på gällande riklinjer (24) försvårades då beskrivning av vissa neurologiska och respiratoriska symtom saknades samt på grund av att subjektiva symtom behövde klassificeras (delarbete I). Bland de 371 barn med akutbesök på grund av reaktioner mot födoämnen under 2007 var jordnötter och trädnötter de födoämnen som orsakade flest reaktioner. Bland barn under tre år var det lika vanligt med reaktioner mot jord- och trädnötter som mot ägg och mjölk. Bland barn med pollenallergi var det vanligare med akutbesök på grund av anafylaxi mot födoämnen under pollensäsong jämfört med resten av året (delarbete II). Majoriteten av de barn som var förskrivna adrenalinspruta använde sig inte av denna i samband med anafylaxireaktioner (delarbete II och III). Bland barn med upprepade akutbesök på grund av reaktioner mot födoämnen skiljde sig svårighetsgraden mellan reaktionstillfällena åt hos merparten. Tidig behandling med adrenalin försvårade dock ofta klassificeringen av förändring i svårighetsgrad (delarbete III).

Riskhantering: Den kvalitativa analysen av fokusgruppsintervjuerna visade att riskhantering genomsyrade de flesta aspekterna av vardagslivet. Även om de flesta föräldrarna följde normen att konstant undvika risker var det några som tog beräknade risker i specifika situationer, till exempel genom att ge barnet mat som kunde innehålla spår av födoämnet barnet var allergisk mot samtidigt som de noggrant observerade barnet och var beredda att ge behandling om barnet skulle få en reaktion. Sådana risker togs för att minska den sociala begränsning sjukdomen medför, inte bara för barnets men också för hela familjens skull (delarbete IV).

Slutsats

Denna avhandling bidrar med nya kunskaper om anafylaxi och svåra reaktioner mot födoämnen hos svenska barn vad gäller förekomst, kliniska kännetecken och utlösande orsaker. Då vi studerat reaktioner som föranlett akutbesök bör det dock påpekas att den av oss rapporterade förekomsten av anafylaxi sannolikt är en underskattning av den verkliga förekomsten i populationen. Resultaten från avhandlingen bidrar vidare till att belysa födoämnesallergins oförutsägbara karaktär samt de svårigheter som är associerade till att studera akuta reaktioner mot födoämnen. Slutligen visar avhandlingen på den stora inverkan riskhantering kan ha i familjer med födoämnesallergiska barn samt att riskundvikande och risktagande kan ses som två sidor av samma mynt; föräldraansvar.

9 ACKNOWLEDGEMENTS

Many people have contributed to make the studies included in this thesis possible. In particular I would like to thank:

First, all participating parents for sharing your time and your experiences.

Magnus Wickman, my main supervisor, for always being optimistic, enthusiastic, generous, encouraging and available. Your creativity and constant flow of ideas never ceases to impress me. Thank you for sharing your vast knowledge in the fields of allergology and epidemiology and for your never-ending support in different aspects of life, not just research.

Gunnar Lilja, my co-supervisor, for employing me at Sachs' Children and Youth Hospital ten years ago, and later presenting me with an offer to engage in research. Thanks for continuously supporting me and believing in me. Your kindness and your excellent skills as a paediatrician and as researcher are truly inspiring.

Eva Östblom, my co-supervisor, for your invaluable involvement during all stages of the studies, for constructive and positive discussions and for your thoughtful and precise feedback.

Tobias Alfvén, my co-supervisor, for sharing epidemiologic knowledge and scientific thinking with me, for your friendly encouragement and for all your useful comments and feedback.

All my other co-authors for sharing your knowledge and time and for all your invaluable comments and ideas. More specifically: **Diana Hoa Ly** and **Daiva Helander** for helping out with data collection, **Charlotta Flodström** for thoughtful advice and friendship, **Caroline Nilsson** for your friendly and sharp-minded support, **Gunilla Hedlin** for your help and valuable feedback, **Niclas Håkansson** for your expertise in statistics, **Marie-Louise Stjerna** and **Sonja Olin Lauritzen** for introducing me to qualitative research methodology and for rewarding cooperation, **Anna Bergström** for your wise constructive advice, sharing your epidemiological knowledge and for always being so kind and supportive.

Lotta Nordenhäll, my external mentor and colleague, for always being ready to sort out issues big and small related to research and life, and for being the extraordinary person that you are.

Benita Lund at Sachs' Children and Youth Hospital, for helping identify eligible children for study I and for your optimistic attitude.

Rolf Timgren, Stockholm County Council, Health Care Provision, for your assistance in identifying children who had visited the local emergency unit at Karolinska University Hospital, Huddinge.

Per Sandstedt and **Eva Berggren Broström**, former and current head of Sachs' Children and Youth Hospital, and **Bodil Schiller**, my boss at Sachs' Children and Youth Hospital, for giving me the opportunity to carry out this work.

Natalia Ballardini, my clinical supervisor at Sachs' Children and Youth Hospital and my room-mate at the Institute of Environmental Medicine, for always helping me out whenever I needed it, and for being you: a pillar of strength, wise, calm, supportive and fun.

My past and present room-mates and fellow PhD students at Sachs' Children and Youth Hospital and the Institute of Environmental Medicine, **Susanne Glaumann**, **Anna Undeman Asarnej**, **Marit Westman**, **Björn Nordlund**, **Elin Dahlén**, **Åsa Neuman**, **Marina Jonsson**, **Helena Marell Hesla** and **Fredrik Stenius** for rewarding discussions and constant support but mostly for making my PhD-time more fun.

Everyone at the Department of Clinical Science and Education, Södersjukhuset, for all your help during my PhD studies, especially **Maaret Castrén**, **Christer Svensén**, **Henrik Ortsäter**, **Jeanette Brynholt Öhrman** and **Mats Jonsson**. A special thanks to **Hans Järnbert Pettersson** and **Fredrik Johansson** for skilled statistical advice.

My colleagues at the Institute of Environmental Medicine – especially **Eva Hallner** and **Sara Nilsson** for always lending a helping hand, **Niklas Andersson** for curing my STATA-related headaches, **André Lauber** for helping me with data management, **Tomas Lind** for statistical expertise and finally **Erik Melén** and **Inger Kull** for friendly and supportive advice.

My friends from the BAMSE journal club for creative discussions.

Anita Stålsäter Pettersson, head secretary at Sachs' Children and Youth Hospital, for all your help in organizing my dissertation.

All dear colleagues and friends at Sachs' Children and Youth Hospital for laughs, support and for being just wonderful.

All my lovely and extraordinary friends for always offering support whenever I need.

My parents **Pia** and **Ulf**, for always believing in me and for your unconditional love and support. And mum, thanks for all your invaluable help with Elsa!

My sister and very closest friend **Rebecca**, for your love and for always being there.

The members of my extended family: **Mikael**, **Julia**, **Hjalmar**, **Thomas**, **Carolina**, **Kerstin**, **Lennart**, **Anton**, **Elin**, **Sigge** and **Agneta**, for support and friendship. And again **Agneta**, for helping out with Elsa whenever we ask.

Finally – **Robert**, my wonderful husband, always loving, supporting and encouraging. And my daughter **Elsa**, for being you and for bringing pure joy to my life. I love you both, endlessly.

For financial support I would also like to thank: the Department of Clinical Science and Education at Södersjukhuset, Sachs' Children and Youth Hospital, the Mjölkdroppen Foundation, the Freemasons in Stockholm Childhood Foundation, Centre for Allergy Research at Karolinska Institutet, Karin and Sten Mörtstedt, the Samariten Foundation, the Asthma and Allergy Foundation and the foundation 'Kerstin Hejdenberg minne'.

10 REFERENCES

1. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol*. 2013:E-pub ahead of print.
2. 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;117(2):391-7.
3. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: food allergy. *J Allergy Clin Immunol*. 2012;129(4):906-20.
4. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. *Allergy*. 2010;65(8):933-45.
5. WAO. White Book on Allergy: World Allergy Organization (WAO); 2011.
6. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet*. 1998;351(9111):1225-32.
7. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368(9537):733-43.
8. Ballardini N, Kull I, Lind T, Hallner E, Almqvist C, Ostblom E, et al. Development and comorbidity of eczema, asthma and rhinitis to age 12: data from the BAMSE birth cohort. *Allergy*. 2012;67(4):537-44.
9. Ker J, Hartert TV. The atopic march: what's the evidence? *Ann Allergy Asthma Immunol*. 2009;103(4):282-9.
10. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol*. 2004;113(5):832-6.
11. Rindsjo E, Scheynius A. Mechanisms of IgE-mediated allergy. *Experimental cell research*. 2010;316(8):1384-9.
12. Leung D, Sampson H, Geha R, Szeftler S. *Pediatric Allergy*: Elsevier; 2010.
13. Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med*. 2010;363(13):1211-21.
14. Wen HJ, Chen PC, Chiang TL, Lin SJ, Chuang YL, Guo YL. Predicting risk for early infantile atopic dermatitis by hereditary and environmental factors. *The British journal of dermatology*. 2009;161(5):1166-72.
15. Allen KJ, Koplin JJ. The epidemiology of IgE-mediated food allergy and anaphylaxis. *Immunol Allergy Clin North Am*. 2012;32(1):35-50.
16. Strachan DP. Hay fever, hygiene, and household size. *Bmj*. 1989;299(6710):1259-60.
17. Brooks C, Pearce N, Douwes J. The hygiene hypothesis in allergy and asthma: an update. *Curr Opin Allergy Clin Immunol*. 2013;13(1):70-7.
18. Alfven T, Braun-Fahrlander C, Brunekreef B, von Mutius E, Riedler J, Scheynius A, et al. Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle--the PARSIFAL study. *Allergy*. 2006;61(4):414-21.
19. Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G. Atopy in children of families with an anthroposophic lifestyle. *Lancet*. 1999;353(9163):1485-8.
20. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 Suppl):S1-58.

21. Sharma HP, Mansoor DK, Mikhail IJ, Nguyen C, Klein BL. Recognition and management of pediatric food allergy in the emergency department. *Pediatr Emerg Care.* 2013;29(4):527-36.
22. Cohen SG, Zelaya-Quesada M, Portier, Richet, and the discovery of anaphylaxis: a centennial. *J Allergy Clin Immunol.* 2002;110(2):331-6.
23. Simons FE. Anaphylaxis. *J Allergy Clin Immunol.* 2010;125(2 Suppl 2):S161-81.
24. 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;62(8):857-71.
25. Simons FE, Arduzzo LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J.* 2011;4(2):13-37.
26. Campbell RL, Hagan JB, Manivannan V, Decker WW, Kanthala AR, Bellolio MF, et al. Evaluation of national institute of allergy and infectious diseases/food allergy and anaphylaxis network criteria for the diagnosis of anaphylaxis in emergency department patients. *J Allergy Clin Immunol.* 2012;129(3):748-52.
27. Bashir ME, Louie S, Shi HN, Nagler-Anderson C. Toll-like receptor 4 signaling by intestinal microbes influences susceptibility to food allergy. *Journal of immunology (Baltimore, Md : 1950).* 2004;172(11):6978-87.
28. Ramesh S. Food allergy overview in children. *Clinical reviews in allergy & immunology.* 2008;34(2):217-30.
29. Gomez E, Mayorga C, Gomez F, Blazquez AB, Diaz-Perales A, Blanca M, et al. Food allergy: management, diagnosis and treatment strategies. *Immunotherapy.* 2013;5(7):755-68.
30. Galli SJ, Tsai M, Piliponsky AM. The development of allergic inflammation. *Nature.* 2008;454(7203):445-54.
31. Abbas AL. *Basic Immunology.* Philadelphia: Elsevier Inc; 2011. third ed. Philadelphia: Elsevier; 2011.
32. 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.* 2013:E-pub ahead of print.
33. Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ, et al. Diagnosing and managing common food allergies: a systematic review. *JAMA.* 2010;303(18):1848-56.
34. 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;97(5):596-602.
35. 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;68(11):1353-61.
36. 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;120(3):638-46.
37. Ostblom E, Lilja G, Ahlstedt S, van Hage M, Wickman M. Patterns of quantitative food-specific IgE-antibodies and reported food hypersensitivity in 4-year-old children. *Allergy.* 2008;63(4):418-24.
38. Ostblom E, Wickman M, van Hage M, Lilja G. Reported symptoms of food hypersensitivity and sensitization to common foods in 4-year-old children. *Acta Paediatr.* 2008;97(1):85-90.
39. Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics.* 2009;124(6):1549-55.
40. Hu Y, Chen J, Li H. Comparison of food allergy prevalence among Chinese infants in Chongqing, 2009 versus 1999. *Pediatrics international : official journal of the Japan Pediatric Society.* 2010;52(5):820-4.
41. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol.* 2010;125(6):1322-6.

42. Canani RB, Nocerino R, Terrin G, Leone L, Troncone R. Hospital admissions for food-induced anaphylaxis in Italian children. *Clin Exp Allergy*. 2012;42(12):1813-4.
43. Rudders SA, Banerji A, Vassallo MF, Clark S, Camargo CA, Jr. Trends in pediatric emergency department visits for food-induced anaphylaxis. *J Allergy Clin Immunol*. 2010;126(2):385-8.
44. Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. *J Allergy Clin Immunol*. 2009;123(2):434-42.
45. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. NCHS data brief. 2013(121):1-8.
46. Ben-Shoshan M, Kagan RS, Alizadehfar R, Joseph L, Turnbull E, St Pierre Y, et al. Is the prevalence of peanut allergy increasing? A 5-year follow-up study in children in Montreal. *J Allergy Clin Immunol*. 2009;123(4):783-8.
47. Venter C, Hasan Arshad S, Grundy J, Pereira B, Bernie Clayton C, Voigt K, et al. Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. *Allergy*. 2010;65(1):103-8.
48. Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *J Allergy Clin Immunol*. 2004;113(3):536-42.
49. Boros CA, Kay D, Gold MS. Parent reported allergy and anaphylaxis in 4173 South Australian children. *Journal of paediatrics and child health*. 2000;36(1):36-40.
50. Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *J Allergy Clin Immunol*. 2008;122(6):1161-5.
51. Harduar-Morano L, Simon MR, Watkins S, Blackmore C. A population-based epidemiologic study of emergency department visits for anaphylaxis in Florida. *J Allergy Clin Immunol*. 2011;128(3):594-600.e1.
52. Tejedor Alonso MA, Moro Moro M, Mugica Garcia MV, Esteban Hernandez J, Rosado Ingelmo A, Vila Albelda C, et al. Incidence of anaphylaxis in the city of Alcorcon (Spain): a population-based study. *Clin Exp Allergy*. 2012;42(4):578-89.
53. Pumphrey R. Anaphylaxis: can we tell who is at risk of a fatal reaction? *Curr Opin Allergy Clin Immunol*. 2004;4(4):285-90.
54. Macdougall CF, Cant AJ, Colver AF. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. *Arch Dis Child*. 2002;86(4):236-9.
55. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol*. 2011;127(3):668-76.e1-2.
56. Miljöhälsorapport 2013, Institute of Environmental Medicine, Karolinska Institutet.
57. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128(1):e9-17.
58. 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;132(5):1216-9.e5.
59. Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, St Pierre Y, et al. Overall prevalence of self-reported food allergy in Canada. *J Allergy Clin Immunol*. 2012;130(4):986-8.
60. Silva R, Gomes E, Cunha L, Falcao H. Anaphylaxis in children: a nine years retrospective study (2001-2009). *Allergologia et immunopathologia*. 2012;40(1):31-6.
61. Novembre E, Cianferoni A, Bernardini R, Mugnaini L, Caffarelli C, Cavagni G, et al. Anaphylaxis in children: clinical and allergologic features. *Pediatrics*. 1998;101(4):E8.

62. Dalal I, Binson I, Reifen R, Amitai Z, Shohat T, Rahmani S, et al. Food allergy is a matter of geography after all: sesame as a major cause of severe IgE-mediated food allergic reactions among infants and young children in Israel. *Allergy*. 2002;57(4):362-5.
63. Osterballe M, Hansen TK, Mortz CG, Host A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol*. 2005;16(7):567-73.
64. Katelaris CH. Food allergy and oral allergy or pollen-food syndrome. *Curr Opin Allergy Clin Immunol*. 2010;10(3):246-51.
65. Westman M, Stjarne P, Asarnej A, Kull I, van Hage M, Wickman M, et al. Natural course and comorbidities of allergic and nonallergic rhinitis in children. *J Allergy Clin Immunol*. 2012;129(2):403-8.
66. Wagner CW. Anaphylaxis in the pediatric patient: optimizing management and prevention. *Journal of pediatric health care : official publication of National Association of Pediatric Nurse Associates & Practitioners*. 2013;27(2 Suppl):S5-17; quiz S8-9.
67. 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;67(5):691-8.
68. Robison RG, Pongracic JA. Chapter 23: Food allergy. *Allergy Asthma Proc*. 2012;33 Suppl 1:S77-9.
69. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S116-25.
70. Arias K, Wasserman S, Jordana M. Management of food-induced anaphylaxis: unsolved challenges. *Curr Clin Pharmacol*. 2009;4(2):113-25.
71. Burks AW, Jones SM, Boyce JA, Sicherer SH, Wood RA, Assa'ad A, et al. NIAID-sponsored 2010 guidelines for managing food allergy: applications in the pediatric population. *Pediatrics*. 2011;128(5):955-65.
72. Soares-Weiser K, Takwoingi Y, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. The diagnosis of food allergy: a systematic review and meta-analysis. *Allergy*. 2013:E-pub ahead of print.
73. Borres MP, Ebisawa M, Eigenmann PA. Use of allergen components begins a new era in pediatric allergology. *Pediatr Allergy Immunol*. 2011;22(5):454-61.
74. Niggemann B, Beyer K. Adrenaline autoinjectors in food allergy: in for a cent, in for a euro? *Pediatr Allergy Immunol*. 2012;23(6):506-8.
75. 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;42(2):284-92.
76. Rudders SA, Banerji A. An update on self-injectable epinephrine. *Curr Opin Allergy Clin Immunol*. 2013;13(4):432-7.
77. Gupta RS, Dyer AA, Jain N, Greenhawt MJ. Childhood food allergies: current diagnosis, treatment, and management strategies. *Mayo Clinic proceedings Mayo Clinic*. 2013;88(5):512-26.
78. Hill DJ, Hosking CS, de Benedictis FM, Oranje AP, Diepgen TL, Bauchau V. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin Exp Allergy*. 2008;38(1):161-8.
79. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics*. 1998;101(3):E8.
80. Wood RA. The natural history of food allergy. *Pediatrics*. 2003;111(6 Pt 3):1631-7.
81. Tsai HJ, Kumar R, Pongracic J, Liu X, Story R, Yu Y, et al. Familial aggregation of food allergy and sensitization to food allergens: a family-based study. *Clin Exp Allergy*. 2009;39(1):101-9.
82. Hourihane JO, Knulst AC. Thresholds of allergenic proteins in foods. *Toxicology and applied pharmacology*. 2005;207(2 Suppl):152-6.
83. Brockow K, Ring J. Food anaphylaxis. *Analytical and bioanalytical chemistry*. 2009;395(1):17-23.

84. Bindslev-Jensen C, Briggs D, Osterballe M. Can we determine a threshold level for allergenic foods by statistical analysis of published data in the literature? *Allergy*. 2002;57(8):741-6.
85. Blom WM, Vlieg-Boerstra BJ, Kruizinga AG, van der Heide S, Houben GF, Dubois AE. Threshold dose distributions for 5 major allergenic foods in children. *J Allergy Clin Immunol*. 2013;131(1):172-9.
86. Eller E, Hansen TK, Bindslev-Jensen C. Clinical thresholds to egg, hazelnut, milk and peanut: results from a single-center study using standardized challenges. *Ann Allergy Asthma Immunol*. 2012;108(5):332-6.
87. Glaumann S, Nopp A, Johansson SG, Borres MP, Nilsson C. Oral peanut challenge identifies an allergy but the peanut allergen threshold sensitivity is not reproducible. *PLoS One*. 2013;8(1):e53465.
88. 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;22(6):568-74.
89. Calvani M, Cardinale F, Martelli A, Muraro A, Pucci N, Savino F, et al. Risk factors for severe pediatric food anaphylaxis in Italy. *Pediatr Allergy Immunol*. 2011;22(8):813-9.
90. 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;122(2):286-9.
91. Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, Joseph L, Harada L, Allen M, et al. Inadvertent exposures in children with peanut allergy. *Pediatr Allergy Immunol*. 2012;23(2):133-9.
92. Yu JW, Kagan R, Verreault N, Nicolas N, Joseph L, St Pierre Y, et al. Accidental ingestions in children with peanut allergy. *J Allergy Clin Immunol*. 2006;118(2):466-72.
93. Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *J Allergy Clin Immunol*. 2007;119(4):1018-9.
94. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med*. 1992;327(6):380-4.
95. Ben-Shoshan M, Clarke AE. Anaphylaxis: past, present and future. *Allergy*. 2011;66(1):1-14.
96. Shah E, Pongracic J. Food-induced anaphylaxis: who, what, why, and where? *Pediatr Ann*. 2008;37(8):536-41.
97. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol*. 2012;129(5):1187-97.
98. 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;21(4 Pt 1):586-94.
99. King RM, Knibb RC, Hourihane JO. Impact of peanut allergy on quality of life, stress and anxiety in the family. *Allergy*. 2009;64(3):461-8.
100. Mandell D, Curtis R, Gold M, Hardie S. Anaphylaxis: how do you live with it? *Health Soc Work*. 2005;30(4):325-35.
101. Marklund B, Ahlstedt S, Nordstrom G. 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.
102. Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life in food hypersensitive schoolchildren and their families: parents' perceptions. *Health and quality of life outcomes*. 2006;4:48.
103. Ostblom E, Egmar AC, Gardulf A, Lilja G, Wickman M. The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. *Allergy*. 2008;63(2):211-8.
104. Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. *Ann Allergy Asthma Immunol*. 2001;87(6):461-4.
105. Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. *Pediatr Allergy Immunol*. 2003;14(5):378-82.

106. Primeau MN, Kagan R, Joseph L, Lim H, Dufresne C, Duffy C, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. *Clin Exp Allergy*. 2000;30(8):1135-43.
107. Klinnert MD, Robinson JL. Addressing the psychological needs of families of food-allergic children. *Curr Allergy Asthma Rep*. 2008;8(3):195-200.
108. Rouf K, White L, Evans K. A qualitative investigation into the maternal experience of having a young child with severe food allergy. *Clinical child psychology and psychiatry*. 2012;17(1):49-64.
109. Munoz-Furlong A. Daily coping strategies for patients and their families. *Pediatrics*. 2003;111(6 Pt 3):1654-61.
110. Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food allergy on the daily activities of children and their families. *Ann Allergy Asthma Immunol*. 2006;96(3):415-21.
111. Parker J, Stanworth H. 'Go for it! Towards a critical realist approach to voluntary risk-taking. *Health, Risk & Society*. 2005;7(4):319-36.
112. Rous T, Hunt A. Governing peanuts: the regulation of the social bodies of children and the risks of food allergies. *Social science & medicine (1982)*. 2004;58(4):825-36.
113. Nettleton S, Woods B, Burrows R, Kerr A. Food allergy and food intolerance: towards a sociological agenda. *Health (London)*. 2009;13(6):647-64.
114. Gallagher M, Worth A, Sheikh A. Clinical allergy has much to gain from engagement with qualitative research. *Allergy*. 2009;64(8):1117-9.
115. DunnGalvin A, Gaffney A, Hourihane JO. Developmental pathways in food allergy: a new theoretical framework. *Allergy*. 2009;64(4):560-8.
116. MacKenzie H, Roberts G, van Laar D, Dean T. Teenagers' experiences of living with food hypersensitivity: a qualitative study. *Pediatr Allergy Immunol*. 2010;21(4 Pt 1):595-602.
117. Marklund B, Wilde-Larsson B, Ahlstedt S, Nordstrom G. Adolescents' experiences of being food-hypersensitive: a qualitative study. *BMC nursing*. 2007;6:8.
118. 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;40(10):1533-40.
119. Fenton NE, Elliott SJ, Cicutto L, Clarke AE, Harada L, McPhee E. Illustrating risk: anaphylaxis through the eyes of the food-allergic child. *Risk analysis : an official publication of the Society for Risk Analysis*. 2011;31(1):171-83.
120. Gillespie CA, Woodgate RL, Chalmers KI, Watson WT. "Living with risk": mothering a child with food-induced anaphylaxis. *J Pediatr Nurs*. 2007;22(1):30-42.
121. Akeson N, Worth A, Sheikh A. The psychosocial impact of anaphylaxis on young people and their parents. *Clin Exp Allergy*. 2007;37(8):1213-20.
122. 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 : journal of the General Practice Airways Group*. 2012;21(4):392-7.
123. Henwood K, Pidgeon N, Sarre S, Simmons P, Smith N. Risk, framing and everyday life: Epistemological and methodological reflections from three socio-cultural projects. *Health, Risk & Society*. 2008;10(5):421-38.
124. *Statistical Yearbook of Sweden 2007*, Statistics Sweden, Stockholm, Sweden2007.
125. Morková I, Linell p, Grossen M, Salazar Orvig A. *Dialogue in Focus Groups. Exploring Socially Shared Knowledge*. London: Equinox Publishing Ltd; 2007.
126. Ben-Shoshan M, La Vieille S, Eisman H, Alizadehfar R, Mill C, Perkins E, et al. Anaphylaxis treated in a Canadian pediatric hospital: Incidence, clinical characteristics, triggers, and management. *J Allergy Clin Immunol*. 2013;132(3):739-41.e3.
127. Huang F, Chawla K, Jarvinen KM, Nowak-Wegrzyn A. Anaphylaxis in a New York City pediatric emergency department: triggers, treatments, and outcomes. *J Allergy Clin Immunol*. 2012;129(1):162-8.e1-3.

128. de Silva IL, Mehr SS, Tey D, Tang ML. Paediatric anaphylaxis: a 5 year retrospective review. *Allergy*. 2008;63(8):1071-6.
129. Fuzak JK, Trainor J. Comparison of the incidence, etiology, and management of anaphylaxis over time. *Pediatr Emerg Care*. 2013;29(2):131-5.
130. Russell S, Monroe K, Losek JD. Anaphylaxis management in the pediatric emergency department: opportunities for improvement. *Pediatr Emerg Care*. 2010;26(2):71-6.
131. Simons FE. Anaphylaxis in infants: can recognition and management be improved? *J Allergy Clin Immunol*. 2007;120(3):537-40.
132. Rudders SA, Banerji A, Clark S, Camargo CA, Jr. Age-related differences in the clinical presentation of food-induced anaphylaxis. *J Pediatr*. 2011;158(2):326-8.
133. Rudders SA, Banerji A, Corel B, Clark S, Camargo CA, Jr. Multicenter study of repeat epinephrine treatments for food-related anaphylaxis. *Pediatrics*. 2010;125(4):e711-8.
134. De Swert LF, Bullens D, Raes M, Dermaux AM. Anaphylaxis in referred pediatric patients: demographic and clinical features, triggers, and therapeutic approach. *Eur J Pediatr*. 2008;167(11):1251-61.
135. Braganza SC, Acworth JP, McKinnon DR, Peake JE, Brown AF. Paediatric emergency department anaphylaxis: different patterns from adults. *Arch Dis Child*. 2006;91(2):159-63.
136. Hoffer V, Scheuerman O, Marcus N, Levy Y, Segal N, Lagovsky I, et al. Anaphylaxis in Israel: experience with 92 hospitalized children. *Pediatr Allergy Immunol*. 2011;22(2):172-7.
137. Mehl A, Wahn U, Niggemann B. Anaphylactic reactions in children--a questionnaire-based survey in Germany. *Allergy*. 2005;60(11):1440-5.
138. 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;122(1):133-8.
139. Ferrari GG, Eng PA. IgE-mediated food allergies in Swiss infants and children. *Swiss medical weekly*. 2011;141:w13269.
140. Clark AT, Anagnostou K, Ewan PW. Cashew nut causes more severe reactions than peanut: case-matched comparison in 141 children. *Allergy*. 2007;62(8):913-6.
141. Boyano-Martinez T, Garcia-Ara C, Pedrosa M, Diaz-Pena JM, Quirce S. Accidental allergic reactions in children allergic to cow's milk proteins. *J Allergy Clin Immunol*. 2009;123(4):883-8.
142. Fleischer DM, Perry TT, Atkins D, Wood RA, Burks AW, Jones SM, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. *Pediatrics*. 2012;130(1):e25-32.
143. Kapoor S, Roberts G, Bynoe Y, Gaughan M, Habibi P, Lack G. Influence of a multidisciplinary paediatric allergy clinic on parental knowledge and rate of subsequent allergic reactions. *Allergy*. 2004;59(2):185-91.
144. Flinterman AE, Pasmans SG, Hoekstra MO, Meijer Y, van Hoffen E, Knol EF, et al. Determination of no-observed-adverse-effect levels and eliciting doses in a representative group of peanut-sensitized children. *J Allergy Clin Immunol*. 2006;117(2):448-54.
145. Wainstein BK, Studdert J, Ziegler M, Ziegler JB. Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level. *Pediatr Allergy Immunol*. 2010;21(4 Pt 1):603-11.
146. Ewan PW, Clark AT. Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: proposal for good practice. *Clin Exp Allergy*. 2005;35(6):751-6.
147. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics*. 1998;102(1):e6.
148. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol*. 2001;107(1):191-3.
149. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol*. 2007;119(4):1016-8.

150. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy*. 2000;30(8):1144-50.
151. 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;41(6):869-77.
152. Mullins RJ. Anaphylaxis: risk factors for recurrence. *Clin Exp Allergy*. 2003;33(8):1033-40.
153. 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;35(6):746-50.
154. DeMuth KA, Fitzpatrick AM. Epinephrine autoinjector availability among children with food allergy. *Allergy Asthma Proc*. 2011;32(4):295-300.
155. Kim JS, Sinacore JM, Pongracic JA. Parental use of EpiPen for children with food allergies. *J Allergy Clin Immunol*. 2005;116(1):164-8.
156. Sicherer SH, Forman JA, Noone SA. Use assessment of self-administered epinephrine among food-allergic children and pediatricians. *Pediatrics*. 2000;105(2):359-62.
157. Arkwright PD, Farragher AJ. Factors determining the ability of parents to effectively administer intramuscular adrenaline to food allergic children. *Pediatr Allergy Immunol*. 2006;17(3):227-9.
158. Chad L, Ben-Shoshan M, Asai Y, Cherkaoui S, Alizadehfar R, St-Pierre Y, et al. A majority of parents of children with peanut allergy fear using the epinephrine auto-injector. *Allergy*. 2013;68(12):1605-9.
159. Simons FE, Clark S, Camargo CA, Jr. Anaphylaxis in the community: learning from the survivors. *J Allergy Clin Immunol*. 2009;124(2):301-6.
160. Simons KJ, Simons FE. Epinephrine and its use in anaphylaxis: current issues. *Curr Opin Allergy Clin Immunol*. 2010;10(4):354-61.
161. Choo K, Sheikh A. Action plans for the long-term management of anaphylaxis: systematic review of effectiveness. *Clin Exp Allergy*. 2007;37(7):1090-4.
162. Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilo MB, et al. Management of anaphylaxis: a systematic review. *Allergy*. 2013:E-pub ahead of print.
163. Nurmatov U, Worth A, Sheikh A. Anaphylaxis management plans for the acute and long-term management of anaphylaxis: a systematic review. *J Allergy Clin Immunol*. 2008;122(2):353-61, 61.e1-3.
164. 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;117(6):1440-5.
165. Noimark L, Gardner J, Warner JO. Parents' attitudes when purchasing products for children with nut allergy: a UK perspective. *Pediatr Allergy Immunol*. 2009;20(5):500-4.
166. Zurzolo GA, Koplin JJ, Mathai ML, Tang MK, Allen KJ. Perceptions of precautionary labelling among parents of children with food allergy and anaphylaxis. *The Medical journal of Australia*. 2013;198(11):621-3.
167. 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;120(1):171-6.
168. Zurzolo GA, Allen KJ, Taylor SL, Shreffler WG, Baumert JL, Tang ML, et al. Peanut Allergen Threshold Study (PATS): validation of eliciting doses using a novel single-dose challenge protocol. *Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology*. 2013;9(1):35.
169. Marrs T, Lack G. Why do few food-allergic adolescents treat anaphylaxis with adrenaline?--Reviewing a pressing issue. *Pediatr Allergy Immunol*. 2013;24(3):222-9.
170. Hu W, Grbich C, Kemp A. Parental food allergy information needs: a qualitative study. *Arch Dis Child*. 2007;92(9):771-5.
171. Guba EG. Criteria for assessing the trustworthiness of naturalistic inquiries. *Educational Communication and Technology Journal*. 1981;29:75-91.

172. Shenton AK. Strategies for ensuring trustworthiness in qualitative research projects. *Education for Information*. 2004;22:63-75.
173. Clark S, Gaeta TJ, Kamarthi GS, Camargo CA. ICD-9-CM coding of emergency department visits for food and insect sting allergy. *Ann Epidemiol*. 2006;16(9):696-700.
174. Harduar-Morano L, Simon MR, Watkins S, Blackmore C. Algorithm for the diagnosis of anaphylaxis and its validation using population-based data on emergency department visits for anaphylaxis in Florida. *J Allergy Clin Immunol*. 2010;126(1):98-104.e4.
175. Heary CM, Hennessy E. The use of focus group interviews in pediatric health care research. *Journal of pediatric psychology*. 2002;27(1):47-57.
176. Krueger RA. *Focus groups: A practical guide for applied research*. 2nd ed. ed. London: Sage; 1994.
177. Vaughn S, Schumm JS, Sinagub J. *Focus group interviews in education and psychology*. London: Sage; 1996.
178. Morgan D. Focus groups. *Annual Review on Sociology*. 1996;22:129-52.
179. Smith MW. Ethics in focus groups: A few concerns. *Qualitative Health Research*. 1995;5:478-86.
180. Pinczower GD, Bertalli NA, Bussmann N, Hamidon M, Allen KJ, DunnGalvin A, et al. The effect of provision of an adrenaline autoinjector on quality of life in children with food allergy. *J Allergy Clin Immunol*. 2013;131(1):238-40 e1.
181. Allen KJ, Remington BC, Baumert JL, Crevel RW, Houben GF, Brooke-Taylor S, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): Clinical implications. *J Allergy Clin Immunol*. 2014;133(1):156-64.