Food hypersensitivity among schoolchildren

-prevalence, Health-Related Quality of Life and experiences of double-blind placebo-controlled food challenges

The Obstructive Lung Disease in Northern Sweden (OLIN) Studies, Thesis XVIII.

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To all the people who are loving and kind to me.
Thank you for the sunshine
you bring into my life.
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Abstract

Background
The prevalence of reported food hypersensitivity among children has increased in Western countries. However, the prevalence varies largely due to differences in methods used in different studies. Double-blind placebo-controlled food challenge (DBPCFC) is the most reliable method to verify or exclude food hypersensitivity. The use of double-blind food challenges is increasing in clinical praxis, but since the method is time- and resource-consuming it is rarely used in population-based cohort studies. There is a lack of knowledge on how adolescents and mothers experience participation in double-blind placebo-controlled food challenges and to what extent the food is reintroduced after a negative challenge. While several studies have described the impact of IgE-mediated food allergy on Health-Related Quality of Life (HRQL), few studies have described HRQL among children with other food hypersensitivity phenotypes.

Aim
The aim of this thesis was to estimate the prevalence of reported food hypersensitivity, associated risk factors, and symptom expressions among schoolchildren. We also examined HRQL among children with total elimination of cow’s milk, hen’s egg, fish or wheat due to food hypersensitivity as a group compared with children with unrestricted diet, and after we categorised the children with eliminated foods into different phenotypes of FHS. Finally, adolescents’ and mothers’ experience of DBPCFC was examined as well if the food had been reintroduced.

Methods
Three studies were based on the Obstructive Lung Disease in Northern Sweden (OLIN) paediatric cohort II. The cohort was recruited in 2006 when all children in first and second grade (7-8 years) in three municipalities in Norrbotten were invited to a parental questionnaire study and 2,585 (96% of invited) participated. The questionnaire included questions about food hypersensitivity, asthma, rhinitis, eczema and possible risk factors. The children in two municipalities were also invited to skin prick testing with 10 airborne allergens, and 1,700 (90%) participated. Paper I is based on this initial survey of the cohort.

Four years later, at age 11-12 years, the cohort was followed up using the same methods and with the same high participation rate. At the follow-up, 125
children (5% of the cohort) reported total elimination of cow’s milk, hen’s egg, fish or wheat due to food hypersensitivity. These children were invited to a clinical examination and to complete a generic (KIDSCREEN-52) and a disease-specific HRQL questionnaire (FAQLQ-TF) (n=75). Based on the clinical examination the children were categorised into different phenotypes of food hypersensitivity: current food allergy, outgrown food allergy and lactose intolerance. In addition, a random sample of children with unrestricted diet from the same cohort, answered the generic questionnaire (n=209). Paper II is based on this HRQL study.

Children categorised as having current food allergy were invited to a further evaluation including DBPCFC. Eighteen months after the challenges, these children were interviewed about their experiences during and after the challenge (n=17). Paper III is based on these interviews.

Paper IV was based on interviews with mothers to children referred to a paediatric allergy specialist for evaluation of food allergy using DBPCFC (n=8). In the two interview studies results were analysed using qualitative content analysis.

**Results**

At age 7-8 years, the prevalence of reported food hypersensitivity was 21%. Food hypersensitivity to milk, egg, fish, wheat or soy was reported by 10.9% and hypersensitivity to fruits or nuts by 14.6%. The most common essential food to trigger symptoms was milk, reported by 9%. The most frequently reported food induced symptoms, were oral symptoms mainly caused by fruits, followed by gastrointestinal symptoms mainly caused by milk. The risk factor pattern was different for food hypersensitivity to milk compared to hypersensitivity to other foods.

No significant difference in distribution in generic or disease-specific HRQL was found among children with reported total elimination of milk, egg, fish and/or wheat due to FHS compared to children with unrestricted diet. However, a trend indicated that the disease-specific HRQL was most impaired among children with current food allergy compared to children with outgrown food allergy and lactose intolerance. The proportion of poor HRQL defined as ≥75 percentile was significantly higher among children with current food allergy than the other phenotypes.

A DBPCFC was an opportunity for the adolescents and the mothers to overcome the fear of reactions to food that had been eliminated for a long time. After the challenge, when the food was partially or fully reintroduced, socializing became easier and both adolescents and mothers experienced more freedom regarding food intake. A negative challenge was not consistently associated with
reintroduction of the food. Reasons for reintroduction failure were fear of allergic reactions, that the adolescent did not like the taste of the food, or that living with an elimination diet was considered as normal.

**Conclusion**

In this population-based study, one in five of children at age 7-8 years reported food hypersensitivity to any food. The generic HRQL was similar among children with and without food hypersensitivity. However, poor disease-specific HRQL was more common among children with *current food allergy* compared to children with other FHS phenotypes. If the tested food was reintroduced after a DBPCFC, both adolescents and mothers described a changed life with less fear, and that life had become easier regarding meal preparations and social events. As reintroduction failure was present despite a negative food challenge, follow-ups and evaluations of food reintroduction should be performed independent of the outcome of a food challenge.
Sammanfattning på svenska

Bakgrund


Syfte

Syfte med avhandlingen var att undersöka rapporterad förekomst av födoämnesöverkänslighet, riskfaktorer och symtomuttryck bland skolbarn. Vi har även studerat hälsorelaterad livskvalitet bland barn som helt eliminerat baslivsmedel, som hel grupp jämfört med barn utan eliminerad föda, samt efter att barnen kategoriserats i olika fenotyper av födoämnesöverkänslighet. Ett ytterligare syfte var att beskriva ungdomars och mödrars upplevelser, konsekvenser av DBPCFC samt i vilken omfattning livsmedlet återintroducerades.

Metod

Tre studier baseras på en barnkohort som rekryterades 2006 inom OLIN studierna (Obstruktiv Lungsjukdom i Norrbotten). Kohorten innefattade alla barn i årskurs 1 och 2 (7-8 år) i Luleå, Kiruna och Piteå där 2585 (96 % av de inbjudna) deltog i en föräldrabesvarad enkät. Enkäten innehöll frågor om födoämnesöverkänslighet, astma, rinit, eksem och möjliga riskfaktorer. Barn från Kiruna och Luleå inbjöds även till pricktest med 10 luftburna allergen och 1700 (90 %) deltog. Artikel I baseras på denna initiala enkätstudie.

Fyra år senare följdes kohorten upp med samma metoder och höga deltagande. Totalt 125 barn (5 % av kohorten) uppgav total elimination av mjölk, ägg, fisk och/eller vete på grund av födoämnesöverkänslighet. Dessa barn inbjöds till en klinisk undersökning och 94 barn deltog. Sjuttiofem (80 %) av dessa barn besvarade hälsorelaterade livskvalitetsfrågor innefattande det generiska...
mätinstrumentet KIDSCREEN-52 samt det sjukdomsspecifika frågeformuläret FAQLQ-TF. Frågeformuläret KIDSCREEN-52 skickades även till ett slumpurval av barn utan eliminationskost från samma kohort, och 209 barn (65 %) deltog. Artikel II baseras på denna hälsorelaterade livskvalitetsstudie.

Baserat på den kliniska undersökningen kategoriserades barnen med eliminierad kost i olika fenotyper av födoämnesöverkänslighet: pågående födoämnesallergi, utläkt födoämnesallergi och laktosintolerans. De barn som bedömdes ha pågående födoämnesallergi inbjöds till DBPCFC. Arton månader efter provokationen intervjuades deltagarna om sina upplevelser av provokationen och i vilken omfattning livsmedlet återintroducerades. Artikel III baseras på dessa intervjuer.

Den fjärde studien baseras på intervjuer av mödrar vars barn remitterats till en pediatrisk barnallergolog för utredning av misstänkt födoämnesallergi med DBPCFC. Intervjuerna har analyserats med kvalitativ innehållsanalys.

Resultat

Vid 7-8 år var prevalensen av rapporterad födoämnesöverkänslighet 21 %. Överkänslighet mot basföda (mjölk, ägg, fisk, vete eller soja) rapporterades av 10.9% och 14.6% uppgav att de reagerade på frukt eller nötter. Klåda i munnen var det vanligaste rapporterade födoämnesutlösta symtomet som huvudsakligen orsakades av frukt. Det näst vanligaste symtomet var mag- och tarmbesvär, huvudsakligen orsakat av mjölk. Riskfaktormönstret för födoämnesöverkänslighet mot mjölk skiljde sig från överkänslighet mot andra födoämnen.

Vi fann ingen statistiskt signifikant skillnad i generisk eller sjukdomsspecifik hälsorelaterad livskvalitet mellan barn som helt eliminerat mjölk, ägg, fisk eller vete på grund av födoämnesöverkänslighet jämfört med barn utan eliminierad kost. En trend indikerade att barn med pågående födoämnesallergi hade sämre sjukdomsspecifik hälsorelaterad livskvalitet jämfört med barn med utläkt födoämnesallergi eller laktosintolerans. Dålig livskvalitet, definierat som den ≥75e percentilen i det sjukdomsspecifika frågeformuläret, var vanligast hos barn med pågående födoämnesallergi.

Deltagande i DBPCFC var en möjlighet för tonåringar och mödrar att övervinna rädslan för födoämnesorsakade symtom. I de fall då det testade livsmedlet helt eller delvis återintroducerades efter provokationen, upplevde både tonåringarna och mödrarna att det sociala umgånet blev lättare och att de inte längre behövde ha samma kontroll över födoämnesintaget. Ett negativt provokationsutfall resultera inte alltid i att det testade livsmedlet
återintroducerades i kosten. Orsaker till att inte återintroducera födoämnet var rädsla för allergiska reaktioner, att livsmedlet inte smakade gott och att det upplevdes som normalt att leva ett liv utan det eliminerade livsmedlet.

**Slutsats**

Vart femte barn rapporterade någon form av födoämnesöverkänslighet i denna populationsbaserade studie. Det var ingen signifikant skillnad i generisk livskvalitet mellan barn med och utan födoämnesöverkänslighet men barn med pågående födoämnesallergi tenderade att ha sämre sjukdomsspecifik livskvalitet jämfört med barn med utläkt födoämnesallergi och laktosintolerans. De deltagare som återintroducerade det testade livsmedlet efter provokationstestet upplevde att livet var mindre begränsat jämfört med innan provokationen. Alla återintroducerade inte det testade livsmedlet trots en negativ provokation, vilket styrker Vikten av uppföljning och utvärdering av födoämnesprovokationer.
## List of Abbreviations

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>DBPCFC</td>
<td>Double-blind placebo-controlled food challenge</td>
</tr>
<tr>
<td>FAQLQ-TF</td>
<td>Food Allergy Quality of Life Questionnaire Teenager Form</td>
</tr>
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<td>FHS</td>
<td>Food Hypersensitivity</td>
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<tr>
<td>HRQL</td>
<td>Health-Related Quality of Life</td>
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<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
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<tr>
<td>IQ</td>
<td>Interquartile Range</td>
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<tr>
<td>ISAAC</td>
<td>International Study of Allergy and Asthma in Childhood</td>
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<tr>
<td>KIDSCREEN-52</td>
<td>Health-Related Quality of Life Screening Instrument for Children and Adolescents</td>
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<tr>
<td>MID</td>
<td>clinical Minimal Important Difference</td>
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<tr>
<td>PCC</td>
<td>Person Centered Care</td>
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<tr>
<td>SPT</td>
<td>Skin Prick Test</td>
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<tr>
<td>tTGA</td>
<td>Tissue Transglutaminase IgA antibodies</td>
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<td>OAS</td>
<td>Oral Allergy Syndrome</td>
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<tr>
<td>OLIN</td>
<td>Obstructive Lung Disease in Northern Sweden studies</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<td>QoL</td>
<td>Quality of Life</td>
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Original Papers


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Introduction

My interest in the topic “food hypersensitivity among schoolchildren” started around the millennium shift during my work as a nurse specialised in allergy. Over the years, the number of children reporting adverse reactions to foods have increased. Therefore, the allergy team in our paediatric clinic performs an increasing number of open food challenges, to verify or rule out food hypersensitivity. During the first years of my work as an allergy nurse, I had no knowledge on how common this health problem was in society, but the increasing amount of children reporting food hypersensitivity became a clinical problem, which was difficult to handle.

In addition, open food challenges were sometimes difficult to interpret due to uncharacteristic symptoms and/or late onset symptoms. To improve our diagnostic methods, my colleagues and I started to develop recipes for double-blind placebo-controlled food challenges, the gold standard for diagnosing food hypersensitivity. When performing these double-blind challenges, I became aware that the children and their parents often experienced fear, since they did not know what symptoms to expect during the challenge. The lack of data on how common reported food hypersensitivity was in the population and also the of lack studies of studies reporting participants’ experiences of double-blind placebo-controlled food challenges, were the starting point of my PhD studies. The opportunity to join the Obstructive Lung disease in Northern Sweden (OLIN) studies made this thesis possible.

The research team from the pediatric allergy team, Lisbeth Nordström, Anna Winberg and myself, working with data sampling in Norrbotten. The picture is from when we visited the mines in Gällivare.
Background

More than two thousand years ago Hippocrates (460-377 BC) described that food can cause illness, diseases and health concerns for some people: “Cheese does not harm all men alike, some can eat their fill out without the slightest hurt...others come off badly. But if cheese were bad for the human constitution without exception, it would have hurt all”. From the same period an often quoted line from a poem of Titus Lucretius Cato (98-55 BC) “what is food to one, to another is rank poison” strongly suggests an understanding of adverse reactions to foods even in early days [1].

During the 1900s many important discoveries and lessons were learned. In 1906, the paediatrician Clemens von Pirquet proposed the term “allergy” (from the Greek allos meaning “other” and ergon meaning “reaction”) for a changed reactivity induced by what he termed an "allergen”, a foreign substance. The term was coined after he recognised that patients who had received injections of horse serum or smallpox vaccine usually had quicker and more severe reactions to second injections. Pirquet was also the precursor to the PPD test, a screening tool for tuberculosis [2, 3]. Both skin prick test (SPT) and Immunoglobulin E (IgE) are helpful tools for the diagnosis of food allergy and useful in epidemiologic research. The first attempt to perform SPT was made by the physician Prausnitz in 1921. He injected sera from his colleague named Kustner, who was suffering from a severe fish allergy into his own skin. The next day he injected fish extract to the same area, with a positive local reaction. This test (Prausnitz-Kustner test) proved that sensitivity could be transferred by a factor in serum from an allergic to a non-allergic individual [4]. This method was further developed and became known as the skin prick test (SPT). In 1967, two separate research groups Mr and Mrs Ishazaka, and Johansson together with Bennich identified IgE [5, 6]. After IgE was identified, radioallergosorbent test (RAST) was developed, a method to measure allergic sensitization [7].

SPT and IgE-levels are sensitive tools for identifying sensitisation to specific IgE-antibodies but sensitisation often exists without clinical symptoms of food allergy [8]. Therefore, it is often necessary to perform food challenges to establish a correct food allergy diagnosis [9, 10]. Charles May and colleagues started studies with double-blind placebo-controlled food challenges (DBPCFC) during the mid-70s [11] resulting in increased interest, clinical use, and development of challenge methods. DBPCFC is now the “gold standard” for diagnosing food allergy, but the methodology has not yet been fully standardized [12, 13].
Definitions of food hypersensitivity

There are different types of mechanisms that can cause adverse reactions to foods. In this thesis the terminology from the World Allergy Organization position paper is used [14]. The definition in this paper is based on terminology originally proposed by the European Academy of Allergy and Clinical Immunology (EAACI) [15].

Food hypersensitivity (FHS) is an umbrella term, defined as objective and reproducible signs or symptoms caused by foods in a dose that people normally can eat [14]. The term can be divided into two subsets: immunologic mechanism i.e. food allergy and non-immunologic mechanism i.e. food intolerance. Food allergy includes IgE and non IgE-mediated food reactions. FHS can also be caused by food intolerance. The most common food intolerances are caused by enzymatic defects in the digestive system or by histamine in foods. [14, 16]. A common enzymatic reaction is lactose intolerance [17] (Figure 1).

![Figure 1](image-url)  
**Figure 1.** Definition of food hypersensitivity. Modified from Johansson et al [15] and printed with permission from Wiley, Copyright @Munksgaard 2001.

In general different phenotypes of FHS are categorised according to the mechanisms that are presumed to be responsible (Figure 1).
**IgE-mediated food allergy**

IgE-mediated food allergy requires IgE sensitisation to the specific food but also the presence of symptoms after exposure to the food. Neither a positive SPT nor the presence of specific IgE are solely enough to diagnose IgE-mediated food allergy and neither do they predict reaction severity [8]. In an IgE-mediated food allergy the symptoms usually start minutes and rarely more than two hours after exposure to the trigger food [18]. Clinical symptoms include e.g. skin symptoms, gastrointestinal symptoms and in some cases anaphylaxis, that can be life-threatening [19]. Common foods causing food allergy in childhood are cow’s milk, hen’s egg, wheat, soy, peanuts, tree nuts, fish and shellfish. In general, tolerance to milk, egg, wheat and soy is achieved during childhood whereas allergies to tree nut, peanut, fish and shellfish often persist into adulthood [9]. It has been shown that tolerance development is more common in food allergic children that are able to eat baked milk or egg compared to children allergic to milk and egg in any form [20, 21].

A secondary type of IgE-mediated food allergy is the **oral allergy syndrome** (OAS) or pollen associated food allergy syndrome [22]. OAS is triggered by a cross reaction between allergens in pollen and allergens in fresh fruits, nuts and vegetables. Sensitization to birch pollen, is strongly associated with OAS [23] and birch pollen allergy is common in Sweden [24]. Symptoms of OAS are usually mild and transient e.g. itching in the mouth and throat after exposure to the offending food, and systemic reactions rarely occur [25].

**Non IgE-mediated food allergy**

Non-IgE mediated food allergy includes a wide range of disorders mostly affecting the gastrointestinal tract and skin. The most common single food to cause non IgE-mediated food allergy is cow’s milk. Symptoms often occur hours to days after ingestion of the offending food [26, 27]. Diagnosis is based on a convincing history and resolution of symptoms if the culprit food is totally eliminated [28]. Some examples of non IgE-mediated food allergy are: **food protein induced enterocolitis syndrome** [29], **food protein induced enteropathy** [28] and **food induced allergic proctolitis** [26]. The age of resolution differs between studies, but is normally seen at young age [27, 30].

**Lactose intolerance**

Lactose intolerance does not involve the immune system [15]. Lactose is a disaccharide sugar found in both breast milk and dairy products. Lactose digestion takes place in the intestine, mediated by the enzyme lactase. Breastmilk, the main source of nutrition during the infant’s first months, is rich in lactose and most people are born with the ability to digest lactose. Down-
regulation of the enzyme lactase is caused by a specific genotype. This genotype is common in most parts of the world. In about 75% or more of the world’s population the ability to digest lactose is reduced at some point, but generally not earlier than 6-7 years. In northern Europe however, lactase persistence into adulthood is common [31, 32].

If the lactase enzyme is deficient, lactose osmotically attracts fluid into the bowel leading to diarrhea and flatulence [31]. Lactose intolerance may be troublesome, but is not considered a condition requiring medical treatment. There are variations in the amount of lactose that can be tolerated among lactose intolerant individuals [31] but it has been suggested that adolescents or adults with lactose intolerance can ingest up to 15 g (one cup of milk) in a single dose with no or minor symptoms if the milk is consumed together with other foods [33]. A secondary lactose intolerance can occur due to a damage to the intestinal mucosa by diseases like, e.g. celiac or crohn’s disease. In most cases, a secondary lactose intolerance resolves with the recovery of the intestine [31, 34].

**Prevalence of food hypersensitivity**

Few studies have focused on the umbrella term FHS. Most studies focus on food allergies that are mediated by IgE, but even among these studies there are large variations in the prevalence. Differences in the definition of food allergy is one possible explanation for these variations.

A review article stated that food allergy affects about 5 % of young children and 3-4 % of adults in westernized countries [10]. The prevalence of food allergy differs between countries. It is described that food allergy is more common in the Northern part than other parts of Europe [35]. Differences in prevalence can be attributed to cultural differences, e.g. different diets, including ingredients, cooking methods and time of introduction of different foods. For instance, the incidence of sesame allergy is higher in Israel and the incidence of rice allergy is higher in China and Japan [36] compared to other countries. The prevalence of reported food allergy also differs according to the study method used. In general, studies with objective testing report a lower prevalence than those without objective testing [37]. In a European meta-analysis the reported prevalence for all age groups of food allergy to cow’s milk, hen’s egg, peanut, tree nuts, fish and shellfish was 6.0% but the prevalence of challenge-proven allergy to these foods was 0.6% [35].

Studies have suggested that the prevalence of food allergy is increasing. However, only a few studies have examined time-trends in food allergy prevalence among children from the same geographic area. One study investigated the prevalence of peanut allergy from three cohorts of children
aged 3-4 years from Isle of Wight, UK. A significant increase was shown among children diagnosed with peanut allergy, based on sensitisation to peanuts and clinical history, from 0.5% in 1993 to 1.4% in 1998-2000 and with a non-statistically significant decrease to 1.2% in 2004-2005 [38]. Another study examined time trends in prevalence of allergy to a number of foods among two cohorts of children aged 0-24 months with suspected atopic symptoms related to foods, from the same geographic area in China. The prevalence of a positive SPT to egg, peanut, soy, fish, shrimp, wheat or orange increased from 9.9% in 1999 to 18.0% in 2009. Food allergy was confirmed by food challenges showing that food allergy had increased from 3.5% in 1999 to 7.7% in 2009. The most common food allergies in this study, was allergy to hen’s egg and cow’s milk [39].

A Swedish birth cohort study is one of the few studies that has examined the prevalence of FHS from birth to older ages. In this study the reported prevalence of FHS to any foods was 9.8% at age 1 years, 10.9% at 4 years of age and increased to 13.8% when the children were 8 years of age [40]. A Danish study examined the prevalence of FHS in an unselected group of young adults 22 years of age. Of 843 participants 26.5% reported FHS to foods [41]. Further, a meta-analysis investigating the prevalence of self-reported FHS to any food showed a variation of FHS prevalence from 3-35% due to differences in study methods, ages and geographic settings [37]. There might be cultural differences in the definition of FHS and how different symptoms are associated to food intake. In addition, many somatic conditions are mistakenly regarded as manifestations of FHS and together with an increasing awareness of different diets in many societies, [42] the prevalence of elimination diets are rapidly increasing.

**Associated factors**

A number of factors have been associated with food allergy. Several studies have indicated that having food allergy is a risk factor for asthma and having asthma is a risk for severe food allergy [43, 44]. Generally the presence of eczema in early childhood [45, 46] and a family history of atopic diseases [47] are described as associated factors of IgE-mediated food allergy. Microbial exposure, as having siblings, attending childcare and probiotic are possibly related to deceased risk of having food allergy while caesarean section is possibly related to an increased risk. However there is still a lack of clear evidence to support microbial protection and further studies are needed [48]. An early infant diet consisting of a variety of different foods is possibly associated with a reduced risk of food allergy [49]. Food allergy is more
common among boys than girls during childhood [50, 51], but more common among women than men after puberty [52].

Parental allergy, atopic diseases and FHS to peanut and tree nut during the child’s first four years in life have been associated to persistence of food related symptoms during adolescence [50]. Studies are inconsistent about associations between reported FHS and sex and further studies are needed. In some studies no difference in FHS between girls and boys are shown [53] while other studies show a higher prevalence of reported FHS among girls [54].

**Food challenges**

Food challenges are usually required to confirm the diagnosis of food allergy, to obtain knowledge about symptom manifestations or to prove oral tolerance to a given food [55]. Elimination of the offended food over a limited period of time, followed by a food challenge is the accepted standard method for diagnosing food allergy [56]. The diagnostic food challenge can be performed at home if the food induced symptoms are mild. For children at risk of serious systemic adverse reactions, food challenges should be performed at a hospital under medical supervision of specially trained personnel, with appropriate medications and equipment easily available [55].

Children diagnosed with food allergy should be followed-up at regular intervals. At these evaluations food challenges should be performed in order to monitor tolerance development and to avoid unnecessary dietary restrictions. The offending food influences the time to follow-up interval. The recommended time intervals for cow’s milk and hen’s egg are re-challenges every 6-12 months, while for peanut and tree nut, where allergy often persists, evaluations every 2 years is recommended, as long as accidental severe reaction has not occurred during that time [55].

**Open food challenges**

During an open challenge the personnel gives the patient increasing doses of the offending food, starting with small amounts. After each dose the patient is observed for a period of time, usually 30 minutes, and if there are no symptoms the doses are gradually increased. The total dose should approximately correspond to an age-appropriate portion size of the challenged food [57]. In an open food challenge, both the patient and the personnel know what is given during the challenge.
Double-blind placebo-controlled food challenges

The gold standard test to verify or rule out food allergy is double-blind placebo-controlled food challenge (DBPCFC) [55]. During the DBPCFC the patient is challenged with either placebo or offending food, although on separate days. There should be no detectable differences between placebo and the offending food regarding taste, smell or texture. Neither the patient nor the personnel conducting the challenge know what is given i.e. blinded test [56, 58].

Quality of Life versus Health-Related Quality of Life

Quality of Life (QoL) measures a subjective wellbeing and is therefore difficult to define. During the 1970s the use of QoL became important in health care since medical treatment made it possible to extend length of life with or without improvement of QoL. Kapkan and Bush used the term “well-years” as a measure of the value of a year in full health [59].

In 1995 the World Health Organization (WHO) defined QoL as “the individual’s perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns” [60]. The definition is a broad concept affected by, for example the individual’s physical and psychological health, social relationships and level of independence [61].

The term HRQL appeared in the mid-1980s. In one of the first papers on the subject, Torrance et al defined HRQL as a subgroup of QoL, and related HRQL to health status [62]. HRQL related to FHS is a relatively new research area. To my knowledge one of the first Swedish article was published in 2004 [63].

HRQL is often defined as self-perceived health status [64]. It is possible to have a chronic disease with an affected health but despite this experience a good self-perceived HRQL. Satisfaction with life is influenced by health, but health status only explains a small part of QoL or HRQL [64], and has different impacts during life. In addition, the opinion of what is a good HRQL differs from person to person. Accordingly, it is important to obtain responses via self-reports whenever possible. It is described that children from the age of eight years have the ability to estimate their HRQL, if the questionnaires are suitable for the children’s reading skills and age [65]. Although the terms QoL, health and HRQL are widely used in the literature, there is still no consensus about the definitions [64, 66].

The number of papers on QoL or HRQL among children or adults with food allergy or FHS was almost non-existent in the early 1990s, but has rapidly increased during the last decade (Figure 2).
Figure 2. Number of publications in PubMed database searched by (food allergy OR food hypersensitivity) quality of life and children ages 0-18 years or adults +19 (search performed January 2017).

**Health-Related Quality of Life instruments**

In order to measure HRQL two types of HRQL instruments can be used: generic or disease-specific HRQL questionnaires. Generic instruments are used if the purpose of a study is to compare the impact of HRQL between different subjects with different diseases or between subjects with a specific disease and a healthy group [67]. Disease-specific instruments focus on a particular disease e.g. food allergy [68] and are designed to have a good sensitivity for HRQL in subjects with the target disease. However, disease-specific instruments are not applicable in other patient groups and have only limited use in patients with multiple diagnoses. During the last decades, a large number of HRQL instruments has been developed for children. A review article published in 2006 found more than 50 HRQL instruments for use in children and adolescents, most of them being disease-specific instruments, and the number has probably increased since the study was performed [69].

Following an increased interest in measuring HRQL among children and adolescents with food allergy or FHS, a number of disease-specific instruments have been developed. Most instruments focus on food allergy and a fewer number focuses on the umbrella term FHS. Table 1 gives an overview of HRQL instruments available during the time of writing this thesis.
<table>
<thead>
<tr>
<th>Instrument</th>
<th>Definition: food allergy</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAQLQ-CF</td>
<td>Self-report for children 8-12 years</td>
<td>Flokstra-de Blok et al, 2009 [71]</td>
</tr>
<tr>
<td>FAQLQ-TF</td>
<td>Self-report for teenager 13-18 years</td>
<td>Flokstra-de Blok et al, 2008 [72]</td>
</tr>
<tr>
<td>FAQLQ-PF</td>
<td>Parent report for children 0-12 years</td>
<td>DunnGalvin et al, 2008 [73]</td>
</tr>
<tr>
<td>FAQLQ-PTF</td>
<td>Parent report for teenagers 13-18 years</td>
<td>The questionnaire are developed ([74, 75] but no studies have not yet used this questionnaire (search Dec 2016).</td>
</tr>
<tr>
<td>PFA-QL</td>
<td>Parent/ child report for children 6-16 years</td>
<td>Avery et al 2003 [76]</td>
</tr>
<tr>
<td>FAIS</td>
<td>Parent report for children 0-18 years</td>
<td>Bollinger et al, 2006 [77]</td>
</tr>
<tr>
<td>FAP-Q</td>
<td>Parent report for children 0-18 years</td>
<td>LeBovidge et al, 2006 [78]</td>
</tr>
<tr>
<td>FAQL-Teen</td>
<td>Self-report for teenagers 13-19 years</td>
<td>Resnick et al, 2010 [79]</td>
</tr>
</tbody>
</table>

**Definition: FHS**

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Definition: FHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLIP</td>
<td>Parent report for children 0.5-7 years (with cow’s milk FHS or other FHS) and the HRQL of the family.</td>
</tr>
<tr>
<td>The You and Your Food Allergy Scale</td>
<td>Self-report for teenagers 13-18 years with FHS</td>
</tr>
</tbody>
</table>
Quantitative studies about Health-Related Quality of Life among children with food hypersensitivity

Children and adolescents with food allergy only experience symptoms during allergic reactions, and for some subjects such reactions can be severe [56]. The feeling of not being in control during meals, always risking accidental intake of the culprit food and not knowing what symptoms might occur, can be a burden for those affected by food allergy as well as their families [82]. Activities such as social events and meal preparations may result in anxiety and increased stress levels for the food allergic child and his/her parents [77, 83].

Symptoms of food allergy can range from mild to severe [9] and it is described that severe symptoms, e.g. respiratory and cardiovascular symptoms, may contribute to a poor HRQL among children with IgE-mediated food allergy [84]. Even if these symptoms are severe, deaths caused by severe food reactions are extremely rare in Sweden. During the period 1993-96 compared to 1997-2003 the number of fatal cases have decreased from 1.75 to 0.86 per year [85].

Apart from food allergy severity, quantitative studies have found that: avoidance of more than two foods [86], atopic comorbidities [84], low parent income and parent-reported anaphylaxis [87] had a negative impact among children with IgE-mediated food allergy and their parents. It is still unknown if there is any association between the specific food avoided and the impact on HRQL. In some studies, no relation was found between food trigger and HRQL [77], while another study has shown that parents to children with milk and egg allergy have more impaired HRQL compared to parents to children with peanut and tree nut allergy [88]. In contrary, another study showed that children with peanut or soy allergy had a greater HRQL impairment than children allergic to other foods [89]. The impact of food allergy on HRQL may also be affected by the age of the child. A younger age of the child has been associated with increased parental anxiety and stress [78], but with a better HRQL for the food allergic child itself [90].

Further, self-perceived disease severity seems to have an equally strong impact on HRQL compared to objective food allergy severity established in a clinical setting [91, 92]. A multicentre study described predictors for poor HRQL in children and adults with self-perceived FHS and physician diagnosed food allergy in four European countries. For children in particularly perceived disease severity or having a soy or peanut allergy had a negative impact on HRQL. It was also shown that country of origin had an impact on HRQL in children, possible related to different attitudes to food allergy and different dietary traditions between countries. Interestingly, in this study HRQL was not affected in either adults or children, by experiences of anaphylaxis or by being prescribed an epinephrine auto-injector [89].
Health-Related Quality of Life after food challenges

A number of quantitative studies show the same result, i.e. that HRQL improves after a food challenge, independent of the challenge outcome [93, 94]. These findings indicate that food challenges are not only diagnostic tools [9], but can also be therapeutic, reducing anxiety and fear of unknown allergic reactions. Following a negative challenge, where the challenged food can be reintroduced, it has been shown that it is easier for the child to participate in social activities e.g. birthday parties and that it becomes easier to prepare meals both at home and in schools [95]. In addition, a positive food challenge can enhance the self-management skills in how to treat a possible food reaction [96].

It seems that DBPCFC have the same positive effects on HRQL as open food challenges. In a quantitative study, parental anxiety was measured before and after the children performed DBPCFC with peanut or hazelnut. Before the challenge, the levels of parental anxiety were high, but the anxiety levels were significantly reduced after the completed food challenge. A reduction in parental anxiety was found even if the child had a positive challenge outcome [97]. HRQL has also been compared among children, adolescents and adults who underwent a DBPCFC. The HRQL improved among children and adults after the DBPCFC, independent of the challenge outcome. However, among adolescents HRQL improved after a negative DBPCFC, but not after a positive challenge outcome [98]. These findings indicate that food challenges and their outcomes can be experienced in different ways among people in different age groups. Since much is still unknown about the effects of DBPCFC on HRQL, further studies are needed to clarify this subject.

The degree of reintroduction after food challenges are poorly studied. However, in a study a questionnaire was sent to parents of children who had participated in open food challenges to egg, milk or peanut with a negative challenge outcome. The questionnaire was answered by 75% (n=83). The challenged food was eaten regularly by 83% of the children, but the fear of accidental reactions had only been completely resolved among 37% of the parents [95]. In another study, parents to 157 children, who had participated in open food challenges or DBPCFC to peanut, hazelnut, milk or egg with a negative challenge outcome, answered a questionnaire. Of these, 28% had failed to reintroduce the challenged food and 16% had only partially reintroduced the food (in processed foods or traces). The main reasons for reintroduction failure were perceived adverse food reactions during the reintroduction, aversion to the food, fear of food induced symptoms and having a habit of avoiding the food [99].

Reintroduction failure after DBPCFC is also described in another study where parents to children who had performed DBPCFC with peanut were interviewed by their physician, with pre-defined questionnaires. Reintroduction of peanut failed in 32 % out of 103 challenges with a negative outcome. Symptoms
following peanut intake or food refusal were the most reported reasons for not reintroducing peanut in the child’s diet [100].

**Qualitative studies about experiences of living with food hypersensitivity**

To provide a deeper insight into what it can be like to live with FHS, qualitative studies can be used. So far, most qualitative studies on FHS have focused on living with the risk of anaphylaxis.

Both parents and adolescents have described that it is a balance between the importances of taking the risk of anaphylaxis seriously and not allowing the fear of an allergic reaction dominate their lives. On the other hand, adolescents’ and parents’ feelings regarding strategies for avoiding food allergic reactions may differ. It is possible that parents are more afraid of anaphylactic reactions than adolescents are. Mothers to children, with risk of anaphylactic reactions, have described fear and worrying about the child’s well-being as being an important part of parenting experiences [101]. Adolescents with risk of anaphylaxis tended to see their risk management strategies as “good enough”, even though their strategies were not always consistent with the best clinical practice [102]. Not only the symptoms related to the culprit food but also impaired social life due to food avoidance, may have a negative impact on the adolescents’ lives and HRQL [103, 104]. There are only a few qualitative studies of children’s or adolescents experiences of living with FHS. In one study, semi-structured interviews were performed among adolescents with FHS to a variety of foods. The adolescents described that having FHS was a way of life, but it was still burdensome [105] which adolescents also had described in another interview study [103].

**Experiences of food challenges**

There are few qualitative studies on participants’ experiences of food challenges, and further studies are needed. In one study, telephone interviews were performed with 46 parents of children, who had participated in open peanut challenges. The interviews were audio-recorded. Closed question responses were analysed using statistical methods and open question responses were thematically analysed. The parents described that the increased knowledge of the severity of the peanut allergy, the support provided by the staff, to determine that the symptoms were mild or that the outcome of the challenge was negative, were the most important experiences from the food challenge [106]. To my knowledge, aside from the studies in this thesis, no study has interviewed participants about their experiences of DBPCFC.
The OLIN studies

Three articles in this thesis are based on studies performed within the Obstructive Lung Disease in Northern Sweden (OLIN studies). Founded in 1985, the OLIN studies celebrated its 30-year anniversary in 2015. The research includes epidemiological studies about asthma, allergies and allergic sensitization among children and adults, chronic bronchitis and chronic obstructive pulmonary disease among adults, and health economics among adults and children [107]. Since the start more than 60 000 subjects aged 7-97 years have participated in studies initiated by the OLIN-study group.

The OLIN study area is Norrbotten, the northernmost province of Sweden and its research base is located in the city of Luleå. The research of the OLIN-studies has grown to a comprehensive activity with connections to several European countries, as well as the USA, Asia, Australia/ New Zealand. To date the OLIN studies have resulted in 18 doctoral theses and a large amounts of original- and review articles.

The paediatric part of the OLIN studies consists of two cohorts of children recruited in 1996 and 2006, respectively. In the latter cohort, the participants have also been examined concerning different aspects of FHS.
Rationale for the present thesis

Most studies about food hypersensitivity, and in particularly studies about HRQL, only include children with IgE-mediated food allergy. Furthermore, the studies are often based on hospital materials that are not representative for the general population. Thus, there is a lack of knowledge about HRQL among schoolchildren with FHS in population-based materials as well as HRQL in children with different phenotypes of FHS. Although there is ongoing research about the clinical usefulness of DBPCFC, there is still a lack of knowledge about how children and their parents experience participation in a blinded food challenge, and whether the challenged food is reintroduced after a negative challenge. Therefore, the overall aim with this thesis was to gain a deeper knowledge about prevalence of food hypersensitivity among schoolchildren, its effect on HRQL, and experiences during and after a DBPCFC.

Specific aims

- To investigate the prevalence and symptom expression of reported FHS in a large population-based cohort of children aged 7-8 years. The associations between FHS and asthma, rhinitis, eczema and other potential risk factors were also studied.

- To compare HRQL among children with and without complete elimination of cow’s milk, hen’s egg, fish or wheat due to FHS, and to study HRQL in relation to different FHS phenotypes.

- To investigate the experiences and consequences of DBPCFC in adolescents with food allergy.

- To investigate mothers’ experiences during their child’s negative DBPCFC, and the following reintroduction of the challenged food.
Materials and methods

Study area

This thesis is mainly based on data from a population-based cohort of children (Figure 3). The cohort is the second paediatric cohort within the OLIN studies in Norrbotten in Northern Sweden.

The county of Norrbotten is the northernmost and largest county in Sweden and covers about one fourth of the area of the country. The county of Norrbotten is divided into 14 municipalities, with only 250 000 inhabitants. The major part of the population is concentrated to the coastline of the Baltic Sea. In the inland, in Kiruna and Malmberget, two large iron ore mines are located, and the Kiruna mine is the largest and most modern underground iron ore mine in the world. Other large industrial productions include ironworks, paper-pulps, and hydropower plants. Today, sectors as communication, tourist, and service are steadily growing. In Luleå the University of Technology is located. Since 1856, Luleå is the county capital.

Paper I-IV were based on children recruited from three municipalities of the Norrbotten County: Luleå and Piteå located by the coast of the Baltic Sea and Kiruna located in the mountain area. Norrbotten has five hospitals: the county hospital is located in Sunderbyn outside Luleå. The local hospitals are located in Gällivare, Kalix, Kiruna and Piteå. The DBPCFC series (Paper III) were performed in the hospitals in Gällivare and Sunderbyn.

Paper IV was based on interviews with mothers to children referred to the paediatric allergy team at the Child and Adolescents Clinic at the University Hospital of Umeå. The clinic has the responsibility for specialist care of children and adolescents aged 0-18 years in Västerbotten County. The paediatric asthma and allergy team in Västerbotten consists of specialised nurses, doctors, dieticians and psychologists, from the departments of paediatrics in 3 cities; Umeå, Skellefteå and Lycksele. The hospital in Umeå is the central hospital for the county of Västerbotten and also the University Hospital of Northern Sweden.
**Study design**

**Paper I**

During early 2006, all children in grades 1 and 2 (aged 7-8 years) in the three municipalities Kiruna, Piteå and Luleå were invited to a parental questionnaire survey and 2,585 (96% of invited) participated. The questionnaire was distributed by the school teachers, completed at home by the parents, and returned to the school in a sealed envelope to the teachers who sent them back to the OLIN study group.

All children in Kiruna and Luleå were also invited to skin prick testing with 10 airborne allergens and 1,700 (90% of invited) participated. The tests were performed between January and April. Details on participation are described in Figure 3 and Table 2.
Table 2. Participating children by municipality 2006, presented as number of participants and percent of invited.

<table>
<thead>
<tr>
<th>2006</th>
<th>Questionnaire n (%)</th>
<th>SPT n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiruna</td>
<td>509 (99.2)</td>
<td>477 (93.0)</td>
</tr>
<tr>
<td>Luleå</td>
<td>1,350 (97.7)</td>
<td>1,223 (88.5%)</td>
</tr>
<tr>
<td>Piteå</td>
<td>726 (89.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Paper II**

During early 2010, when the children were 11-12 years of age, there was a follow-up study of the cohort. The parents of 2,612 children (96% of invited), answered the questionnaire as in 2006 [54]. At the follow-up in 2010, 1,657 (86% of invited) of the children participated in SPT, which was performed with identical materials and methods as in 2006. The SPT results were used for comparison of basic characteristics among participants and non-participants in Paper II. Details on study participation are described in Figure 3 and Table 3.

Table 3. Participating children by municipality 2010 presented as number of participants and percent of invited.

<table>
<thead>
<tr>
<th>2010</th>
<th>Questionnaire n (%)</th>
<th>SPT n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiruna</td>
<td>502 (96.5)</td>
<td>448 (86.2)</td>
</tr>
<tr>
<td>Luleå</td>
<td>1,364 (96.1)</td>
<td>1,209 (85.1)</td>
</tr>
<tr>
<td>Piteå</td>
<td>746 (91.8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

The 125 children (5% of the cohort) who reported total elimination of cow’s milk, hen’s egg, fish and/or wheat due to FHS in the 2010 questionnaire, were invited to a clinical examination and 94 (75% of invited) children participated. The clinical examinations were performed between October and November in 2010. Children with physician diagnosed celiac disease, as reported in the questionnaire, were not invited. The clinical examination included a structured interview and a blood sample for analyses of specific IgE to the culprit food. In addition, a celiac screening test was taken in children avoiding milk or wheat.

At the clinical examination visit, the children were invited to complete a disease-specific HRQL questionnaire FAQLQ-TF [72] and a generic HRQL questionnaire KIDSCREEN-52 [108, 109], and 75 (80% of invited) participated. In addition, generic HRQL questionnaires were sent to 320 controls from the same cohort. The control group consisted of children with no reported FHS and an unrestricted diet, randomly selected from the children who had participated.
in SPT in 2010. Of the invited controls, 209 children (65%) participated in the HRQL questionnaire (Figure 4).

Based on the results of the clinical examination, the children with eliminated foods due to FHS were categorised into the different FHS phenotypes: current food allergy, outgrown food allergy, lactose intolerance, and non-definable cases (Figure 4). The clinical examinations and categorisation of the children into different phenotypes of FHS was performed by the same paediatric allergist (AW). The criteria used for categorisation are presented under the heading “Definitions” and have been described in detail in a previous study [110]. The categorisation of children into different FHS phenotypes was made after the children had completed the HRQL questionnaires but prior to the analyses of the HRQL results.

**Figure 4.** Categorisation of children into different phenotype after they answered the HRQL questionnaires.

**Paper III**

The 94 children who participated in the clinical examinations were categorised in different FHS phenotypes, and of them 27 children were diagnosed as having current food allergy. In total, 25 of these children were invited to a DBPCFC. Two children were not invited, one because of a recent anaphylactic reaction to the culprit food and one child because of a concomitant chronic disease that could have affected the challenge result. Eighteen children participated (72% of invited) in a total of 20 DBPCFC with the foods; cow’s milk, hen’s egg or cod [110]. The blinded food challenges were performed during February and March 2011. The recipes that were used in the DBPCFC have been previously validated [13, 110].
In October 2012, 18 months after the DBPCFC, a research nurse contacted the families and invited the children who had participated in the blinded food challenges to a follow-up interview, and 17 children (94%) participated. One child had moved from the study area and could thus not be invited. The children were 14-15 years of age at time of the interview.

**Paper IV**

Between March 2004 and March 2007, the paediatric allergy team at the Child and Adolescents Clinic, Umeå University Hospital performed 34 DBPCFC in 28 children.

Ten mothers, whose children had participated in DBPCFC between March 2004 and October 2006, were consecutively invited to an interview study. Inclusion criteria were a negative outcome of the challenge and that the challenged food had been partially or completely reintroduced into the child’s diet. A postal letter with information about the interview study was sent to the mothers. One week after the letter was sent a research nurse, not involved in the DBPCFC, contacted the mothers by telephone, in order to ask whether the mother accepted the study invitation. Two of the invited mothers reported that the challenged food had not been reintroduced into their child’s diet. Eight mothers met the inclusion criteria and accepted participation in the study. Informed consent was collected from the mothers and the interviews were performed during spring 2007.

**Methods**

**The OLIN questionnaire**

The questionnaire has been used within the OLIN studies since 1996 [111-113]. It included the International Study of Asthma and Allergies in Childhood (ISAAC) core questions [114] but was substantially expanded with questions about symptoms, use of medications, and physician diagnosis of asthma, rhinitis, and eczema, and possible risk factors for the diseases. Since 2006 the questionnaire has also included questions about FHS.

The questions regarding FHS in the 2006 questionnaire included the questions “Is the child allergic to any food?” followed by “Has your child had any reactions to the following foods and if so, what kind of reactions?” Foods listed in the questionnaire were foods commonly related to FHS, but the parents could also report other foods that were not mentioned in the table. Listed alternatives for symptoms caused by food reactions were itching of the mouth, airway
symptoms, gastrointestinal symptoms and skin symptoms. The questionnaire was somewhat modified in the follow-up study in 2010 [54]. In the follow-up questionnaire the parents who reported that the child eliminated cow’s milk, hen’s egg, fish and/or wheat because of FHS also answered to what extent the food was eliminated: not at all, partially or completely. The Swedish version of the OLIN questionnaire from 2006 and the Swedish versions of the questions regarding food hypersensitivity in the OLIN questionnaire from 2010 can be found in Appendix 1 and 2, respectively.

**Skin prick testing**

SPTs were performed according to the guidelines of the European Academy of Allergy and Clinical Immunology [115]. Ten airborne allergens were tested: birch, timothy, mugworth, cat, dog, horse, two house dust mite extracts, D. Pteronyssinus and D. Farinae, and two mould extracts, Claudosporidium and Alternaria. Histamine 10mg/ml was used as positive control and glycerol as negative control. The potency of the allergens was 10 HEP (histamine equivalent prick test) except Clausporidium and Alternaria which were 1:20 weight/volume. A positive test was defined as a mean wheal ≥3mm in diameter recorded after 15 minutes.

**Generic Health-Related Quality of Life questionnaire**

At the clinical examination visit, children with FHS completed the generic and disease-specific HRQL questionnaires without interference of the parents. The generic HRQL questionnaires together with a cover letter with information about the study were sent to the control group by regular post. In the cover letter the families were told that the questionnaire should be completed by the child without interference from the parents. The questionnaire was returned to the OLIN study group in a prepaid envelope together with informed consent from the parents.

Generic HRQL was measured using the Health-Related Quality of Life Screening Instrument for children and adolescents (KIDSCREEN -52), a generic self-report instrument for children and adolescents aged between 8 to 18 years [108]. KIDSCREEN-52 has predominantly been used in European countries. The Swedish version of this instrument has previously been validated [67]. The KIDSCREEN Group gave permission to use the Swedish version of KIDSCREEN-52 and its manual for this study.

The KIDSCREEN -52 measures HRQL in 10 domains with the underlying items: Physical Well-being (five items), Psychological Well-being (six items), Moods and Emotions (seven items), Self-Perception (five items), Autonomy (five
items), Parent Relation and Home Life (six items), Financial Resources (three items), Social Support and Peers (six items), School Environment (six items) and Social Acceptance and Bullying (three items). Responses are given on a five point Likert type scale. The scale for negatively worded items was reversed. The crude scores were computerised and the final score ranges from 0-100 [108]. Higher scores indicate a better HRQL.

Based on an international survey from 13 European countries, a mean of 50 and a standard deviation of 10 is regarded as a population norm [109] (Figure 5).

**Figure 5.** Ruler with response category thresholds and the t-value distribution. [109]. Published with granted permission from Ravens-Sieberer, U., & the European KIDSCREEN Group.
**Disease-specific Health-Related Quality of Life questionnaire**

Disease-specific HRQL was measured using the Food Allergy Quality of Life Questionnaire Teenage Form (FAQLQ-TF) for adolescents in ages 13-17 years [72]. The FAQLQ-TF has been translated and used in Sweden in a previous study [116]. The FAQLQ questionnaires can be downloaded free of charge at the FAQLQ website [74].

The FAQLQ-TF questionnaire measures HRQL in three domains with the underlying items: Allergen Avoidance & Dietary Restrictions (10 items), Risk of Accidental Exposure (six items) and Emotional Impact (seven items).

The responses are given on a seven-point scale, 1-7. The total FAQLQ-TF score is the mean score of all items and ranges from one (minimal impairment) to seven (maximal impairment). In this instrument, higher scores indicate poorer HRQL. The clinical Minimal Important Difference (MID) of the FAQLQ-TF is still undecided, and the same is true for other disease-specific HRQL questionnaires for food allergy [117].

**Semi-structured interviews**

The results in Paper III and IV were based on semi-structured interviews using an interview guide with questions relevant for the aim. In addition, the interviewer was allowed to pose follow-up questions based on the participant’s responses [118]. In a semi-structured interview, descriptive answers can be obtained by starting questions with words like what, where, when or how [118]. The interview guide used in Paper III and IV invited the participants to talk freely about their experiences during DBPCFC and thereafter follow-up questions were posed.

The main questions in the interviews in Paper III were:
- Can you describe how you experienced the food challenge?
- Describe what happened the time after the food challenge.
- Did you reintroduce the challenged food or not after the challenge?

The main questions in Paper IV were:
- Can you describe how you experienced the double-blind provocation?
- What feelings did you have when the food was reintroduced after the double blind provocation?

The interview guides used in Paper III and IV are presented in Appendix 3 and Appendix 4, respectively.

The interviews in Paper III and IV were performed by research nurses that had not been involved in the DBPCFC. Prior to the studies, pilot interviews were
performed to evaluate the interview guide. In Paper III, the pilot interviews were performed with two colleagues at the paediatric clinic, and with two adolescents after they had completed an open food challenge. In Paper IV, pilot interviews were performed with two colleagues at the paediatric clinic, and with two mothers whose children had participated in a DBPCFC. The interviews were performed at the adolescent’s school (Paper III) or in the mother’s home (Paper IV).

All interviews were recorded and transcribed verbatim with marks on words that were emphasised. In addition, emotions as laughs or silences were noted. The interviews were listened to and read through several times before the content analysis was performed.

**Definitions**

**Paper I**

*Any FHS:* was defined as questionnaire-reported symptoms to at least one of the specific foods: cow’s milk, hens’ egg, fish, wheat, soy, kiwi, orange, apple, carrots, banana, tree nuts, peanuts and almonds.

*FHS essential foods:* was defined as questionnaire-reported symptoms to one or more of the specific foods; cow’s milk, hen’s egg, fish, wheat and/or soy.

*FHS essential foods excluding milk:* was defined as questionnaire-reported symptoms to one or more of the specific foods; hen’s egg, fish, wheat and soy.

*FHS milk:* was defined as questionnaire-reported symptoms to cow’s milk only.

*FHS fruits:* was defined as questionnaire-reported symptoms to one or more of the specific foods; kiwi, orange, apple, carrots or banana.

*FHS nuts:* was defined as questionnaire-reported symptoms to one or more of specific foods; tree nuts, peanuts or almonds.

Positive SPT to animal: Positive SPT to cat, dog, or horse.

*Positive SPT pollen:* Positive SPT to birch, timothy or mugworth.
Paper I and II

Asthma/rhinitis/eczema: Positive response to the question “Has the child been diagnosed by a physician as having asthma/rhinitis/eczema”, respectively.

Allergic heredity or Heredity asthma/rhinitis/eczema: was defined as questionnaire reported parental history of asthma, rhinitis or eczema.

Any positive SPT: Positive SPT to at least one of the tested airborne allergen.

Paper II

FHS: was defined as questionnaire reported total elimination to at least one of the specific foods due to food allergy or food hypersensitivity; cow’s milk, hen’s egg, fish or wheat.

Heredity FHS: was defined as questionnaire reported parental history of food hypersensitivity.

FHS phenotypes: current food allergy, outgrown food allergy or lactose intolerance.

Criteria for these FHS phenotypes were sorted according to pre-set criteria in a previous study of this cohort [110]. The categorisation was performed by the same paediatric allergist (AW) that performed the clinical examinations. All mandatory criteria had to be fulfilled for each FHS phenotypes, and for diagnosis of food allergy at least two secondary criteria had to be fulfilled (Table 4).

If a child reported symptoms to more than one food and the adverse reactions to the foods were categorised as different phenotypes (e.g. if the child was classified as both IgE-mediated egg allergy and lactose intolerance) the child was sorted in the category with the highest priority for the study: current food allergy followed by outgrown food allergy and last priority, lactose intolerance.
**Table 4.** Criteria for food hypersensitivity phenotypes. Modified from Winberg et al [110]. Published in PLOS ONE, Open access license, Creative Commons Attribution.

<table>
<thead>
<tr>
<th>FHS phenotype</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current IgE mediated</strong></td>
<td><strong>Mandatory criteria</strong></td>
</tr>
<tr>
<td><strong>Non-IgE mediated</strong> food allergy*</td>
<td><strong>Mandatory criteria</strong></td>
</tr>
<tr>
<td><strong>Outgrown food allergy</strong> <strong>Mandatory criteria</strong></td>
<td>A convincing clinical history of IgE or non IgE mediated food allergy but the child can now tolerate at least 100 ml milk or a portion size of egg, cod or wheat products</td>
</tr>
<tr>
<td><strong>Lactose intolerance</strong> <strong>Mandatory criteria</strong></td>
<td>Onset after 5 years of age. Symptoms limited to flatulence, stomach-ache, and/or diarrhea. Symptoms triggered by more than 100 ml milk. Symptom-free on lactose reduced or lactose-free diet. No celiac disease</td>
</tr>
</tbody>
</table>

* All mandatory and at least 2 secondary criteria had to be fulfilled for diagnosis
** All mandatory criteria had to be fulfilled for diagnosis.
Statistical analysis

**Paper I and II**

All statistical analyses were performed by using the Statistical Package of Social Science Software, version 19-22, SPSS Inc. New York, USA. The chi-square test was used for comparison of categorical variables. A p-value of <0.05 was considered statistically significant.

In paper I, factors that were significantly associated with FHS in the bi-variate analysis were included in multiple logistic regression models and presented as odds ratios (OR) with 95% confidence interval (CI). Dependent variables were any FHS, FHS essential foods excluding milk, FHS milk and FHS fruits or nuts. Regression analyses were performed including all children in the paediatric cohort and separately for children who had participated in the SPTs.

Since the HRQL data in paper II was not normally distributed, the Mann-Whitney U test was used to assess differences between children with FHS and children with an unrestricted diet. For comparisons of HRQL between children categorised in the three FHS phenotypes and children with unrestricted diet, the Kruskal Wallis test was used. Poor HRQL was defined as ≥75th percentile for the FAQLQ-TF score and differences in proportions between groups was analysed by linear association (Mantel Haenszel).

**Qualitative content analysis**

**Paper III and IV**

The interviews in paper III and IV were analysed using qualitative content analysis in accordance with Graneheim and Lundman [119]. Content analysis aims to describe variations in texts, e.g. interview text, by identifying differences and similarities which are then expressed as domains, categories and themes [119]. The analysis is a process of condensing and abstracting the text. The aim of condensation is to shorten the text but still preserve the core. The aim of abstraction is to reconstitute the meaning units to a higher logical level. The abstraction analysis is made stepwise through code, domains, category, subtheme and theme [120]

The text was read through several times, in order to get a sense of the overall content. Meaning units corresponding to the aim were identified and condensed, and thereafter labelled with codes. The codes were then compared and sorted according to similarities and differences. Similar codes were grouped into domains (Paper III) or categories (Paper IV) and used to formulate themes
and subthemes. The analysis process was not linear and many steps of the process were repeated several times until all authors reached an agreement. We strived to keep the interpretations on a concrete level, as the results of the studies could be useful in future clinical interventions.

The Open Code Software version 4.0 (ICT Services and System Development and Division of Epidemiology and Global Health, Umeå University, Sweden) was used in the analyses of paper III. The Open code is a tool for coding qualitative data generated from text information such as interviews, field notes, or observations [121]. In Paper IV the coding was performed manually.

“Education is the most powerful weapon

which you can use to change the world”

Nelson Mandela
Results

Prevalence, symptoms expressions and risk factors for food hypersensitivity (Paper I)

Prevalence

In 2006, when the children in the cohort were 7-8 years of age, the reported prevalence of any FHS was 21.3 %. FHS to essential foods (cow’s milk, hen’s egg, fish, wheat and/or soy) was reported by 10.9 % of the children and FHS to fruits and nuts by 14.6 %.

The prevalence of any FHS was higher among girls than boys, mainly because of a higher prevalence of reported FHS to milk among the girls (11.0 % vs. 7.0 % p<0.001). Cow’s milk was the most common essential food causing FHS, reported by 9% of the children. A majority, 303 children (55.0%) reported FHS to one single food, and in this subgroup, milk was the most frequently reported food trigger (46.2%), followed by kiwi fruit and oranges.

Symptoms expressions

Among children with any FHS, oral symptoms (47.4%), were the most commonly reported food induced symptom, followed by gastrointestinal symptoms (45.7%), skin symptoms (35.2%), and respiratory symptoms (10.3%). Children with FHS to the essential foods milk, wheat and soy, predominantly reported food induced symptoms from the gastrointestinal tract, while skin symptoms were the most frequently reported food induced symptoms in children with FHS to egg and fish (Figure 6).

Fruits were the most commonly reported food triggers for skin and oral symptoms, nuts the most commonly reported food triggers for respiratory symptoms and milk was reported as the most common trigger of gastrointestinal symptoms.
**Figure 6.** Prevalence (%) of different symptoms expressions to milk, egg, fish, wheat and soy, respectively, among children at 7-8 years of age.

**Risk factors for food hypersensitivity**

In the bi-variate analyses, *any FHS, FHS essential foods, FHS essential food milk excluded* and *FHS fruits or nuts* were associated with any positive SPT, SPT pollen and SPT animal, asthma, rhinitis, eczema, and allergic heredity. *FHS milk* showed a different pattern of association and was only found to be associated with eczema and allergic heredity. The prevalence of *any FHS, FHS essential foods*, and *FHS milk* was highest in Luleå compared to the other areas: Piteå and Luleå.

In the multivariate analyses *any FHS* was associated with female sex (OR 1.7, 95%CI 1.3-2.2), allergic heredity (OR 1.9, 95%CI 1.4-2.4), any positive SPT (OR 1.5, 95%CI 1.1-2.0), rhinitis (OR 2.8, 95%CI 1.9-4.3), and eczema (OR 2.4, 95%CI 1.8-3.3).
**FHS essential foods milk excluded** was associated with rhinitis and eczema. **FHS fruits and nuts** was associated with female sex, allergic heredity, any positive SPT, rhinitis and eczema. **FHS milk** was associated with female sex, allergic heredity and eczema (Figure 7).

**Figure 7.** Factors related to different groups of FHS, presented as odds ratios (OR) and 95% confidence intervals (CI).

**Main results:**

*The reported prevalence of any FHS was 21%.*

*Symptom caused by milk was most common, reported by 9% of the children.*

*The most frequently reported symptoms were oral (47.4%) and gastrointestinal symptoms (45.7%) with fruits and milk respectively being the main symptom-triggers.*

*Children with FHS to milk showed different symptom expressions and risk factor patterns compared to children with FHS to other foods.*
Health-Related Quality of Life among children with food hypersensitivity and children with unrestricted diet (Paper II)

At the time of the clinical examination, 75 children with total elimination of milk, egg, fish or wheat due to FHS, answered a generic HRQL questionnaire (KIDSCREEN–52) and a disease-specific HRQL questionnaire (FAQLQ-TF). In addition, 209 children with unrestricted diet, randomly selected from the same cohort, answered the generic HRQL questionnaire. The prevalence of physician diagnosed asthma, rhinitis, eczema and reported parental history of FHS were significantly higher among children with FHS than children without FHS, but other background factors were similar in the two groups.

Health-Related Quality of Life among children with and without food hypersensitivity

No statistically significant differences in distribution in generic HRQL score was found between children with or without FHS, and all children reported a good generic HRQL according to the KIDSCREEN-52 manual [109]. As HRQL may differ between boys and girls [122], stratified analyses by sex were performed. Girls with FHS had a slightly lower score in the domain Social Acceptance and Bullying compared to girls without FHS. In the other domains there were no differences between girls with and without FHS. Among boys, no differences were found between those with and without FHS in any of the domains.

Health-Related Quality of Life among different phenotypes of food hypersensitivity

No statistical significant differences of generic HRQL scores were found between children with different phenotypes of FHS and children with unrestricted diet. In addition, no differences in distribution in the disease-specific HRQL scores were found between children in the FHS phenotypes. However, there was a trend of higher scores, indicating more impaired HRQL, among children with current food allergy. The proportion of poor HRQL, defined as the ≥ 75th percentile in the disease-specific HRQL score, was significantly more common among children with current food allergy compared to children with other phenotypes of FHS (Table 5).
Table 5. Prevalence (%) of poor HRQL, defined as scores ≥75th percentile, in each FAQLQ-TF domains by FHS phenotypes. A higher score indicates a poorer HRQL. Differences between FHS phenotypes are measured by test for trend (Mantel Haenszel).

<table>
<thead>
<tr>
<th></th>
<th>Allergen Avoidance and Dietary restrictions</th>
<th>Risk of Accidental Exposure</th>
<th>Emotional Impact</th>
<th>Total FAQLQ score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current food allergy (n=23)</td>
<td>39.1 (9) p-value: 26.1 (6) Impact: 47.8 (11)</td>
<td>34.8 (8) p-value: 0.119</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outgrown food allergy (n=16)</td>
<td>18.8 (3) Impact: 21.9 (7) p-value: 0.903 Impact: 21.9 (7) p-value: 0.001</td>
<td>6.3 (1) p-value: 25.0 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose intolerance (n=32)</td>
<td>18.8 (6) Impact: 25.0 (8) p-value: 0.045 p-value: 0.903 Impact: 25.0 (8) p-value: 0.045</td>
<td>0.119 Impact: 25.0 (8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| ≥ 75 percentile | 25.5 (18) p-value: 23.9 (17) Impact: 25.4 (18) p-value: 23.9 (17) |

Main results

Overall, children with and without FHS had a good generic health related quality of life.

No difference in generic HRQL was found when comparing children with and without FHS, nor after categorising the children with eliminated foods into different phenotypes of FHS.

The prevalence of poor disease-specific HRQL was higher among children with current food allergy compared to children with other phenotypes of FHS.
Adolescents’ and mothers’ experiences of double-blind placebo-controlled food challenges (Paper III and IV)

Adolescents in paper III and children to the mothers in paper IV reported an early onset of FHS, in general before three years of age. Descriptive data on the adolescents and children participating in DBPCFC, outcome of the food challenge, and eventual food reintroduction is presented in Appendix 5 and Appendix 6, respectively. If the participants reacted with mild symptoms to milk or egg during the DBPCFC, they were advised to try partial reintroduction of the food at home, using baked milk or egg products.

The qualitative content analysis of the adolescents’ experiences of DBPCFC (Paper III) resulted in two domains and six themes. The analysis of mothers’ experiences of DBPCFC (Paper IV) resulted in two themes and six subthemes (Table 6).

Table 6. Overview of domains, themes and subthemes in Paper III and Paper IV.

<table>
<thead>
<tr>
<th>Adolescents’ experiences of DBPCFC (Paper III)</th>
<th>Domains</th>
<th>Themes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiences during the DBPCFC</td>
<td></td>
<td>Facing fear in a secure environment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Being hesitant but also curious about unknown tastes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Waiting for unknown food reactions</td>
</tr>
<tr>
<td>Experiences after the DBPCFC</td>
<td></td>
<td>Gaining control and freedom</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continuing old habits</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mothers’ experiences of DBPCFC (Paper IV)</th>
<th>Theme</th>
<th>Subtheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear of the unknown</td>
<td>Fear of losing control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Having faith even though fear prevails</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reintroducing despite fear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fear of causing harm</td>
<td></td>
</tr>
<tr>
<td>Re-evaluating earlier experiences</td>
<td>Daring to take new challenges</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Refraining from new challenges</td>
<td></td>
</tr>
</tbody>
</table>
Fear associated with the double-blind placebo-controlled food challenge

The DBPCFC was a way to reduce fear, and to gain knowledge of possible food reactions. The participants expressed a feeling of fear during the challenge, and this feeling was described more detailed and profound by the mothers than the adolescents. In most cases, the challenged food had been avoided for a long period and neither the adolescents participating in the DBPCFC nor their parents knew what symptoms to expect during the challenge. In participants with a positive challenge outcome, symptoms were often milder, or in some cases more severe, than the participants had expected. However, the fear of possible allergic reactions to the challenged food was powerful. Both the adolescents and the mothers described that they trusted the personnel responsible during the challenge and that it was a relief to have someone else to take care of possible allergic reactions. On the other hand, the mothers also described fear of losing control over their children’s symptoms, or that they did not trust the result of the challenge.

The participants’ experiences during the food challenge differed, and could sometimes be ambiguous. Even though they felt fearful during the challenge, many of the participants simultaneously hoped for a test result where the challenged food could be reintroduced. In contrary, some of the adolescents described that they were doubtful about the taste of the challenged food. Furthermore, both the mothers and the adolescents expressed that the DBPCFC was time consuming.

Experiences after the double-blind placebo-controlled food challenge

A majority of the study participants who were advised to reintroduce the challenged food after the DBPCFC, did so. If the challenged food was reintroduced, completely or partially, the study participants described feelings of freedom and that life had become easier regarding meal preparations and social events, such as eating at restaurants and spending time with friends. Even when an anaphylactic reaction occurred during the DBPCFC, the adolescents described the DBPCFC as a positive experience, because they now had gained preparedness for accidental reactions, which they did not have before the challenge. However, despite the experience of an anaphylaxis during DBPCFC, some of the adolescents chose not to carry the epinephrine auto injector during school- and spare time because they did not believe that an anaphylactic reaction would occur again.
In addition, some study participants stayed in old habits and did not reintroduce the challenged food, or chose only to make a partial food reintroduction after a negative challenge. Reason for reintroduction failure were that the study participants had no wish to reintroduce the food because they still feared food reactions, that they were used to an elimination diet, and that they did not like the taste of the challenged food.

“We’re one, but we’re not the same.
We get to carry each other, carry each other.”
U2

Main results

Both the adolescents and the mothers experienced fear of allergic food reactions during DBPCFC - but also a hope that the challenged food could be reintroduced.

A negative outcome was not always associated with reintroduction of the challenged food.

Reasons for reintroduction failure were fear of food reactions, not liking the taste of the challenged food and being used to an elimination diet.
Discussion of main results

To gain a deeper insight into the topic of “food hypersensitivity among schoolchildren” this thesis includes both quantitative and qualitative studies. Several aspects have been studied: prevalence and risk factors for FHS, symptoms expressions related to exposure to different foods, HRQL in relation to FHS, and finally, experiences of double-blind placebo-controlled food challenges expressed by both adolescents and mothers.

Prevalence, associated factors and symptoms expressions of food hypersensitivity

In our population-based cohort study, the reported prevalence of any FHS was high at age 7-8 years, 21%, and increased further to 26% in the follow-up of the cohort four years later [54]. Due to the use of different study methods and definitions, the prevalence of reported FHS varies largely between studies [37]. In the Swedish BAMSE study, following a population-based birth cohort in Stockholm, the prevalence of FHS was 13.3% at age 8 years [40]. However, among children 10-11 years of age from randomly selected schools in Tallinn, Estonia, the reported prevalence of FHS was 20.2 % compared to 24.4 % among children from schools in Linköping and Östersund in Sweden [123]. Thus, the prevalence of reported FHS found in the latter study confirms our findings.

In Paper I, different symptom expressions of FHS were associated with different foods. Oral symptoms were most common and these symptoms were mainly triggered by fruits and nuts. A possible explanation for this finding could be the presence of oral allergy syndrome (OAS) caused by cross-reactions between birch pollen and birch-pollen like proteins in various fruits and vegetables. Oral symptoms due to a cross reactivity between birch and fruits or nuts are often mild and transient e.g. itching in the mouth and throat after exposure to the offending food, and systemic reactions rarely occur [25]. Birch pollen allergy is common in Sweden [24], the prevalence increases with age [124] and OAS is common among people with allergy to birch [40]. This is in line with our study findings, showing an association between reported FHS to fruits and nuts and the presence of a positive SPT to pollen. However, symptoms from the oral mucosa can also be the first symptom of a more serious allergy [55]. In these cases, oral symptoms usually co-occur with symptoms also from other organ systems [125]

The other common symptom of FHS in our study was gastrointestinal symptoms, mainly caused by milk. It is well known that symptoms from the gastrointestinal tract are common in food allergy and FHS [40, 55] and that
gastrointestinal symptoms are main symptoms of lactose intolerance [31]. Gastrointestinal symptoms may also be caused by other conditions. In a previous study, children visiting a gastroenterology clinic for the first time were compared to healthy controls. It was shown that children with gastrointestinal complaints and disorders had higher levels of anxiety and depression and impairments in social functioning compared to the controls [126].

Psychological factors e.g. stress and anxiety may influence development of gastrointestinal symptoms, but psychological factors can also worsen the symptoms of FHS [103] and other gastrointestinal conditions [127]. The direction of causality is not always clear; abdominal pain is common in childhood and may lead to feelings of anxiety and depression. On the other hand, feelings of anxiety can lead to gastrointestinal symptoms [128] and impaired HRQL but these symptoms are not always related to the food intake. Thus, the associations between gastrointestinal symptoms and FHS during childhood may be difficult to disentangle.

Having any FHS was associated with female sex, allergic heredity, any positive SPT, rhinitis and eczema. Both the analyses of symptom expressions to different foods and the risk factor analyses confirm that FHS is a heterogeneous condition including several phenotypes [15]. Reported FHS to different foods showed different patterns of association. While FHS to fruits and nuts and FHS to essential foods milk excluded were strongly associated with several atopic variables such as allergic sensitisation to airborne allergens, asthma and rhinitis, FHS to milk was only associated with the atopic variable eczema. A possible explanation for this finding is that the groups FHS to fruits, nuts and FHS essential foods milk excluded were more likely to contain children with IgE-mediated food allergy than the FHS milk group. The co-existence of food allergy with atopic diseases is well known from previous studies [45, 129].

Allergic heredity and female sex were associated with FHS to fruits and nuts and FHS milk. The association between reported parental history of atopic diseases and FHS is in line with the findings in other studies [47, 130]. Results from studies investigating the association between FHS and sex are unclear. Several studies have shown that food allergy is more common among boys than girls during childhood [50, 51]. In our study the reported prevalence of any FHS was higher among girls than boys and the difference was mainly due to a higher prevalence of FHS to milk among the girls. This could probably partly be explained by a low proportion of IgE-mediated milk allergy among children reporting FHS to milk. At our study follow-up, when the children of the cohort were 11-12 years of age, the prevalence of partial or complete avoidance of milk due to FHS was 14, 5%, but only 3% of the children with FHS to milk were diagnosed as having current milk allergy [131]. Previous studies have shown a higher female prevalence of reported FHS among adolescents and adults [52, 132]. The reasons why women report more symptoms of foods are unknown.
Probably there are multiple causes. A contributing factor could be that girls may recognize differences in taste between foods better than boys do [13]. In addition, studies have found that men tended to under-report health problems and delayed seeking medical care compared to women [133].

Health-Related Quality of Life among children with and without food hypersensitivity

Our hypothesis was that HRQL was impaired among children with total elimination of cow’s milk, hen’s egg, fish or wheat due to FHS, but the hypothesis could not be verified. Social relationships with friends and family are important during adolescence [134] and one possible explanation could be that those who eliminated essential foods wanted to downplay the impact it had on their HRQL, in order not to be perceived as troublesome or different [103]. A necessary part of living with food allergy or FHS is coping with the risk of symptoms of foods. However, coping strategies and degree of fear of possible symptoms can differ between adolescents [102, 105]. Therefore, children with a clinically similar disease severity may experience very different degrees of impairment in their daily life [92, 135]. Examples of FHS related factors that may affect HRQL among children are shown in Figure 8.

In opposite to hospital-based studies, our study was population-based and included children with all types and severity grades of FHS, which could be another explanation why HRQL was not significantly affected. It is possible that HRQL is more impaired for children who developed FHS later in life, because of the feeling of being deprived of certain foods that they had been eating before and also because they had not developed strategies to cope with the disease [105, 136]. In our study, the children had developed symptoms of FHS at an early age, which could also have contributed to the non-affected HRQL. Children with food allergy from young age do not know another way to live and report a better HRQL [90] compared to the parents [78, 101] who take care of the children’s everyday life. On the other hand, avoiding food for a long time can lead to fear of possible symptoms during a reintroduction of the eliminated food, which was shown in Paper III and IV.
Poor HRQL was defined as the ≥75th percentile in the disease-specific HRQL score, and was most common among children with current food allergy. In recent years an increasing number of studies have shown that IgE-mediated food allergy has a negative impact on HRQL especially regarding fear of possible food reactions, dietary limitations and limitations in social activities [88, 102, 116]. Poor HRQL in the overall and domain-specific scores of the FAQLQ-TF questionnaire was also shown in a Swedish study among adolescents with diagnosed food allergy to cow’s milk, hen’s egg and/or wheat [116]. Furthermore, severe reactions are common among children with food allergy [56]. This was in line with our study where children with current food allergy had more severe reactions compared to children with outgrown food allergy and lactose intolerance [110].

Thus, there is a need to increase the knowledge of the different FHS phenotypes in the general population in order to reduce the risk of children with severe food allergy being mistrusted, and thereby risk unnecessary exposure to the culprit food. In general, many people do not have knowledge that food allergy may differ in severity between individuals: if the eliminated food is eaten by mistake, some react with mild symptoms while for others it may be life-threatening. These differences in severity of reactions contribute to confusion in the general population. One study in the U.S. showed that it was as a general misconception...
in the general population about the amount of food that can trigger an allergic reaction, and half of the participants believed that lactose intolerance and food allergy was synonymous [137].

**Experiences of double-blind placebo-controlled food challenges**

The participants in Paper III and Paper IV described that DBPCFC was a positive experience because they trusted the personnel, they received information about the severity of their food allergy and knowledge whether they could reintroduce the challenged foods or not. The same positive experiences were also described in a study investigating parents’ experiences of their children’s open food challenges to peanuts [106].

Fear during the DBPCFC and the reintroduction process was also described among adolescents and mothers in our studies. A “healthy” degree of fear helps to maintain vigilance regarding allergen avoidance, but fear can also prevent reintroduction of food. Among our study participants, the described food induced symptoms that had resulted in an eliminated diet (presented in Appendix 5 and 6) varied from mild to severe. However, for the participants it was often unclear which symptoms they should expect if they were exposed to the food. These feelings of uncertainty were reasons for their distress, and the fear of possible reactions was strong and powerful. This is in line with other studies showing that not merely the diagnosed disease severity, but also the self-perceived disease severity can affect HRQL [91, 92]. All of the participants in our studies had avoided the food for a long period, which may have resulted in that the fear for possible food reactions had grown and become more and more powerful. A study from the Netherlands described that long elimination diet (>2 year) was a risk factor for reintroduction failure among children who underwent a negative peanut challenge [100].

It has been shown in other studies that food challenges have a positive impact on HRQL independent of outcome [94, 96] and this statement was also described among the participants in our studies. When the challenged food was reintroduced, it was easier to socialize and prepare meals, which has also been shown in other studies [95]. However, reintroduction failure following DBPCFC is sparsely described in other studies.

In Paper III the outcome was negative in 11 challenges but the food was reintroduced in only five cases. In Paper IV the criteria for participating was that the outcome of the challenges was negative and that the food was reintroduced, but nevertheless, two of the participating mothers reported in the interviews that the food was only reintroduced partially in the child’s diet, while six mothers had reintroduced the challenged food totally. Reintroduction failure
occurred when the participants felt fear of food reactions, did not accept the
taste or experienced a normal life without the eliminated foods. These
statements are consistent with the findings in other studies regarding main
reasons for reintroduction failure after food challenges [95, 99, 100].

The feelings of fear due to possible symptoms after a negative challenge
emphasize the importance of a correct and clear diagnosis [10] as well as close
follow-ups and a management plan following a food challenge, both after a
negative and a positive outcome. It is not easy to remember information given
during the ongoing food challenge. In one study 46 parents to children
participating in food challenges to peanut were interviewed and they found that
94% of the parents could not remember the amount of peanut ingested during
the challenge and 24% could not remember if management advice was given
[106]. The difficulties to remember all information given during the
challenge may result in underestimation of severe reactions also among subjects
at risk for anaphylaxis. In our study, some of the children who had an
anaphylactic reaction during DBPCFC chose not to carry the prescribed
epinephrine auto-injector at school and/or in their spare time. Similar findings
have been seen in other studies [138]. Regular follow-ups where parents and
children can receive feedback on how they have perceived and interpreted the
information on how to treat symptoms in case the food is eaten by mistake is
therefore important.

In addition, children’s interest in tasting new foods differs [139] and this was
particularly true in our study among children challenged with cod since none
had reintroduced this food, independent of the outcome. Cod had been avoided
a long time before the challenge, and studies have shown that dietary
restrictions during infancy may influence later eating behaviour [140].

The purpose to perform oral food challenges is to diagnose or rule out food
allergy. The intention is that the participants act according to the outcome in
order to unnecessarily eliminate foods. A successful reintroduction after a
negative outcome includes that challenged food is reintroduced and the child
continues to eat the food. Our studies indicate that the children and their
parents need to be informed and given the opportunity to comment and ask
questions about the indications and the consequences of the outcome before the
challenge, which is also discussed in other studies [99].

A strength of this thesis is that the research-questions are illuminated by the
combination of quantitative and qualitative studies and its population-based
design. We have found that reported FHS is common among schoolchildren in
Northern Sweden, and that HRQL was not necessarily impaired among children
with FHS. Food challenges can be a way to overcome the fear of possible food reactions but our studies also indicated that the challenged food is not always reintroduced after a negative challenge, and highlights possible reasons for these reintroduction failures. Our findings show the importance of diagnosing FHS and indicate that there is a need for follow-ups after a completed food challenge. The results of this thesis give insights about FHS, the impact on HRQL of FHS and experiences of DBPCFC, information useful for clinicians as well as patients with FHS and their families.
Discussion of methodology

The quantitative studies are discussed in terms of validity and reliability, while the qualitative studies are discussed in terms of credibility, dependability and transferability.

Validity and reliability

Validity refers to the extent to which we measure what was intended, and can be divided into two subgroups. Internal validity describes to what extent the result of a study reflects the true situation of the study population while the external validity tells us if the results are applicable to other populations [141].

In the questionnaire survey in 2006, the participation rate was exceptionally high, 97%, and the cohort represents about 60% of all children in this age group in Norrbotten, thereby supporting both the internal and external validity. One fifth of the children reported FHS which is a rather high prevalence but similar prevalence has also been reported in other parts of Sweden [40, 123]. This supports the external validity of the results in Sweden, and possibly also in other parts in Europe.

In Paper II we invited all 125 children from the entire large cohort who reported total elimination of milk, egg, fish or wheat due to FHS (5% of the population-based cohort) to a clinical examination and to answer HRQL questionnaires and also in this sample, the participation rate was high. The HRQL of children with eliminated foods was compared with a random sample of children with unrestricted diet from the same population, using a generic questionnaire. In this sample, the participation rate was slightly lower, 65%, but still acceptable for a postal questionnaire. Even though we invited all children reporting total elimination of milk, egg, fish and wheat due to FHS in this large population based cohort, the number of children in each FHS-phenotype was small, which affected the power of our results. Thus, the high participation rate and the population-based study design strengthen the results and contribute to representative results for the general population. However, if the aim is to study severe or unusual types of food allergy, a hospital-based study design would be preferable.

A limitation in Paper I is that the prevalence estimate of FHS and different FHS groups were based on parentally reported symptoms only. Furthermore, information about allergic sensitization to different foods would have been interesting regarding prevalence itself in the cohort but also in relation to reported symptoms to the food. The participation rate in the skin prick testing
to common airborne allergen in the entire cohort was very high, 90\% of the invited. The skin prick tests were performed in the schools which is why we could not test for food due to safety reasons. However, a strength of the study was that allergic sensitisation was based on objective methods i.e. skin prick testing and that the categorisation of the children to different phenotypes of FHS was based on clinical examinations which also included IgE-antibodies to the culprit food.

**Bias**

Bias is a systematic error that may affect the validity of the results by creating errors in prevalence estimates. Bias makes an association stronger or weaker than it really is and thereby affects the study results [141].

Other family members may influence the responders’ answers, which may result in information bias. The children with total elimination of milk, egg, fish or wheat were instructed to answer the HRQL questionnaires without interference from the parents. However, the control group of children with unrestricted diet completed the questionnaire at home. Although a cover letter addressed to the parents instructed them to let their child complete the questionnaire without their interference, it is unknown if all did so. This possible interference from the parents may have resulted in an information bias.

Another information bias is recall bias, the ability to remember exposures or situations in the past. Regarding the OLIN questionnaire data on symptoms of FHS, we asked for current symptoms and current avoidance of food, which is why recall bias probably not was a problem. The phenotype classification was partly based on parental reports of children’s age at onset of FHS symptoms. Even though the children were 12-13 years at the time of the interview, we believe that recall bias is not a major issue that affected the main results. Under- or over reporting of events or diseases, i.e. reporting bias may have occurred in families with a history of allergic diseases, as they may be more observant of their children’s possible symptoms of FHS compared to parents without allergic diseases. For instance, the significant association between allergic heredity and FHS to milk may have been affected by this type of bias. The children completed the HRQL questionnaires at the clinical examination. At that time, the children had not yet been classified into different phenotypes as the classification was based on the structured interview and specific IgE-level in a blood sample, which was analysed after the examination. Thereby, the children were not influenced of having been diagnosed by the study team when they completed the HRQL questionnaire.
Selection bias may occur if one specific group of subjects are more prone to participate or stay in the study than others [141]. The risk of selection bias in Paper I was small since the participation was close to 100%. The response rate was lower in the clinical examinations, including the HRQL study, than in the questionnaire survey. However, the responders and non-responders to the HRQL questionnaires did not differ regarding sex, atopic diseases, heredity of FHS, allergic sensitisation or living conditions why selection bias was not an issue in our study.

The questionnaires

The use of a validated standardised questionnaire increases the reliability, which refers to the repeatability of findings, that we obtain the same or a very similar result every time a measurement is repeated. The reliability increases with the size of the study population. If data are valid, they must be reliable, however a test can be reliable but not valid, i.e. if the wrong result is obtained in a very repeatable way [142].

The OLIN questionnaire includes the International Study of Asthma and Allergy in Childhood (ISAAC) questions about asthma, rhinitis and eczema. The ISAAC questionnaire was developed for international comparisons by using identical methods and the questionnaire has been translated and validated in several countries [143, 144]. The OLIN questionnaire includes additional questions about asthma, rhinitis, eczema and FHS and possible risk factors. The same questionnaire was used in the first OLIN pediatric cohort recruited 1996 and in the second pediatric cohort 2006, with a few questions added or removed [54, 111]. The questions addressing FHS in the 2006 OLIN questionnaire included the question: “År barnet allergisk mot något i maten?” /Is your child allergic to any food?” This question has also been used in the Swedish BAMSE cohort examining food hypersensitivity at the age of 8 years [40]. The agreement between answers given in the OLIN questionnaire by the adolescents and the parents have been evaluated in another cohort, and the agreement for both atopic diseases variables and environmental variables was very good [145, 146].

KIDSCREEN-52 assesses generic HRQL for children and adolescents, aged between 8 and 18 years [109]. The instrument was developed simultaneously in 13 different countries in Europe and has shown to have good validity and reliability [67, 109]. A review article published in 2014 reported that the KIDSCREEN instrument was translated into 38 languages and has been used in Europe including Sweden, and in North and South America, Africa and Asia [67, 109]. Thus, it is possible to compare results from different studies and countries.
The increasing interest to measure HRQL among children and adolescents with food allergy or FHS have contributed to the development of disease-specific HRQL questionnaires, and to increase the validity many questionnaires are age specific. Although FAQLQ-TF is primarily developed for adolescents with IgE-mediated food allergy [72], we used it in our study. At the time of the study there was no available FHS-related HRQL questionnaire in Swedish designed to describe adolescents’ own perspective of living with FHS. However, the FAQLQ parent form has been used by others in studies of FHS [92]. The use of the FAQLQ-TF questionnaire in our study may contribute to the finding that children with current food allergy had the lowest HRQL compared to the other phenotypes of FHS, as the questionnaire is specific for food allergy. The validation of the original adolescent form was carried out in the Dutch language and translated into English [72]. A research team at The Centre for Allergy Research, Karolinska Institute has translated the FAQLQ-TF to Swedish and the questionnaire was pilot tested in 10 Swedish speaking adolescents [116] but has not yet been validated in a larger group of adolescents in Sweden.

**Credibility, dependability and transferability**

Some researchers argue that reliability and validity, terms used in quantitative studies, also should be used in qualitative studies [147, 148]. However, traditionally in qualitative research the terms credibility, dependability and transferability are used [119] and I have discussed my results in Paper III and IV in relation to these terms.

**Credibility** has a meaning similar to internal validity. It confirms the extent to which the researcher presents the participants’ reality and the meanings they give to their experiences [149]. A result is credible if the characteristic it highlights is representative or typical for the phenomenon. In both Paper III and IV, the text was first analysed by two of the authors (ÅS and VL) and all authors discussed the result in order to gain credibility. However, we are aware that there is always a risk that text will lose its meaning during the condensation and abstraction process. Quotations from the interviews were used when presenting the findings to allow the reader to assess the reasonableness of the interpretations [119].

Strategies for selection of participants may have affected the credibility of the studies [150]. In Paper III, 94% of the children who performed DBPCFC also participated in the interview study and both girls and boys were represented, indicating good credibility. In Paper IV only mothers participated in the
interviews and the sample size was smaller. The reason for only inviting the mothers was that it was the mothers who participated at the child’s challenge occasions, and not the fathers. It is possible that the results would have been different if the study illuminated also the fathers’ experiences of the DBPCFC, or if mothers to children with a positive outcome were included in the study which would have provided a greater variety of experiences.

**Dependability**, is similar to reliability in quantitative studies. It is important that the same areas were covered in all interviews and the same main questions were asked in order to cover the phenomena “experiences of DBPCFC”. On the other hand, interviewing is a process that acquires new insights about the studied phenomena. Semi-structured interviews allowed the participants the freedom to express their views in their own terms, which resulted in some interviews in Paper III and IV being rich and some fragmented, but all still provided a wide range of experiences. During the analysis participants who did not have the same experiences as the majority were analysed as carefully as the others. These differences in experiences provided the key to a deeper understanding of the process as a whole [147]. We strived to keep the interpretations on a concrete level [148]. However, recall bias, i.e. that the participants did not remember their experiences of the challenge and the reintroduction process, may have occurred due to the 18 month follow-up time between the challenge and the interview.

During the DBPCFC the participants must transfer the responsibility for possible symptoms to the researchers which may lead to dependence on the researcher. If the researcher involved in the challenge had performed the interviews, it could have resulted in reporting bias that the participants under-reported negative experiences during the challenge. As the interviews were performed by study nurses not involved in the challenge procedure, such bias was avoided.

**Transferability** is similar to external validity in quantitative studies and describes to what extent the findings can be transferred to other settings or groups [119]. Few studies have explored the experiences of DBPCFC but because our results are in line with the few available studies [97-100], the transferability of the study finding is supported.

“There is no regret in life, just lessons learned”

*Jennifer Aniston*
Ethical considerations

The questionnaire studies were approved by the Regional Ethical Review Board at Umeå University, Sweden, (05-157M, 09-206M)). The parents invited to the questionnaire studies in 2006 and 2010 received a cover letter explaining the aim and design of the study. Upon returning the completed questionnaire they gave their informed written consent.

The studies about FHS were all approved by the Regional Ethical Review Board at Umeå University, Sweden (03-295, 2010-247-31M, and 2011-34-32 M). Both the children and parents gave their informed written consent. Information about the interview study was given via telephone by the research nurses. During the interviews, the participants were free to ask questions. The same was true for those completing the HRQL-questionnaires who could ask questions during the clinical examination.

In total, the DBPCFC resulted in four anaphylactic reactions in four children. Three of these children had not been prescribed an epinephrine auto-injector before the challenge and neither the children nor their parents were aware of these severe symptoms. The children who reacted with anaphylaxis explained that despite these reactions, the challenge was positive for them because it resulted in a preparedness for possible reactions in the future. The challenges were performed by an experienced allergist (AW) and allergy nurse (ÅS) and took place in a hospital setting, with adequate equipment and medication for treatment of allergic reactions. None of the challenges resulted in dissatisfaction among the participants or the parents, and there were no drop-outs.
Conclusions

- In this population-based cohort of children aged 7-8 years, the prevalence of reported FHS to any food was 21%, and FHS was more common among girls than boys. The most commonly reported symptom trigger was milk, reported by 9%. Among those with FHS oral symptoms were reported by 47% and were mainly triggered by fruits. The second most common symptom was gastrointestinal symptoms, 45% and mainly triggered by milk. Other symptoms of FHS were symptoms from the skin and the respiratory tract, and the main triggers for these symptoms were fruits and nuts, respectively. Having FHS to milk was associated with eczema and allergic heredity, while other groups of FHS were strongly associated also with other atopic conditions like asthma, rhinitis and allergic sensitization.

- In general, children aged 12-13 years, with or without complete elimination of cow’s milk, hen’s egg, fish or wheat due to FHS, reported a good generic HRQL and there was no difference in HRQL between the two groups. Furthermore, there were no significant differences in disease-specific HRQL after categorising the children with FHS into the different phenotypes current food allergy, outgrown food allergy and lactose intolerance. However, poor HRQL, defined as ≥75th percentile for the disease-specific score, was more common in the current food allergy phenotype in the domain Emotional Impact and the total FAQLQ domain compared to the other phenotypes of FHS.

- Both for the adolescents and the mothers, the DBPCFC was a complex experience involving both fear for adverse reactions to the challenged food and hope that the culprit food could be reintroduced after the completed challenge. The DBPCFC was described as a positive experience and a way to achieve knowledge about whether or not food reactions would occur, and if so, the degree of severity of these reactions. If the food was reintroduced after the challenge, the study participants expressed that it was easier to socialize with friends and easier to prepare meals. However, not all challenges with a negative outcome resulted in reintroduction of the challenged food. Reported reasons for reintroduction failure were fear for food reactions, not appreciating the taste of the challenged food and being used to an elimination diet.
Future research – How to proceed

“When nothing goes right... go left”

Epidemiology includes studies of prevalence and associated risk factors of a disease [141,151]. Without studies based on random samples of the population it is impossible to know if a common clinical problem in a hospital setting also is common in the general population. Qualitative studies explain why and how people act in a complex situation [152] which is equally important, e.g. participants’ perceived experiences of food challenges and the reintroduction process.

Definitions of food hypersensitivity and The clinical Minimal Important Difference

A challenge during this thesis was the lack of consensus regarding definitions of symptoms related to foods. Future studies of FHS would improve if the same terminology were used. It is also important to develop disease-specific HRQL instruments including other phenotypes than IgE-mediated food allergy, and making these questionnaires available in a wider range of languages.

It is important to identify children with impaired disease-specific HRQL due to FHS. One helpful tool is the clinical Minimal Important Difference (MID), defined as the smallest difference of improvement that patients perceive as meaningful, which would imply a change in the patients’ management. Regarding FAQLQ-TF, a minimum difference score of 0.5 in domains of questionnaires with a seven point scale has been described as clinically meaningful [73]. By using both generic and disease-specific questionnaires before and after an intervention, the change in disease-specific HRQL can be validated against the generic HRQL.

Person-centred care

In medical care the traditional way of counselling, is giving patients advice and expecting adherence to that advice. However, only to receive a diagnosis, will not be sufficient for the children who choose to seek medical care due to FHS. Clinicians need a dialogue about the families’ expectations, knowledge and experiences about living with FHS. For this purpose person-centred care (PCC) needs to be incorporated in the health care organisation. PCC means something different than individual care, as a child is an individual but also dependent of parents’ care and of the physical and social settings in which they live [153, 154].
The Swedish Agency for Health and Care Services Analysis (Myndigheten för vårdanalys i Sverige) has described PCC that does not focus only on medical information and treatment but also on the person’s experiences e.g. fear and anxiety, and to involve family and friends to the extent desired by the patients [155]. PCC focuses on the person’s right to have values and beliefs respected as an individual and his/her perspective of own health status and future care. PCC is a way to treat and care for the whole person, to deal with the person’s problems, but with respect for the autonomy, and also focusing on social relationship and other determinants of health [156]. Furthermore, it means that the person’s own story and description of the needs are given equal importance in the planning and implementation of health and care, as the professional assessments and identified needs. As shown in this thesis it is not always easy for the family to reintroduce foods to the child that had been avoided a long time without support, nor, after a positive severe outcome, to be aware that severe reactions occur if the child eats the culprit food by mistake.

Centre for Person Centred Care is an institution in Sweden conducting patient–oriented research about PCC [157]. It is reported that PCC is a way to reduce health care costs [155, 157, 159] and this type of health care improves the patients’ self-management abilities concerning long-term diseases e.g. diabetes [158] or cancer [160]. FHS can be a chronic or a long-term disease, but no studies so far have used PCC among patients with FHS, which is a shortcoming. The results in this thesis highlight the need of implementing PCC among children with FHS and their parents.

**Interventions to prevent reintroduction failure**

Our study as others, have shown that reintroduction failure after a negative challenge is common, which highlights the importance of further studies in this area. To reduce the number of reintroduction failures, follow-ups including serving a normal portion size of the food at the clinic after food challenges could be a possible solution. This would be interesting to do in future studies.

“Food (is) a complex entity, replete with contradictions and oppositions, full of confusions and a potential source of anxiety, particularly in relation to health”

*Chamberlain, K, page 468. [161]*
Acknowledgements

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Anna Winberg, my dearest friend and colleague in this project. Always calm under the stormiest times. Thank you for being my friend, in good and bad times. You are the best!
To be a good writer, you must first be a good reader. And being able to read your own work is the most difficult thing of all. Thank you Eva, Viveca, Linnea and Anna for helping me in this process!

“You don’t have to be great to get started, 
But you have to get started to be great” 
Les Brown

Lisbeth Nordström. So much fun we have shared! Thank you for your never ending enthusiasm in the clinical work and during all our research projects.

Helena Backman for helping me to understand the role of statistics, the coolest statistician ever.

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All my colleges at the Department of Pediatrics and my colleges at the Child and Adolescents Clinic at the University Hospital, Umeå. You all deserve to be mentioned by name but the space is limited. A special thanks to Itay, for being my happy roommate.

To all fantastic reviewers and language Editors who improved my articles, but the question is still: Am I allergic to hen’s egg or hens’ eggs?
Also, my gratitude to my colleagues at the paediatric allergy team in Västerbotten: Birgitta Höber, Birgitta Domeij, Stig Örjedst, Therese Lundgren, Christina West, Sara Liljeholm, Anna Crusell, Erik Reynevik, Elena Lundberg, Ulrika Jonsson, Nina Ekman, Britt-Marie Rönnfjord-Isaksson, Julia Dahlberg, Patrik Andersson and Malin Borgström. It is a pleasure working with you all!

To all my friends all not mentioned by name, but you all are in my heart. Alone is not strong. Thanks for your patience, I will be more present now! (...and do my exercise, Sanna)

My mother Gertrud for your never ending love and support in all of the windings in my life, starting with making me feel I am loved and gifted. My father Gösta, I know you are with me today, proud as always.

My brother Torbjörn with family for always being there, no matter what comes up.

Mother in law, Gunborg for excellent dinners and for always supporting me and my family. My father in law Nils, I wish you were here today.

My husband Anders for putting up with me even though I have been more distracted than ever. To all the future laughs and memories!

And to the most important in my life: My family!! Anders, Sofia and Erik. Love you!

Success

What people think it looks like.

Success

What it really looks like.

“Read, write, think-repeat”
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66


121. Umdac Open Code (Version 4.01) Umdac and Epidemiology and Public Health Sciences, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden.


Appendix 1-6

Appendix 1
The Swedish version of the OLIN postal questionnaire from 2006.

Appendix 2
The Swedish version of the questions regarding food hypersensitivity in the OLIN postal questionnaire from 2010.

Appendix 3
Interview guide, Paper III

Appendix 4
Interview guide, Paper IV

Appendix 5
Descriptive characteristic of the adolescents who performed double-blind placebo-controlled food challenge, outcome and archived reintroduction, Paper III.

Appendix 6
Descriptive characteristic of the children who performed double-blind placebo-controlled food challenge, outcome and archived reintroduction, Paper IV.
Appendix 1

The Swedish version of the OLIN postal questionnaire from 2006, Paper I

ENKÄT OM LUFTVÄGS-, NÄS- OCH HUDBESVÄR HOS BARN I ÅRSKURS 1 OCH 2 I LULEÅ, KIRUNA OCH PITEÅ KOMMUNER, 2006

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Namn på den förälder/vårdnadshavare som besvarat enkäten

.................................................tel nr hem ........................................ tel nr arb .........................................

Information om pricktest


☐ Ja, jag ger mitt godkännande till att mitt barn pricktestas.

☐ Nej, jag vill inte att mitt barn pricktestas.
Frågor numrerade med *fet* siffra besvaras av alla.

**Huvudfrågor – pipande och väsande andning**  
Sätt kryss i ja, nej eller lämplig ruta.

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| 1. Har barnet någonsin haft väsande eller pipande andningsljud i bröstet?  
Om du svarat ”nej” var god gå direkt till fråga 6. |   |   |
| 2. Har barnet haft väsande eller pipande andningsljud i bröstet någon gång **under de senaste 12 månaderna**?  
Om du svarat ”nej” var god gå direkt till fråga 6. |   |   |
| 3. Hur många episoder med väsande andning har barnet haft **under de senaste 12 månaderna**? | Ingen | 1 - 3 ggr | 4 - 12 ggr | Mer än 12 ggr |
| 4. **Under de senaste 12 månaderna**, hur ofta har i genomsnitt barnets sömn störts av väsande andning? | Aldrig vaknat med besvär | Mindre än 1 natt/vecka | 1 eller Flera Nätter/vecka |
| 5. **Under de senaste 12 månaderna**, har barnets väsande andning någon gång varit så svår att det endast kunnat säga ett- två ord mellan andetagen? |   |   |
| 6. Har barnet någonsin haft astma? |   |   |
| 7. **Under de senaste 12 månaderna**, har barnet haft väsande i bröstet under eller efter ansträngning? |   |   |
| 8. **Under de senaste 12 månaderna**, har barnet haft nattlig torrhosta utan att ha varit förkylt eller att ha haft en infektion i bröstet? |   |   |
### Tilläggsfrågor – pipande och väsande andning

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<td>Har barnet <strong>under de senaste 12 månaderna</strong> haft pipande eller väsande andning utan samtidig förkylning?</td>
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<td>10.</td>
<td>Tycker Du att barnet har lika bra ork (kondition) som sina jämnåriga kamrater?</td>
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<td>11.</td>
<td>Deltar barnet i skolans gymnastik och idrott <strong>i full omfattning</strong>?</td>
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<td>12.</td>
<td>Har barnet <strong>under de senaste 12 månaderna</strong> varit hemma från skolan vid något tillfälle pga andningsbesvär eller astma?</td>
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<td>13.</td>
<td>Har barnet av läkare fått diagnosen astma?</td>
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<td>14.</td>
<td>Går barnet på regelbundna kontroller för astma?</td>
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<td>15.</td>
<td>Hur ofta har barnet behövt ta medicin pga astma <strong>under de senaste 12 månaderna</strong>?</td>
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<td>16.</td>
<td>Om barnet behövt ta medicin, har barnet använt något av följande?</td>
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<td>Becotide, Pulmicort, Flutide eller andra kortisonpreparat</td>
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<td>17.</td>
<td><strong>Under de senaste 12 månaderna</strong>, hur mycket påverkade barnets andningsbesvär/astma barnets dagliga aktiviteter?</td>
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<tr>
<td>18.</td>
<td>Tycker du att barnets andningsbesvär/astma förvärras när barnet är i skolan?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Huvudfrågor vid näsbesvär
19. Har barnet **någonsin** varit besvärat av nysningar, rinnsnuva eller nästäppa **utan att** ha varit förkyld? Om du svarat ”nej” var god gå direkt till fråga 25

<table>
<thead>
<tr>
<th>JA</th>
<th>NEJ</th>
</tr>
</thead>
</table>

20. Har barnet **under de senaste 12 månaderna** varit besvärat av nysningar, rinnsnuva eller nästäppa **utan att** ha varit förkylt? Om du svarat ”nej”, var god gå direkt till fråga 25

<table>
<thead>
<tr>
<th>JA</th>
<th>NEJ</th>
</tr>
</thead>
</table>

21. Har **under de senaste 12 månaderna** dessa näsbesvär förekommit samtidigt med kliande, rinnande ögon?

<table>
<thead>
<tr>
<th>JA</th>
<th>NEJ</th>
</tr>
</thead>
</table>

22. Vilken/vilka månader hade barnet dessa näsbesvär? Sätt X i lämpliga rutor

<table>
<thead>
<tr>
<th>Januari</th>
<th>Februari</th>
<th>Mars</th>
<th>April</th>
<th>Maj</th>
<th>Juni</th>
<th>Juli</th>
<th>Augusti</th>
<th>September</th>
<th>Oktober</th>
<th>November</th>
<th>December</th>
</tr>
</thead>
</table>

23. **Under de senaste 12 månaderna**, hur mycket på verkade näsbesvären barnets dagliga aktiviteter?

<table>
<thead>
<tr>
<th>Inte alls</th>
<th>Något litet</th>
<th>Måttligt</th>
<th>Ganska mycket</th>
</tr>
</thead>
</table>

24. Hur ofta har barnet behövt ta medicin pga allergisk näs- eller ögonbesvär **under de senaste 12 månaderna**?

| Aldrig | Ibland | Ofta/periodvis | Varje dag |

25. Har barnet **någonsin** haft ”hösnuva”?

<table>
<thead>
<tr>
<th>JA</th>
<th>NEJ</th>
</tr>
</thead>
</table>

26. Har barnet av läkare fått diagnosen hösnuva eller allergiska näs-/ögonbesvär?

<table>
<thead>
<tr>
<th>JA</th>
<th>NEJ</th>
</tr>
</thead>
</table>
**Huvudfrågor vid hudbesvär**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>JA</th>
<th>NEJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.</td>
<td>Har barnet <strong>någonsin</strong> haft ett kliande utslag som kommit och gått under minst 6 månader? Om du har svarat &quot;nej&quot; var god gå direkt till fråga 34.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28.</td>
<td>Har barnet haft detta kliande utslag någon gång <strong>under de senaste 12 månaderna</strong>? Om du har svarat &quot;nej&quot; var god gå direkt till fråga 34.</td>
<td>JA</td>
<td>NEJ</td>
</tr>
<tr>
<td>29.</td>
<td>Har detta kliande utslag <strong>vid något tillfälle</strong> förekommit på något av följande ställen: armvecken, knävecken, fotleder, på lärens baksidor, eller på halsen, kring öronen eller ögonen?</td>
<td>JA</td>
<td>NEJ</td>
</tr>
<tr>
<td>30.</td>
<td>Vid vilken ålder fick barnet detta kliande utslag för första gången?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31.</td>
<td>Har detta utslag helt försvunnit vid något tillfälle <strong>under de senaste 12 månaderna</strong>?</td>
<td>JA</td>
<td>NEJ</td>
</tr>
<tr>
<td>32.</td>
<td><strong>Under de senaste 12 månaderna</strong>, hur ofta, i genomsnitt, har detta kliande utslag hållit barnet vaket nattetid?</td>
<td>Aldrig</td>
<td>Ej så ofta som 1 natt/v 1 el flera nätter/vecka</td>
</tr>
<tr>
<td>33.</td>
<td>Hur ofta använder barnet kortisonsalva för eksemet?</td>
<td>Aldrig</td>
<td>Ibland</td>
</tr>
<tr>
<td>34.</td>
<td>Har barnet <strong>någonsin</strong> haft eksem?</td>
<td>JA</td>
<td>NEJ</td>
</tr>
<tr>
<td>35.</td>
<td>Har barnet av läkare fått diagnosen eksem?</td>
<td>JA</td>
<td>NEJ</td>
</tr>
<tr>
<td>36.</td>
<td>Har barnet någonsin haft symtom på nickelallergi, dvs klåda/utslag av smycken, tex halssmycken, öronringar, metallknappar eller spänn?</td>
<td>JA</td>
<td>NEJ</td>
</tr>
<tr>
<td>37.</td>
<td>Har barnet hål i öronen?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

78
Frågor om matallergi

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Fråga</th>
<th>JA</th>
<th>NEJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>38.</td>
<td>Är barnet allergisk mot något i maten? Om ”ja” besvara fråga 39.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

39. Reagerar barnet på något av följande? Kryssa lämpliga alternativ. (Flera alternativ på varje rad möjliga)

<table>
<thead>
<tr>
<th>Alternativ</th>
<th>Vet ej</th>
<th>Inga besvär</th>
<th>Klåda i munnen</th>
<th>Andningsbesvär</th>
<th>Kräkningar, diarré eller ont i magen</th>
<th>Kliande utslag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mjölk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ägg</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fisk</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Skaldjur</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vetemjöl</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soja</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Äpplen</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Persikor</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kiwi</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Avokado</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Banan</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Apelsin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Råa morötter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potatis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jordnötter</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nötter</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annat, vad?</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
### Barnets bakgrundsdatal

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>40.</td>
<td>Vad var barnets födelsevikt? ……………………………………..gram</td>
</tr>
<tr>
<td>41.</td>
<td>Till vilken ålder fick barnet bröstmjölk? ……………………………………..månader</td>
</tr>
<tr>
<td>42.</td>
<td>Vid vilken ålder fick barnet för första gången tillägg/ersättning/välling? …………..månader</td>
</tr>
<tr>
<td>43.</td>
<td>Hur många syskon har barnet?</td>
</tr>
<tr>
<td>44.</td>
<td>Vilket barn i ordningen är barnet?</td>
</tr>
<tr>
<td>45.</td>
<td>Vad är barnets nuvarande längd? …………………  cm</td>
</tr>
<tr>
<td>46.</td>
<td>Vad är barnets nuvarande vikt? …………………… kg</td>
</tr>
<tr>
<td>47.</td>
<td>Förekommer allergiska besvär hos övriga familjemedlemmar? Sätt kryss i aktuell ruta, även om besvären försvunnit.</td>
</tr>
<tr>
<td></td>
<td>Astma</td>
</tr>
<tr>
<td></td>
<td>allergiska näs/ögonbesvär</td>
</tr>
<tr>
<td></td>
<td>Eksem</td>
</tr>
<tr>
<td></td>
<td>ofta luftvägskatarr</td>
</tr>
<tr>
<td></td>
<td>Började första gången före ett års ålder</td>
</tr>
<tr>
<td></td>
<td>Började första gången mellan 1 och 2 års ålder</td>
</tr>
<tr>
<td></td>
<td>Började första gången efter 2 års ålder</td>
</tr>
<tr>
<td>49.</td>
<td>Vistades barnet på familjedaghem/dagmamma före skolåldern? Kryssa för lämpligt alternativ.</td>
</tr>
<tr>
<td></td>
<td>Började första gången före ett års ålder</td>
</tr>
<tr>
<td></td>
<td>Började första gången mellan 1 och 2 års ålder</td>
</tr>
<tr>
<td></td>
<td>Började första gången efter 2 års ålder</td>
</tr>
<tr>
<td>50.</td>
<td>Har barnet haft</td>
</tr>
<tr>
<td></td>
<td>Kikhosta</td>
</tr>
<tr>
<td></td>
<td>Krupp</td>
</tr>
<tr>
<td></td>
<td>Lunginflammation</td>
</tr>
<tr>
<td></td>
<td>svårare luftvägssjukdom, t ex RS-virus</td>
</tr>
<tr>
<td></td>
<td>övrig svårare infektionssjukdom</td>
</tr>
</tbody>
</table>
Brukar barnet vara förkylt mer än 6 ggr/år? 

JA  NEJ

Brukar barnet hosta mer än 2 veckor i samband med förkylning? 

JA  NEJ

Barnets bostad och miljö

53. Var och i vilken typ av bostad bodde barnet under det första levnadsåret? Ange bostadsort samt sätt kryss i lämplig ruta för typ av område (stad/tätort eller ute på landet) och typ av bostad. (Om flera bostäder, ange den som barnet bott längst i under det första levnadsåret)

<table>
<thead>
<tr>
<th>Bostadsort</th>
<th>Typ av område</th>
<th>Typ av bostad</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stad</td>
<td>Landsbygd</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Nuvarande bostad</th>
<th>Tidigare bostad</th>
<th>Aldrig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecken på fukt- eller mögelskada</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Förekomst av imma/fukt på insidan av fönstren</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Braskamin/vedeldning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Större trafikerad väg eller mycket använd busshållplats inom 200 m från hemmet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilverkstad, större garage eller bensinstation inom 200 m från hemmet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stall eller ladugård inom 200 m från hemmet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

55. Nuvarande bostaden är:

<table>
<thead>
<tr>
<th>Ungefärligt bostadsyta</th>
<th>Ungefärligt bostadsyta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villa/radhus</td>
<td>Byggnadsår</td>
</tr>
<tr>
<td>Lägenhet</td>
<td>inkl kök</td>
</tr>
</tbody>
</table>

56. Hur många vuxna bor i hemmet?

57. Hur många barn bor i hemmet?
### Djur, fritid och kost

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Nu</th>
<th>Tidigare under barnets uppväxt</th>
<th>Aldrig</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>58.</strong> Har Ni nu eller har Ni tidigare haft husdjur någon gång under barnets uppväxt?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kryssa i tillämpliga rutor i tabellen.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hund</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanin/marsvin/hamster</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annat pälsbärande djur</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burfågel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annat husdjur</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **59.** | Fanns pälsdjur under någon period under barnets första två levnadsår? | JA | NEJ |
| **60.** | Har Du/Ni valt att **inte** ha pälsdjur (tex katt eller hund) på grund av allergi i familjen? |   |    |
| **61.** | Har Du/Ni valt att **inte** ha pälsdjur (tex katt eller hund) på grund av rädsla för att barnet ska bli allergiskt? |   |    |

| **62.** | Har eller har familjen haft jordbruk? |   |    |
| **63.** | Rider barnet? | JA | NEJ |
| Rider annan familjemedlem? |   |    |

| **64.** | Idrottar barnet regelbundet inomhus? | JA | NEJ |
| Idrottar barnet regelbundet utomhus? |   |    |
| Idrottar barnet regelbundet i ishall? |   |    |

| **65.** *Hur ofta* åter barnet någon slags frukt? | Varje dag, minst två |
| Varje dag, ungefär en |
| Närstan varje dag |
| 1-3 gånger per vecka |
| Mindre än en gång per vecka |

| **66.** *Hur ofta* åter barnet fisk? | Minst 3 gånger per vecka |
| Ungefär 2 gånger gånger per vecka |
| Ungefär 1 gång per vecka |
| Ungefär 1-3 gånger per vecka |
| Mindre än 1 gång per månad |
| Aldrig |
### 67. Hur ofta äter barnet snabbmat (t.e.x mat från Mac Donalds, Frasses, Max eller andra grill- och korvkiosker)?

<table>
<thead>
<tr>
<th>Ofta åter barnet snabbmat</th>
<th>Ungefär 1 gång per dag</th>
<th>Ungefär varannan dag</th>
<th>Ungefär 2 gånger per vecka</th>
<th>Ungefär 1 gång per vecka</th>
<th>Enstaka gånger per månad</th>
<th>Aldrig eller nästan aldrig</th>
</tr>
</thead>
</table>

**Rökvanor i familjen.** Kryssa i tillämpliga rutor i tabellen.

<table>
<thead>
<tr>
<th>Röker inte</th>
<th>Röker 0-4 cig/dag</th>
<th>Röker 5-14 cig/dag</th>
<th>Röker 15-24 cig/dag</th>
<th>Röker 25 cig/dag eller mer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Far</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Röker inte</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Röker inte</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annan familjemedlem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Röker inte</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**69. Brukar någon röka inomhus eller under köksfläkten i hemmet?**

<table>
<thead>
<tr>
<th>Röker inte</th>
<th>Nej, aldrig</th>
<th>Ja, högst 1 ggr/vecka</th>
<th>Ja, mer än 1 dag/vecka</th>
</tr>
</thead>
</table>

**70. Förekom rökning hemma under barnets första levnadsår?**

<table>
<thead>
<tr>
<th>Rökte under första levnadsår</th>
<th>JA</th>
<th>NEJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Far rökte</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mor rökte</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annan familjemedlem rökte</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**71. Rökte modern under graviditeten?**

<table>
<thead>
<tr>
<th>Rökte under graviditeten</th>
<th>JA</th>
<th>NEJ</th>
</tr>
</thead>
</table>

Tack för Din medverkan!
The Swedish version of the questions regarding food hypersensitivity in the OLIN postal questionnaire from 2010.

**Frågor om födoämnesöverkänslighet**

<table>
<thead>
<tr>
<th></th>
<th>JA</th>
<th>NEJ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>37.</strong></td>
<td>Har barnet någonsin varit allergisk/överkänslig mot något i maten?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **38.** | Är barnet nu allergisk/överkänslig mot något i maten?  
Om "ja" besvara fråga 39-45. Om "nej" gå direkt till fråga 46. | JA | NEJ |
|   |   |   |
| **39.** | Reagerar barnet på något av nedan följande?  
Kryssa lämpliga alternativ. (Flera alternativ på varje rad möjliga) | Vet ej | Inga besvär | Kläda i munnen | Andningsbesvär | Kräkningar, diarré eller ont i magen | Kliande utslag |
|   | Mjölk |   |   |   |   |   |
|   | Ågg |   |   |   |   |   |
|   | Fisk |   |   |   |   |   |
|   | Vetemjöl |   |   |   |   |   |
|   | Soja |   |   |   |   |   |
|   | Applen |   |   |   |   |   |
|   | Kiwi |   |   |   |   |   |
|   | Banan |   |   |   |   |   |
|   | Apelsin |   |   |   |   |   |
|   | Råa morötter |   |   |   |   |   |
|   | Potatis |   |   |   |   |   |
|   | Jordnötter |   |   |   |   |   |
|   | Nötter |   |   |   |   |   |
|   | Mandel |   |   |   |   |   |
|   | Annat, vad? |   |   |   |   |   |
Undvikar inte alls  
Undvikar delvis  
Undvikar helt

40. I vilken utsträckning undviker barnet följande födoämnen på grund av allergi/överkänslighet?

- Mjölk
- Ägg
- Fisk
- Vetemjöl

41. Har barnet någonsin behövt göra några akuta besök på sjukhus eller vårdcentral på grund av födoämnesöverkänslighet?

JA  NEJ

42. Har barnet under de senaste 12 månaderna behövt göra några akuta besök på sjukhus eller vårdcentral på grund av födoämnesöverkänslighet?

JA  NEJ

43. Har barnet någonsin fått förskrivet adrenalin (Epipen, Anapen) för att ha i beredskap?  
Om ja, för vad? ....................................................................

JA  NEJ

44. Har barnet under de senaste två åren fått förskrivet adrenalin (Epipen eller Anapen) för att ha i beredskap?  
Om ja, för vad? ....................................................................

JA  NEJ

45. Har barnet av läkare fått diagnosen celiaki (glutenintolerans)?

JA  NEJ

### Barnets bakgrundsdata

<table>
<thead>
<tr>
<th>46.</th>
<th>Förekommer allergiska besvär hos övriga familjemedlemmar? Sätt kryss i aktuell ruta, även om besvären försvunnit.</th>
<th>Far</th>
<th>Mor</th>
<th>Syskon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>astma</td>
<td>allergiska näs/ögonbesvär</td>
<td>eksem</td>
<td>födoämnesöverkänslighet</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 3

Interview guide, Paper III

Hur är det att inte kunna äta allt?
Hur hanterar du det i din vardag?
Hur var dina känslor före matprovokationen?
Hade du några förväntningar innan matprovokationen?

*Kan du beskriva hur du upplevde provokationen?
Vad hände under provokationen?
Hur smakade drycken du drack?

*Vad hände efter provokationen?
Har ditt liv förändrats på något sätt efter provokationen (jämfört med innan provokationen)?
Om svaret är ja.. hur? Om svaret är nej.. varför?
Vilka känslor hade du om provokationen visade att du kunde börja äta maten du provocerats för

*Äter du den maten nu?
(äter helt, delvis eller inte alls)

Följfrågor för att förklara eller föra samtalet vidare kunde vara:
Beskriv dina känslor..
Vad är din upplevelse av..
Vad hände då..

*huvudfrågor
Appendix 4

Interview guide, Paper IV

Den intervjuades ålder ..........
Har födoämnet som barnet dubbelblind provocerats för införts i barnets kost?
Helt i mat och dryck/delvis endast i mat

*Hur upplevde du provokationen?

*Vilka känslor hade du när livsmedlet hade återintroducerats efter provokationen?
Hur tänkte du, hur gick det?)
Kan du berätta om en situation då du kände så?
Kan du berätta om en annan situation då det kändes på ett annat sätt?
Nu när ditt barn ätit detta livsmedel ett längre tag, är det då någon skillnad i din upplevelse?
Vad har dubbelblind provokationen inneburit för dig?
Har vardagen förändrats för dig jämfört innan dubbelblind provokationen genomfördes?

Följdfrågor för att förklara eller föra samtalet vidare kunde vara:
Berätta vidare...Hur menar du då..
Hur tänker du då..Vad betyder det att..
Hur uppfattade du situationen..Nu hänger jag inte riktigt med, kan du hjälpa mig..

*huvudfrågor
Appendix 5

Descriptive characteristic of the adolescents who performed double-blind placebo-controlled food challenge, outcome and archived reintroduction, Paper III.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Challenged food</th>
<th>Age at onset</th>
<th>Reported symptoms before DBPCFC</th>
<th>Challenge outcome</th>
<th>Achieved reintroduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Milk</td>
<td>2-3 y</td>
<td>Flatulence</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Female</td>
<td>Milk</td>
<td>2-3 y</td>
<td>Diarrhea, flatulence</td>
<td>Negative</td>
<td>Completely</td>
</tr>
<tr>
<td>Female</td>
<td>Milk</td>
<td>2-3 y</td>
<td>Eczema, diarrhea, obstipation, flatulence</td>
<td>Negative</td>
<td>Partially</td>
</tr>
<tr>
<td>Female</td>
<td>Milk</td>
<td>&lt;1 y</td>
<td>Itching in the mouth, swollen lips, flatulence</td>
<td>Mild</td>
<td>Partially</td>
</tr>
<tr>
<td>Female</td>
<td>Milk</td>
<td>&lt;1 y</td>
<td>Eczema, vomiting, flatulence, diarrhea</td>
<td>Mild</td>
<td>Partially</td>
</tr>
<tr>
<td>Female</td>
<td>Test 1 Milk</td>
<td>&lt;1 y</td>
<td>Itching in the mouth, nausea and vomiting</td>
<td>Mild</td>
<td>Partially</td>
</tr>
<tr>
<td>Test 2 Egg</td>
<td>&lt;1 y</td>
<td>Asthma, eczema</td>
<td>Severe</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Egg</td>
<td>4-5 y</td>
<td>Urticaria</td>
<td>Negative</td>
<td>Completely</td>
</tr>
<tr>
<td>Female</td>
<td>Egg</td>
<td>1 y</td>
<td>Diarrhea, flatulence</td>
<td>Mild</td>
<td>Partially</td>
</tr>
<tr>
<td>Female</td>
<td>Egg</td>
<td>5 y</td>
<td>Eczema</td>
<td>Severe</td>
<td>No</td>
</tr>
<tr>
<td>Female</td>
<td>Cod</td>
<td>1 y</td>
<td>Eczema</td>
<td>Mild</td>
<td>No</td>
</tr>
<tr>
<td>Female</td>
<td>Cod</td>
<td>1-2 y</td>
<td>Flatulence</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Male</td>
<td>Milk</td>
<td>1 y</td>
<td>Eczema, diarrhea, flatulence</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>Male</td>
<td>Milk</td>
<td>5-7 y</td>
<td>Vomiting, diarrhea, flatulence, tiredness</td>
<td>Negative</td>
<td>Partially</td>
</tr>
<tr>
<td>Male</td>
<td>Egg</td>
<td>1-2 y</td>
<td>Vomiting</td>
<td>Negative</td>
<td>Partially</td>
</tr>
<tr>
<td></td>
<td>Test 1</td>
<td>&lt;1 y</td>
<td>Itching in the mouth, flatulence, stomach pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---------</td>
<td>------</td>
<td>------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Egg</td>
<td></td>
<td>Severe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Test 2</th>
<th>1-2 y</th>
<th>Itching in the mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Cod</td>
<td></td>
<td>Negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cod</th>
<th>1 y</th>
<th>Eczema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>Negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cod</th>
<th>5-6 y</th>
<th>Itching in the mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>Negative</td>
</tr>
</tbody>
</table>

If the participants reacted with mild symptoms to milk or egg during the DBPCFC, they were advised to try partial reintroduction of the food at home, using baked milk or egg products.
Appendix 6

Descriptive characteristic of the children who performed double-blind placebo-controlled food challenge, outcome and archived reintroduction, Paper IV.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Challenged food</th>
<th>Age at onset</th>
<th>Reported symptoms before DBPCFC</th>
<th>Challenge outcome</th>
<th>Achieved reintroduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Test 1 Milk</td>
<td>1 y</td>
<td>Diarrhea, blue under the eyes</td>
<td>Negative</td>
<td>Completely</td>
</tr>
<tr>
<td></td>
<td>Test 2 Wheat</td>
<td>1 y</td>
<td>Diarrhea, blue under the eyes, stomac pain</td>
<td>Negative</td>
<td>Completely</td>
</tr>
<tr>
<td>Female</td>
<td>Milk</td>
<td>&lt;1 y</td>
<td>diarrhea, flatulence, urticaria, mucos in the throat</td>
<td>Negative</td>
<td>Completely</td>
</tr>
<tr>
<td>Female</td>
<td>Milk</td>
<td>&lt;1 y</td>
<td>Eczema, stomac pain, diarrhea or obstipation</td>
<td>Negative</td>
<td>Partially</td>
</tr>
<tr>
<td>Female</td>
<td>Wheat</td>
<td>6y</td>
<td>Stomac pain</td>
<td>Negative</td>
<td>Completely</td>
</tr>
<tr>
<td>Male</td>
<td>Milk</td>
<td>&lt;1 y</td>
<td>Diarrhea, stomac pain</td>
<td>Mild</td>
<td>Partially</td>
</tr>
<tr>
<td>Male</td>
<td>Milk</td>
<td>&lt;1 y</td>
<td>Eczema, diarrhea, flatulence</td>
<td>Negative</td>
<td>Completely</td>
</tr>
<tr>
<td>Male</td>
<td>Milk</td>
<td>&lt;1 y</td>
<td>Stomac pain</td>
<td>Negative</td>
<td>Completely</td>
</tr>
<tr>
<td>Male</td>
<td>Milk</td>
<td>&lt;1 y</td>
<td>Diarrhea, urticaria</td>
<td>Negative</td>
<td>Completely</td>
</tr>
<tr>
<td>Male</td>
<td>Milk</td>
<td>&lt;1 y</td>
<td>Diarrhea</td>
<td>Negative</td>
<td>Completely</td>
</tr>
</tbody>
</table>

If the participants reacted with mild symptoms to milk or egg during the DBPCFC, they were advised to try partial reintroduction of the food at home, using baked milk or egg products.