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SYMPTOMS OF FOOD HYPERSENSITIVITY IN RELATION TO SENSITIZATION TO FOOD AND HEALTH-RELATED QUALITY OF LIFE IN CHILDREN

Stockholm 2008

Det är med idéer som med små barn.
Man tycker bäst om sina egna
Moa Martinsson

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ABSTRACT

Intensive research in the field of food hypersensitivity (FHS) and food allergy has resulted in determination of serum levels of IgE antibodies to food above which the probability of demonstrating symptoms is ≥ 95%. However, data concerning clinical phenotypes of FHS and the relationship between sensitization to food and symptoms are presently scarce. Moreover, research on the impact of FHS on health-related quality of life (HRQL) is still in its infancy.

Accordingly, the general aim of this thesis was to characterize children reported by their parents to have FHS with regards to symptoms, sensitization, different phenotypes and the impact on HRQL, employing a population-based study design. A prospective birth cohort (BAMSE) of 4,089 children was followed up to the age of 8-9 years by having their parents fill in questionnaires concerning the children's exposures and health outcomes at various time-points. Blood samples were collected at 4 and 8 years of age for analysis of IgE antibodies to food. At 9 years of age, a separate questionnaire concerning HRQL was filled out by the parents of a subgroup of 1,376 children.

Paper I describes different phenotypes of FHS observed in children during their first 8 years of life. An increased risk of having asthma, rhinitis and/or atopic eczema at 8 years of age was seen for children reported to have FHS at an early age. Children who demonstrated only a single symptom of FHS and/or little or no sensitization to food had the most favourable prognosis for later remission of their food-related symptoms

Paper II characterizes different aspects of sensitization and reported FHS in 4-year-old children. Half of all the children with gastrointestinal symptoms or atopic dermatitis exhibited only a single symptom and less than 50% of these same children were sensitized to food. Among the children with reported urticaria, facial oedema or wheeze related to food, a majority had multiple symptoms and where sensitized to food as well.

Paper III documents a positive association between reported FHS and elevated levels of IgE antibodies to milk, eggs or fish. For peanuts, this association was also significant, although not as pronounced as expected; whereas for soy beans and wheat the association was very weak.

The final investigation reveals that as reported by their parents, the HRQL of children with FHS is lower than that of both children with no allergic disease and children suffering from other allergic disorders. This impairment in HRQL was most pronounced for children with food-related symptoms originating from the airways. High levels of IgE antibodies to food were also associated with a reduced HRQL.

In conclusion, children demonstrating only a single symptom of FHS and/or no sensitization to food seem to recover from this disease. Increasing levels of IgE antibodies to milk, egg or fish are associated with an enhanced risk of having FHS elicited by these items of food, but this is not seen to the same extent particularly for soy bean, but also for wheat and peanuts. FHS leads to a negatively affected HRQL for both children and their families. This is especially true if the disease is pronounced or associated with high levels of IgE antibodies to food.

Key words: BAMSE, children, food hypersensitivity, food allergy, health-related quality of life, IgE antibodies, sensitization

LIST OF PUBLICATIONS

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IV. Östblom E, Egmar A-C, Gardulf A, Lilja G, Wickman M. The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. Allergy 2008, in press.

CONTENTS

LIST OF ABBREVIATIONS

BAMSE	Children Allergy Milieu Stockholm an Epidemiological Study (Barn, Allergi, Miljö i Stockholm, en Epidemiologisk studie [Swedish])
CHQ-PF28	Child Health Questionnaire - Parental Form 28
CI	Confidence interval
DFA	Food allergy diagnosed by a physician
ETS	Environmental tobacco smoke
FHS	Food hypersensitivity
HRQL	Health-related quality of life
IgE	Immunoglobulin E
ISAAC	International Study of Asthma and Allergies in Childhood
kU_A/L	Kilo units of allergens per litre
NPV	Negative predictive value
OAS	Oral allergy syndrome
OR	Odds ratio
PPV	Positive predictive value
QoL	Quality of life
SPT	Skin prick test

1 INTRODUCTION

1.1 NOMENCLATURE

The investigation and diagnosis of food hypersensitivity, particularly in children whose symptoms are not always easy to identify and interpret, involves numerous difficulties. Perceived food hypersensitivity (FHS) is much more common than verified FHS. Thus, 20% or more of the subjects in several population-based studies believe that they or their children are food hypersensitive[1,2] However, scientific investigations indicate that approximately 6% of all children in the westernized countries suffer from food allergy, i.e., FHS caused by immunological mechansims.[1-4] This discrepancy may be caused by several factors. A major problem being that no criteria for definition of FHS or food allergy were agreed upon until recently. In 2001 Johansson *et al*. described such criteria that most clinicians and researchers in the field of allergy accept today (Fig. 1),[5] although total consensus has not yet been attained.[4,6]

By definition, food allergy is mediated by allergen-specific IgE antibodies to food or via other immunological mechanism such as allergic gastroenteritis/eosophagitis which is characterized by the presence of elevated numbers of eosinophils in the affected tissue, but an absence of IgE antibodies to food in the blood.[5,7] Furthermore, for both FHS and food allergy the symptoms must be elicitable by oral challenge with the suspected food. Unaware of these definitions of FHS and food allergy, the general lay population probably considers any physical or psychological symptom or discomfort caused by anything you eat to be “food allergy” or “FHS”.[8] For the physician, of course, the underlying mechanism is extremely significant influencing not only the diagnostic procedures employed and prognosis, but also secondary preventive efforts, including the provision of information and recommendations to the patients or their parents. The afflicted individual on the other hand, simply wants to know “Is it safe or not for me to eat this”?

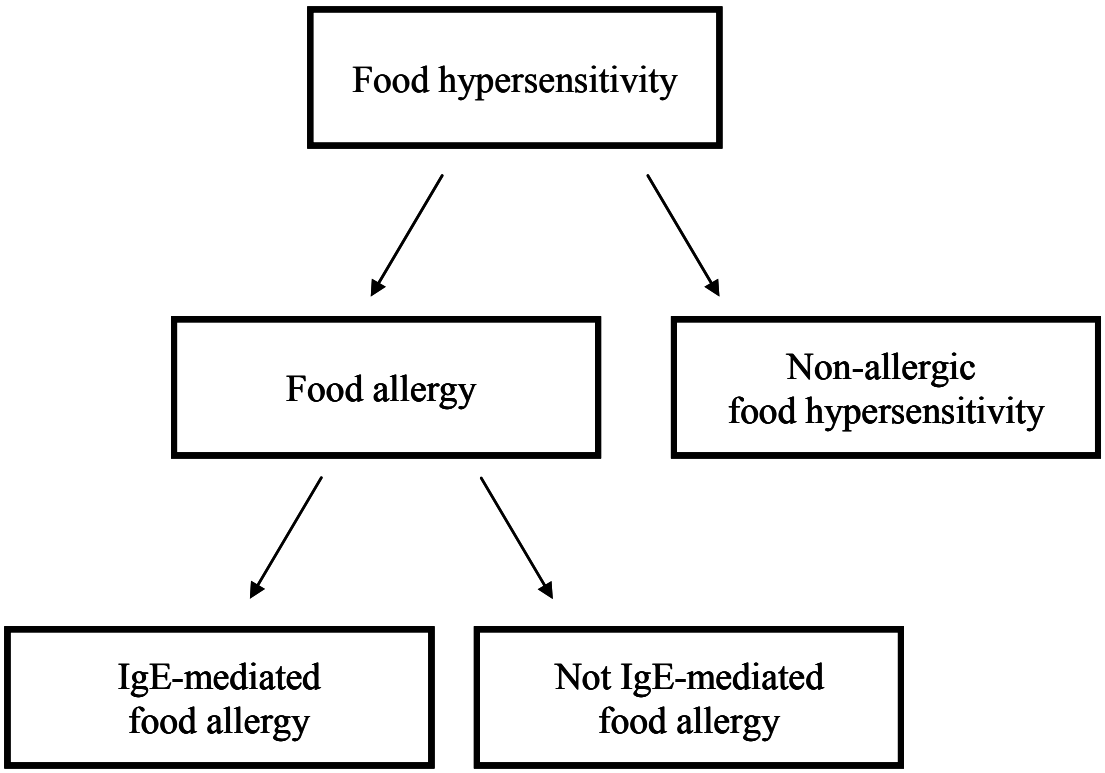


Figure 1. Schematic representation of different kinds of food hypersensitivity modified from SGO Johansson, Allergy 2001.[5]

1.2 EPIDEMIOLOGY OF ALLERGIC DISEASE IN GENERAL AND FOOD HYPERSENSITIVITY IN PARTICULAR

It is general knowledge that the frequencies of allergic disease such as asthma, allergic rhinitis and atopic dermatitis have increased during the last 2-3 decades.[9-11] The prevalence of such allergic diseases in children, vary considerably between different geographic regions and countries. An apparently consistent world-wide pattern is that the prevalence is higher in countries with a Western lifestyle than in developing countries.[12-24] Furthermore, several studies have revealed that children who grow up in urban areas develop allergic diseases more frequently than those who grow up in rural areas.[25-29] Moreover, an anthroposophic lifestyle seems to reduce the risk for such allergic diseases.[30-33]

The International Study of Asthma and Allergies in Childhood (ISAAC), documented prevalence ratios of asthma in children ranging from 1.6% (Indonesia) to 30% (Australia),[34] the highest frequencies being present in English-speaking countries. In Sweden, the prevalence of asthma in children is approximately 6-9%.[16,24,35] Allergic rhinitis, which is uncommon in children younger than five years of age, demonstrated a similar pattern, i.e., higher prevalence in westernized countries. Accordingly, for this

disease the ISAAC study reported prevalences of 9-33% within Europe,[18] and of 2.2-24% in Asia, South America and Africa. In Sweden, the corresponding prevalence ranges between 10-22% with higher prevalences being observed in adolescents.[13,21] As in the case of these other allergic diseases, the prevalence of atopic dermatitis also varies between countries and geographic regions, from 10% in Nigeria to 21% in Sweden.[13-15,19,20,36]

FHS in one and the same individual varies during childhood, and less is known about the prevalence of this condition in comparison to the other allergic diseases discussed above. Furthermore, there are so far no population-based studies having demonstrated changes in time trends of FHS or food allergy although there are a few reports on increased frequencies of peanut allergy [37,38] and food allergy in general. [39] The prevalence of food allergy has in children three years of age or younger been estimated to 6-8%.[4] Among infants, this prevalence is higher than among schoolchildren and adolescents.[4,40] In an early study by Bock in 1987, 8% of the participating children exhibited adverse reactions to at least one item of food.[1] Similar results have been obtained by other investigators, although not all of these have performed food challenges.[3,4,41,42] In short, there is a heterogeneity in prevalence of FHS, both due to possible differences in different regions in the world, but also due to differences in definition and methodology.[42] All of this is surprising in light of the fact that together with atopic dermatitis (which is also sometimes food-related), FHS is one of the most common diseases that develop during the two years of life.[4,43] Moreover, little is presently known about the changes in the population regarding severity of FHS.[6] In addition, only limited information concerning different phenotypes of FHS is available, and the data that do exist are based on case or cross-sectional studies. Finally, the association between various phenotypes of FHS and sensitization to food (allergen-specific IgE antibodies ≥ 0.35 kU_A/L) has not been examined in detail.

Food allergy can lead to potentially fatal reactions including anaphylaxis, a severe, systemic allergic reaction that occurs suddenly after contact with the appropriate allergen.[44] Recently, the Epidemiology of Anaphylaxis Working Group of the American College of Allergy, Asthma and Immunology estimated that the lifetime prevalence of anaphylaxis is 0.05% to 2.0%,[45] but it is not known how much of this is food-related. An Australian study found the rate of anaphylaxis in children to be 0.59 per 100. [46] Fatal allergic reactions to food are uncommon: during the period of 1999 to 2006, 48 such deaths were reported in the UK, (which is assumed to be an underestimation),[47] while in Sweden there were five fatal cases reported between 1993 and 1996,[48] and six between 1997 and 2003.[49] Certain foods, including peanuts and tree-nuts, cause severe or even fatal reactions more frequently than others.[48,50-55]

1.3 NATURAL COURSE OF FHS AND FOOD ALLERGY

Only limited longitudinal data concerning the natural course of FHS in children are presently available. However, allergy to cow's milk and hen's eggs are most common in children less than three years of age (with a prevalence of approximately 2-

3% and 1-2%, respectively) with the prevalence of allergies to other items of food being only 0.1-0.8%.[4,56] The majority of children who develop food allergy exhibit their first symptoms during the early years of life. Fortunately, the majority of those afflicted eventually develop tolerance to milk (70-90%) or eggs (60-70%).[4,57-61] In children of school-age and older, peanuts, tree-nuts and different types of fruit appear to be the food items that most frequently evoke clinical symptoms.[4,62,63] Simultaneous allergy to foods is associated with an enhanced risk for persistent food allergy.[61] Furthermore, allergy to cow's milk during infancy is associated with respiratory atopy and persistency and severity of atopic dermatitis, as well as with allergy to other items of food.[64, 65, 66]

1.4 FACTORS THAT INCREASE THE RISK OF DEVELOPING FOOD ALLERGY/HYPERSENSITIVITY

In general, genetic factors play a major role in the development of allergic disease. In some studies, certain genes were found to be associated with an increased risk for having asthma or sensitization.[67-72] Furthermore, Sicherer and co-workers found a genetic influence on peanut allergy.[73] Otherwise, information concerning genetic determinants of FHS, mediated via development to IgE antibodies or not, is scarce.

Environmental risk factors associated with food allergy have also been identified. For example, infants who are breastfed exclusively during the first months of life have been found in certain studies to run a lower risk of developing food allergy, especially to cow's milk.[74-76] It is not known whether breast milk is protective *per se*, and/or if the later introduction of cow's milk in the diet reduces the risk. In children with a family history of allergies, who require supplementary feeding during their first four months of life, the use of formulas based on hydrolyzed cow's milk is associated with a lower risk for the development of food allergy, once again especially to cow's milk.[77,78] One investigation concluded that maternal avoidance of certain foods during pregnancy and/or lactation is associated with a decreased risk for sensitization of the child to certain foods,[79] whereas in other studies no correlation between maternal diet during pregnancy or lactation and the risk for clinical food allergy in the child was observed.[80-83] Likewise, pre- and postnatal exposure to tobacco smoke has been associated with sensitization to food, but again, no association with food allergy has been demonstrated.[84]

Eggesbo and co-workers have reported that delivery by caesarean section is associated with elevated incidences of verified allergies to eggs and cow's milk.[85,86] Furthermore, Lauberau *et al.* found sensitization to food to be twice as common among children delivered by caesarean section as among those delivered vaginally.[87] The mechanism by which caesarean section may enhance the risk for atopy in children has not been elucidated, but differences in the gut flora have been proposed as one possible explanation.[85,87]

1.5 DIAGNOSIS OF FHS

In the case of children who exhibit high levels of IgE antibodies towards a certain item of food together with typical adverse reactions to this same food, diagnosis of food allergy is relatively straightforward. However, many children do not demonstrate clear symptoms and analysis of their IgE antibodies and/or skin prick test, (SPT) is often inconclusive. Another problem in this context is cross-reactivity, both with respect to the test procedures available and different food allergens that elicit clinical symptoms. Moreover, sensitization to food without any development of clinical signs of food allergy is common and leads to a considerable risk for misinterpretation by both health-care personnel and by parents.[4,40,88] Some of these difficulties are illustrated by the fact that sensitization to soy beans is relatively common in the absence of any related clinical symptoms and the majority of children sensitized to soy beans are also sensitized to peanuts.[89] Another example is that children who are allergic to birch pollen may exhibit allergic symptoms (oral allergy syndrome, OAS) characteristically evoked by fruits with pips without being sensitized to these fruits, due to the similar epitopes (i.e., protein structures) present on the antigens in birch pollen and these fruits.[90]

In the past few years considerable effort has been focused on a better understanding and improvement of the tools employed to diagnose FHS and food allergy. Sampson and co-workers have determined the levels of IgE antibodies directed towards specific items of food above which the probability of developing clinical reactions is $\geq 95\%$.[4,91] Corresponding value for tree nuts has been established by Clark *et al.*[92] These values are presented in Table I together with the positive predictive value (PPV). It is now known that the levels of IgE antibodies to food associated with symptoms are lower in young children than in older children. These levels in the case of allergy to cow's milk or eggs in children less than two years of age are also presented in Table I.[4,91,93-95] In a study from Japan the results indicate that the specific IgE antibody levels might be even lower in young infants.[95]

Allergen	95% predictive IgE-ab level, kU_A/L	PPV
Eggs		
- children ≤ 14 years[a]	7	98
- children ≤ 2 years[b]	2	95
Cow's milk		
- children ≤ 14 years[a]	15	95
- children ≤ 2 years[c]	5	95
Peanuts[a]	14	100
Tree nuts[d]	15	ca. 95
Fish[a]	20	100
Soy bean[a]	30	73
Wheat[a]	26	74

Table I. Predictive values of IgE antibody levels with respect to clinically verified symptoms. Modified from Sampson HA. J Allergy Clin Immunol 2004;113:805-19.

[a]Sampson HA et al., J Allergy Clin Immunol 2004;113:805-19.
[b]Boyano-Martínez T et al., Clin Exp Allergy 2001;31:1464-9.
[c]García-Ara C et al., J Allergy Clin Immunol 2001;107:185-90.
[d]Clark AT et al., Clin Exp Allergy 2003;33:1041-5.

Skin prick tests (SPT) are employed widely in attempts to diagnose FHS. The advantages offered by this approach in comparison with measuring circulating IgE antibodies in serum are that the results are obtained within 15 minutes and cost less. In addition, many children experience such a test as less scary and painful than the taking of a blood sample. The specificity of SPT is comparable to that of measuring IgE antibodies, although the sensitivity is somewhat lower.[93] However, the SPT must be performed by highly experienced personnel.

In a study on a high-risk population of children with a mean age of three years, Sporik and co-workers found that weal diameters of seven mm for eggs and eight mm for both cow's milk and peanuts were associated with a 100% probability for a positive response to an open food challenge.[96] Also focusing on a high-risk population, Verstege *et al.* reported a 95% probability for a positive response to challenge with milk in association with weal diameters of 7.9 and 13.2 mm in children younger and older than one year of age, respectively. The corresponding weal diameters for eggs were 9.3 and 11.2 mm, respectively.[97]

The atopy patch test (APT) has also been evaluated as a procedure for diagnosing FHS and food allergy, but consensus concerning the usefulness of this test has not yet been reached. Thus, certain studies conclude that APT is a useful or promising tool in

this context,[98,99] while others report less promising findings and call for standardization of this procedure.[100-102]

The gold standard for diagnosis of FHS or food allergy is double-blind, placebo-controlled food challenges (DBPCFC).[103,104] However, these are expensive and time-consuming procedures, as well as being potentially dangerous for the patient (even though serious incidents are rare).[4,105] Furthermore, the outcome of an oral challenge can be difficult to interpret. Thus, among children with atopic dermatitis, a condition often associated with FHS[106], an aggravation of the skin disease is not always detected in connection with a food challenge, since the reaction sometimes appears many hours later. In addition, 10% of the positive food challenges observed in children with atopic dermatitis, are not mediated by IgE antibodies.[107] In certain cases, e.g., in very young children, open challenges are acceptable.[104] In a clinical setting it is not always possible to subject all patients suspected of having FHS to a food challenge. The cost would be prohibitive since as many as 20% of the general population has perceived reactions to food. Therefore, many paediatric clinics dealing with patients suffering from FHS perform challenges only on a minority of their patients. Furthermore, in connection with such challenges, ready access to emergency equipment and personnel trained in managing acute anaphylactic reactions are necessary, and these are not always available. In research settings, food challenges are often performed, but usually on a relatively limited number of participants, most of whom are patients, which explain why population-based data concerning prevalence of FHS and food allergy are so scarce.

1.6 THE IMPACT OF FHS ON HEALTH-RELATED QUALITY OF LIFE

Quality of life (QoL) is a highly subjective concept and has been defined as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[108] Health-related quality of life (HRQL), the aspect of QoL related directly to the health of the individual, involves physical, psychological and social factors.[109] Thus, the physiological severity of disease, i.e. asthma or rhino-conjunctivitis in children, as measured by different objective methods is not the only factor influencing the HRQL.[110,111] It is also known that the perception of a disease or an illness is not the same for the affected individual and for people close to the affected person.[112-114]

FHS can be potentially life-threatening,[47,48] and irrespective of whether this condition can be verified clinically its suspected presence imposes a significant burden on the patient and his/her family, in physical as well as in psychological terms. At present, research on FHS and HRQL is still in its infancy. However, the few studies that have been published consistently reveal that FHS exerts a negative impact on the HRQL of both the child and the family.[115-124]

In connection with efforts to clarify the impact of FHS on HRQL, a number of approaches are available. So far, most such studies have applied a quantitative approach, involving various questionnaires. Qualitative analyses are another way to approach this field of research and by using these kinds of methods even more detailed information on an individual level is obtained.

In some cases the impact of different types of disorder on HRQL has been compared. For instance, Avery and co-workers found that the HRQL of children with peanut allergy is more highly impaired than that of children suffering from insulin-dependent diabetes.[115] In addition, Primeau *et al.* concluded that the parents of children with peanut allergy report more disruption of daily life than do parents whose children are afflicted by rheumatologic diseases.[118]

A generic instrument, Child Health Questionnaire-Parental Form 50 (CHQ-PF50), was used in this context by Sicherer and co-workers.[119] The considerable advantages offered by a generic instrument include easier comparison of different groups, and the more ready availability of normative data. In their study Sicherer *et al.,* showed that in terms of General health, Parental impact – emotional and Family activities the HRQL of children with a food allergy is significantly lower than that of the general population in the United States.[119]

Employing a shorter version of this same instrument, designated CHQ-PF28, Marklund and co-workers concluded that the negative impact of FHS on the HRQL of children were more closely related to measures taken in attempt to avoid the offending food than to the clinical symptoms themselves.[125] In another investigation involving a qualitative approach, Marklund *et al.* demonstrated that avoidance of the food in itself and not only the somatic reactions alone has a significant impact on the lives of adolescents.[126] A further qualitative study based on in-depth interviews and performed by Akeson *et al*. revealed that an anaphylactic reaction in their child could exert a long-term psychological impact on parents and that their anxiety may be transferred to the child.[127]

Together, these findings provide insights of considerable importance to the management of children and adolescents with FHS and should be taken into consideration by health-care personnel and other professionals who deal with such patients and their families. To date, only a few investigations designed to identify the specific issues that actually cause the impairment of HRQL in children with FHS have been performed.[116,128] In a recently published state-of-the art paper, from the EuroPREVALL network, the importance of developing such disease-specific instruments for use in clinical practice, research and food manufacturing was highlighted.[129] A preliminary questionnaire dealing with parental psychosocial adjustment to the food allergies of their child has been developed, and in addition another questionnaire focusing on the burden experienced by the parents of a child with food allergy has recently been published.[128,130] However, the available information concerning the impact of FHS on a child's HRQL and specific issues of particular importance in this context is still severely limited.

1.7 PROBLEM FORMULATION

The extensive prevalence of FHS, places a heavy burden on the medical care system. [4,131-134] It is thus important to develop more effective diagnostic tools and management strategies for this large group of patients. However, as discussed above, the diagnosis of FHS and food allergy involves substantial difficulties.[4,40,88,89,103-105,107] The positive predictive value of the objective diagnostic approaches presently available, primarily SPT and determination of levels of IgE antibodies to food, is limited when these tests not are used in a quantitative fashion.[91,93,94,135] Therefore, most children suspected of suffering from FHS should also be subjected to a food challenge, preferably a DBPCFC.[103,104] Furthermore, the negative impact of FHS on the HRQL of children with FHS and their families requires elucidation in much greater detail.[115-119,125,126] Finally, different aspects of reported FHS such as different phenotypes of FHS and the relationship to sensitization to common food allergens has only been assessed in a few studies. Thus, more population-based studies designed to elucidate the relationship between perceived FHS and sensitization to food need to be carried out. The associations between different symptoms of FHS and sensitization, as well as different aspects of the various phenotypes of FHS, also need further investigation. Such studies will not only improve the treatment and thereby increase both the physical health and HRQL of this large group of patients and their families, but also help to achieve proper allocation of resources within the health-care system. Accordingly, the findings presented here could be of interest not only for further research, but also to general practitioners and specialists who care for children with FHS.

2 AIMS

The general objective here has been to investigate and characterize various aspects of reported FHS in a large birth cohort that was followed up to eight-nine years of age. The specific aims were as follows:

- to examine the relationship between different phenotypes of reported FHS among children during their first eight years of life and clinically diagnosed food allergy (DFA), symptoms and allergic sensitization to common food allergens, and subsequent development of allergic diseases other than FHS **(Paper I);**

- to characterize the relationship between reported symptoms of FHS and sensitization to common items of food in 4-year-old children **(Paper II);**

- to investigate the association between reported symptoms evoked by certain items of food and the corresponding levels of IgE antibodies to food, among 4-year-old children **(Paper III);** and

- to investigate the parent-reported HRQL of children suffering from FHS and also to investigate the impact of the child's disease on the family's life situation **(Paper IV).**

3 MATERIAL AND METHODS

The four separate articles on which this thesis is based focus on the prospective BAMSE study, which involves a birth cohort of 4000 children.

3.1 STUDY DESIGN AND STUDY POPULATION

The main objective of the longitudinal and prospective BAMSE study of a Swedish birth cohort is to examine relationships between certain environmental factors and the development of allergic disease in children. This study was planned in 1991 and 1992 and is being conducted by the Department of Environmental and Occupational Health of the Stockholm County Council in collaboration with the Institute of Environmental Medicine at Karolinska Institutet in Stockholm. All parents living in predetermined areas of Stockholm County (i.e., the inner city and the Sundbyberg, Solna and Järfälla suburbs) who had a baby born between February 1994 and November 1996 were invited to participate. These geographical areas of recruitment were thought to be representative of Stockholm with respect to housing conditions, exposure to traffic and socio-economic factors.

Of the 7,221 infants born during the recruitment period, 97% were seen regularly at Child Health Centres, and all 53 of these centres within the designated geographical areas agreed to help us with recruitment. In connection with their first visit to the Child Health Centre, when the infant was approximately three weeks old, the families received information concerning the questionnaires and the clinical examinations included in the study from the attending nurse and their current address was recorded. Nonetheless, 477 families could never be contacted because their address was incorrect (Fig. 2). A total of 1,256 children were purposely excluded. This group consisted of 699 children whose families planned to move within one year; another 169 children with an older sibling already enrolled in the study; 57 children who were seriously ill and 331 children whose parents had insufficient knowledge of the Swedish language. Furthermore, 1,399 families either never answered the questionnaire or declined to participate. Thus, the BAMSE study encompass 4,089 children (2,065 boys and 2,024 girls), i.e., 75% of 5,488 eligible children.

In order to determine whether non-responders or children actively excluded differed from the children included with respect to parental allergies and early exposure to tobacco smoke (ETS), a short questionnaire was sent out in 1996 to the parents of 1,418 children 3 to 30 months of age. These families were originally considered for inclusion but not involved in the end.[136] The response rate for the parents of children actively excluded and non-responders were 83% and 58%, respectively. The proportion of children with allergic parents was the same in these groups and in the final BAMSE cohort studied, but parental smoking was significant less common in the BAMSE study population at two months of age as compared to the group consisting of non-responders

and excluded children (maternal smoking 9% versus 18% and paternal smoking 17% versus 23%).

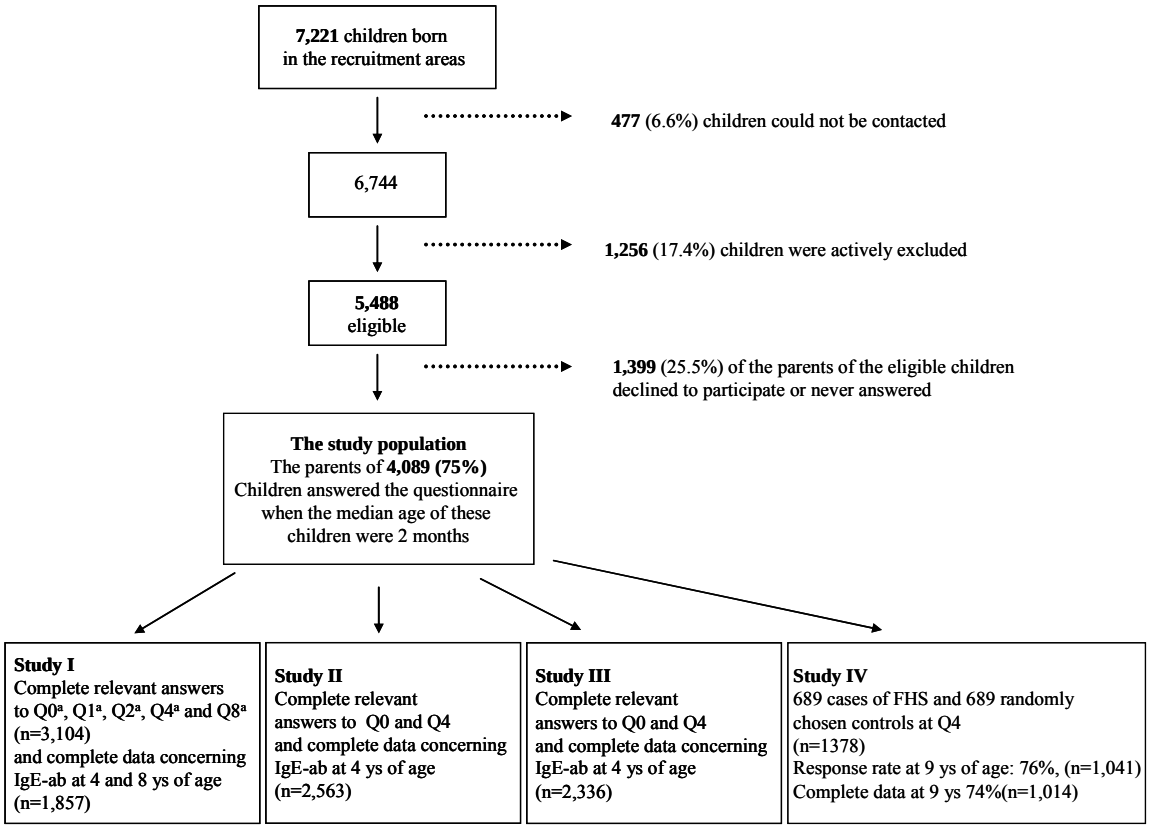


Figure 2. The BAMSE study population investigated in papers I-IV. [a] Questionnaire answered at 2 months, at 1, 2, 4 and 8 years, respectively.

Study I included all children for whom complete questionnaire data on relevant issues were available at 2 months (Q0) and one (Q1), two (Q2), four (Q4) and eight (Q8) years of age (n=3,104), (Fig. 2). For analyses involving IgE antibodies to food in this investigation complete questionnaire data and complete data on IgE antibodies to food at both four and eight years were required, n=1,857.

To be included in study II complete Q0 and Q4 questionnaire data on relevant issues as well as complete data on IgE antibodies at four years of age were required (n=2,563) (Fig. 2).

Study III involved all children for whom complete Q0 and Q4 parental questionnaire data on for this study relevant questions and complete data on IgE antibodies to food at four years age were available, (n=2,336) (Fig. 2). The number of participants is not equal to the number of participants in Study II due to internal missing on some questions relevant in this study but not in Study II.

In the case of study IV a nested case-control design based on data from the BAMSE questionnaire at four years of age was employed. At this age 689 children were described by their parents as demonstrating symptoms of FHS. An equal number of children with no such symptoms were selected randomly from the remaining children in the cohort, providing a total of 1,378 subjects. When these children had reached an age of nine (range eight to ten years), their parents were sent a questionnaire concerning health-related quality of life, which 76% responded to. Complete data was obtained from 74% (n=1,014). At this time-point, the 212 children with current symptoms of FHS (see Figure 3) were compared to 221 children with allergic disease other than FHS as well as to 581 children without any parent reported allergic disease. The majority of children with FHS at nine years of age had symptoms of FHS already at four years (n=183, 86%) while 29 other children had developed FHS between the ages of four and nine.

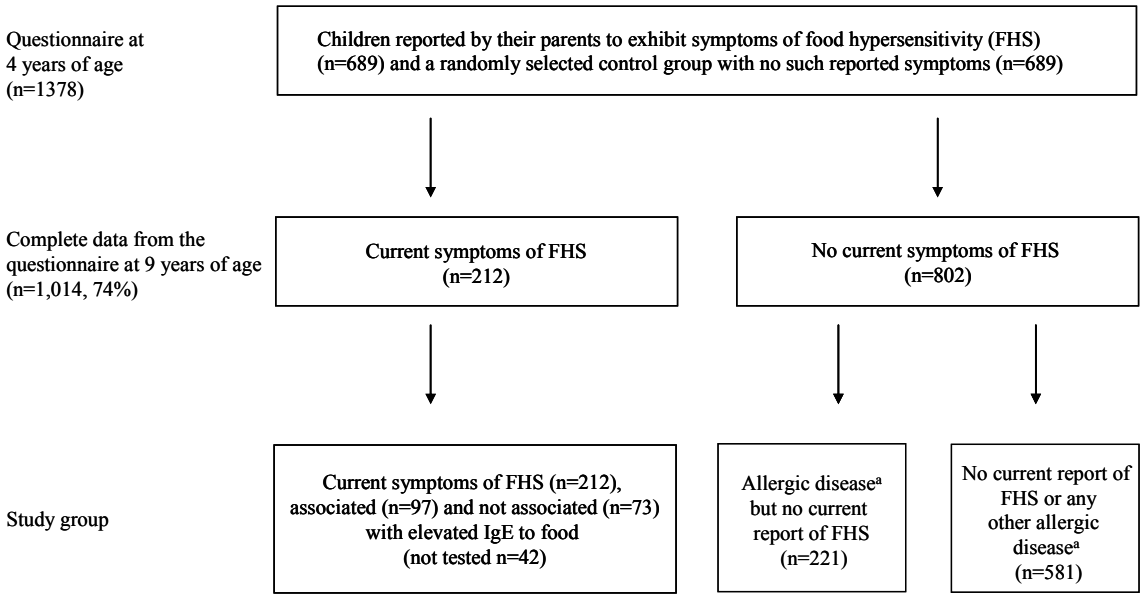


Figure 3. Flow-chart illustrating our recruitment of children from the BAMSE birth cohort for a nested case-control study of health-related quality of life (Paper IV).
[a] Presence of asthma, allergic rhinitis and/or eczema.

3.2 METHODS

3.2.1 The questionnaires employed in the main project (Papers I-III)

When their children were at a mean age of 2 months, the parents filled in the first questionnaire (Q0) dealing with detailed information concerning living conditions, socio-economic status, a possible family history of allergic disease and exposure to environmental factors at home. When the children had reached one (Q1), two (Q2), four (Q4) and eight years (Q8) of age (Fig. 2), new questionnaires focused primarily on symptoms of allergic disease and exposures to certain key agents such as tobacco smoke, pets, etc were sent out. The response rates to questionnaires Q1, Q2, Q4 and Q8 were 96%, 92%, 91% and 84%, respectively.

3.2.2 The questionnaire on health-related quality of life (Paper IV)

For the study described in Paper IV a generic instrument, the Child Health Questionnaire - Parental Form 28 (CHQ-PF28), designed to elucidate general issues of health-related quality of life (HRQL), was distributed together with disease-specific questions.

3.2.2.1 Child-health Questionnaire - Parental Form 28

In order to characterize parental perception of their child's HRQL, as well as to detect differences in HRQL between the groups, the CHQ-PF 28, a generic instrument was chosen. This instrument has been validated in Sweden and several other countries and is widely used.[137,138] There are consistent indications that the scores provided by this test are psychometrically reliable, with an acceptable level of internal consistency, discriminant validity and factor structure.[139] The 28 different items in this instrument can be aggregated into 13 subscales, and interpretation simplified by converting the raw scores obtained to values between 0-100, with higher values indicating a better HRQL (Table II).

Subscale	Abbreviation	No. of items	Definition[139]
Physical functioning	PF	3	Limitations in physical activities
Role/social limitations – emotional/behavioural	REB	1	Limitations in school and/or social activities due to emotional or behavioural problems
Role/social limitations – physical	RP	1	Limitations in school and/or social activities due to physical problems
Bodily pain/discomfort	BP	1	Intensity/frequency of pain/discomfort
Behaviour	BE	4	Ability to get along with others, behavioural problems including aggression, delinquency, impulsiveness and social withdrawal
Mental health	MH	3	Positive and negative states, including anxiety, depression and positive affect
Self esteem	SE	3	Satisfaction with school, athletic ability, appearance, ability to get along with others
General health perceptions	GH	4	Perception of overall health and illness
Parental impact-emotional	PE	2	Distress and worry experienced by the parents or guardians concerning the child's condition
Parental impact-time	PT	2	Limitations on personal time experienced by the parents as a result of the child's condition
Family activities	FA	2	Limitations in and interruption of normal family activities and family tension as a result of the child's condition
Family cohesion	FC	1	Ability of family-members to get along with one another
Change in health	CH	1	Changes in health compared to the situation one year ago

Table II. Description and description of the subscales included in the CHQ-PF28.

3.2.2.2 Disease-specific questions

It is generally advisable to use generic instruments in combination with disease-specific questions.[140] At the time this study was planned, no disease-specific instrument for children with FHS was available. In order to elucidate parental perceptions of limitations in daily life, as well as the consequences and/or emotional impact of the child's FHS on the child him/herself and on the parents, we designed such appropriate disease-specific questions on the basis of clinical experience, scientific literature and interviews with both children suffering from food allergy and their parents. Thereafter, the disease-specific questions formulated were tested on parents of 8-9-year-old children with a food allergy, but who were not participants in the BAMSE project. Their comments prompted only minor revisions.

3.3 THE CLINICAL INVESTIGATIONS

At four years of age, all of the children for whom questionnaire data were available were invited to participate in a first clinical testing, and the parents of 2,965 children (73%) agreed to take part. The clinical examination took place at the Department of Occupational and Environmental Health and was performed by three paediatric nurses in the BAMSE study group. The clinical examination included blood sampling which was carried out under a local anaesthetic (EMLA®). In this manner serum samples were obtained from 2,614 children, i.e., 88% of those undergoing the examination or 64% of the total cohort. For the other 351 children (8.6% of the cohort or 12% of those undergoing the physical examination) either no blood could be drawn or they refused to be subjected to that procedure. In the cases of 10 children from whom blood samples were available (0.5% of all available blood samples) data concerning at least one allergen-specific IgE antibody to food were missing due to either scarce amount of blood or to laboratory errors. At eight years of age the same method was used, and blood samples at both four and eight years were obtained from 2,033 children, 60% of all children remaining in the study at eight years of age.

3.3.1 Definition of the outcomes

Food hypersensitivity (FHS) is in Papers I-III defined as reported development of at least one of following symptoms in connection with ingestion of a specific type of food: wheezing, itchy eyes and/or runny nose, facial oedema, urticaria, eczema and/or vomiting/diarrhoea. At eight years of age, the oral allergy syndrome was also taken into consideration.[141] Due to a technical error in the questionnaire administrated at eight years of age, information on facial oedema at this time-point was not available.

In Paper IV a slightly different definition of FHS was employed. In addition to the criteria applied in Papers I-III, children who had previously demonstrated such food-related symptoms, but not during the previous 12-month period as a result of

avoidance of the type of food in question, were also considered as having FHS. These rather broad inclusion criteria were utilized in this context, since parental perception of FHS might lead to dietary restrictions and also exert a negative impact on the health-related quality of life.[130,142]

Diagnosed food allergy (DFA) was identified on the basis of parentally reported diagnosis of food allergy made by a physician. In the case of children with transient symptoms (i.e., no symptoms at four years or later), DFA was considered to be present if such a medical diagnosis had been made at any time between one and four years of age. For the other phenotypes (where symptoms were present at eight years of age), identification DFA was based on a diagnosis made at any time at eight years of age.

Asthma was considered to be present in cases where at least four episodes of wheezing had occurred during in the previous 12-months period, or at least one such episode had occurred in individuals taking steroids by inhalations.[22,69,143,144]

Eczema was identified on the basis of parentally reported diagnosis of eczema by a physician and/or the presence of dry skin in combination with a rash for two weeks or more with typical localization (i.e., face; extension surfaces and/or flexures of the arms or legs; the wrists or ankles; and/or the neck) at any time during the previous 12-month period.[22,43]

Allergic rhinitis was identified on the basis of parentally reported diagnosis of allergic rhinitis by a physician, or sneezing, a runny nose blocked nose and/or itch, red and watery eyes following exposure to furry pets or pollen at any time during the previous 12-month period.[143,145]

3.3.2 Sensitization to food

Plasma levels of *food allergen-specific IgE antibodies* directed towards a mixture of common food allergens (fx5®; cow's milk, egg white, cod fish, peanut, soybean and wheat, Immuno-CAP™, Phadia AB, Uppsala, Sweden) were determined by a certified laboratory (the Unit of Clinical Immunology and Allergy, Department of Medicine, Karolinska University Hospital). A level of IgE-antibodies ≥0.35 kU_A/L was considered positive and levels >100 kU_A/L were recorded as 100 kU_A/L. Serum samples which were positive for antibodies to the mixture (fx5®) were analyzed further with respect to the individual allergens present in the mixture.

In Papers I and IV *sensitization* was defined as the presence of serum levels of IgE antibodies to food (fx5®) ≥0.35 kU_A/L. In Papers II and III sensitization to *specific* food item (i.e., serum levels of IgE antibodies against at least one of the allergens in cow's milk, hen's eggs, fish, peanuts, soy beans or wheat ≥0.35 kU_A/L) was employed as an outcome.

3.3.3 Statistical analyses and ethical permission

Background factors (i.e., sex, parental allergies, exclusive breast-feeding, the socio-economic status of the family and early exposure to tobacco smoke) which could influence the development of FHS and serum levels of IgE antibodies to food were examined to determine whether there were any differences between the children who dropped out between two months and eight years of age and those who remained in the study for the entire period.

Prevalence ratios are presented both as total numbers and percentages, and the 95% confidence intervals (CI). Differences in proportions in the different groups were analyzed with the χ^2 or proportionality test, as appropriate. In Paper IV, where the data are based on Likert scales, the Kruskal-Wallis test was utilized for analyzing differences between the median values for the various groups.[146] A p-value of <0.05 was considered to be statistically significant. Two-by-two tables were employed to calculate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the dichotomized serum levels of food-allergen specific IgE antibodies (using a cut-off value of 0.35 kU_A/L) and FHS.

In calculating the odds ratios (OR) in Paper I, adjustments were made for parental allergies which was the only background factor that affected the risk estimates by 10% or more. In analyzing the OR for FHS at eight years of age in relationship to FHS caused by individual food allergens at two years of age, adjustments were made for all of the other food allergens examined. All children exhibiting food-related asthma, allergic rhinitis or eczema at one or two years of age were excluded from the analyses of risk for allergic diseases other than FHS at eight years of age since having any of these diseases at a certain age is dependent of having them at an earlier age.

Where levels of IgE antibodies are presented as mean levels geometric means are used. A multiple logistic regression was used to evaluate the relationship between the levels of IgE antibodies to food and the risk for reported food hypersensitivity towards any of the foods tested. This association is expressed in terms of odds ratios (OR) and 95% confidence intervals (CI). Logarithmic transformation of the levels of IgE antibodies was performed and used to plot predicted probability curves with 95% confidence intervals and the results of the multiple logistic regression analysis. The Spearman rank test was applied to evaluate the correlation between sensitization to soy beans and peanuts.

In Paper IV, the internal consistency demonstrated for the subscales of the CHQ-PF28 ranged from 0.86 - 0.88, as determined by Cronbach's alpha analysis.[147]

All statistical analyses in Papers I and II were performed using STATA 9.2 (Stata, College Station, TX, USA), while those in Paper III and IV were carried out with the 8.0 version of STATA.

Permission for the performance of this study has been obtained from the Ethics Committee of Karolinska Institutet, Stockholm. Informed consent was obtained from the parents in all families participating in the study.

4 RESULTS AND COMMENTARIES

4.1 PHENOTYPES OF FOOD HYPERSENSITIVITY DEVELOPING DURING THE FIRST EIGHT YEARS OF LIFE (PAPER I)

The prevalence ratios for food hypersensitivity (FHS) at one, two, four and eight years of age were 10%, 9%, 11% and 13%, respectively. The prevalence ratios for reported doctor's diagnosis of food allergy (DFA) at these same ages were 3%, 4%, 5% and 7%, respectively. The proportion of children who demonstrated FHS at any time during the first eight years of age was 31%.

FHS in combination with sensitization to common food items (milk, egg, fish, wheat, peanuts or soy beans), i.e., IgE antibodies to food ≥0.35 kU_A/L, was observed in 3% and 5% of the children at four and at eight years of age, respectively. At one and two years of age, the foods most commonly reported to cause FHS were milk and egg, while peanuts were added to this list at four years of age. At the age of eight, peanuts and tree nuts were by far the foods most commonly reported to cause symptoms.

Children with report of FHS were divided into four different phenotypic categories as follows:

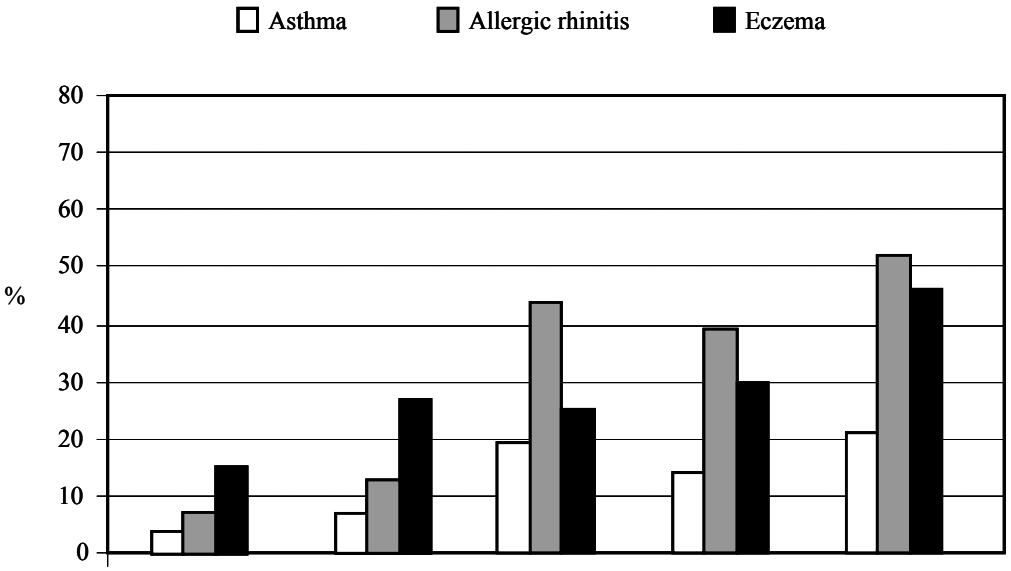
Transient FHS (n=399, 13%): symptoms reported between one and four years of age, but not thereafter.
Intermittent FHS (n=51, 2%): symptoms reported at one and/or two years of age, not at the age of four, but again at eight years of age.
Late onset FHS (n=239, 8%): symptoms reported at four and eight or at eight years only.
Persistent FHS (n=115, 4%): symptoms reported at one and/or two, at four and eight years of age.

Gastrointestinal reactions and eczema were the most frequently reported symptoms in children with transient FHS at four years of age and in children exhibiting the other phenotypes at eight years of age. More than 70% of the children with transient FHS were reported to have only a single symptom, in contrast to children with persistent FHS, where the majority of afflicted individuals suffered from multiple symptoms. Twenty-three percent of the children with transient symptoms were reported to have DFA, and the corresponding values for the children with intermittent, late onset or persistent symptoms were 37%, 61% and 83%, respectively.

In this context, the majority of children with *transient* (81%) or *late onset* FHS (57%) were not sensitized to food at either of these ages; while two thirds of those with *intermittent* or *persistent* FHS were sensitized at least at one of the time-points, and they also exhibited significantly higher levels of IgE-antibodies. Among the children sensitized to food, the serum level of IgE antibodies was significantly higher among those found to be sensitized at both four and eight years of age (geometric mean = 6.2

kU_A/l (CI 95% 4.4-8.6)) than in the children demonstrating sensitization only at four (0.65 kU_A/l (CI 95% 0.50-0.84)) or eight (0.36 kU_A/L(CI 95% 0.34-0.37)).

The odds ratio (OR) for having allergic symptoms but not caused by foods at eight years of age was significantly elevated in connection with all phenotypes of FHS, and especially in the case of children with persistent FHS (Fig. 4). For this latter group, the odds ratios (OR_{adj}) for having asthma, allergic rhinitis or eczema at eight years of age were 6.9 (CI 95% 4.1-11), 13 (CI 95% 8.0-22) and 2.3 (CI 95% 1.1-5.1), respectively, in comparison to children without FHS, i.e., the risk for having asthma for instance, was at eight years of age approximately seven times as high in children with persistent FHS as compared to children without any FHS.



FHS phenotype:	**None**	**Transient**	**Intermittent**	**Late onset**	**Persistent**
OR_{adj} and 95% CI for:					
Asthma at 8 y	1.0	1.6 (1.0-2.5)	7.7 (3.7-16)	4.5 (2.9-6.9)	6.9 (4.1-11)
Allergic rhinitis at 8 y	1.0	1.6 (1.1-2.3)	6.8 (3.5-13)	8.5 (6.2-12)	13 (8.0-22)
Eczema at 8 y	1.0	1.7 (1.2-2.4)	n.d*	2.3 (1.6-3.2)	2.3 (1.1-5.1)

Figure 4. The odds ratios for demonstrating another allergic disease in children exhibiting different phenotypes of food hypersensitivity at eight years of age. In this analysis ***all children with food-related asthma, eczema or allergic rhinitis at one or two years of age were excluded***. In addition, adjustments were made for non-food-related asthma, eczema and allergic rhinitis at one or two years of age. *n.d: not determined due to the presence of too few children in this group.

4.1.1 Major findings

In Paper I we identified four different phenotypes of FHS that develop during the first eight years of life. Diagnosis of food allergy by a physician (DFA) and sensitization to common food allergens was observed most commonly by far among children with persistent symptoms of FHS. Serum levels of IgE antibodies to food were also significantly higher in this group of children at both four and eight years of age than in children exhibiting the other phenotypes. In contrast, at four years of age children with *transient* symptoms of FHS did not demonstrate sensitization to the food allergens tested more often than children with no report of symptoms of FHS. Furthermore, there were no differences in the serum levels of IgE antibodies to food in these two latter groups.

The incidence of DFA increased from 3% at one year of age to 7% at the age of eight. All phenotypes of FHS exhibited a positive association to non-food-related asthma, allergic rhinitis and eczema at eight years of age. Furthermore, early symptoms of FHS of all kinds, were associated with an elevated risk for later onset of asthma, allergic rhinitis and eczema.

4.1.1.1 Comments and interpretation

The findings may suggest that children who develop symptoms of FHS at an early age without sensitization to common food allergens have a good chance of outgrowing these symptoms, which is valuable and encouraging to know in the clinical situation. When caring for these children and their parents, it is important to determine whether a food allergy is present or not in order to avoid unnecessary dietary restrictions in certain cases, and to eliminate unnecessary symptoms in others.

Despite the good prognosis for children with FHS even employing our rather broad definition, early symptoms of FHS were found to be associated with an elevated risk for later onset of allergic disease unrelated to food. This suggests that mechanisms early in life that are not obviously linked to symptoms and sensitization to food may influence development of allergic disease later in life. Little is known concerning the influence of genetics and/or environmental factors on FHS or food allergy. However, other studies have revealed that early sensitization to eggs enhances the risk for later onset of respiratory allergic disease.[66,148] In the present study we have no information concerning sensitization to food at ages younger than four years, so the increased risk for later onset of allergic disease may be linked to sensitization prior to this age, although other mechanisms cannot be ruled out.

4.2 FOOD HYPERSENSITIVITY IN RELATIONSHIP TO SYMPTOMS AND SENSITIZATION TO FOOD AT FOUR YEARS OF AGE (PAPERS II AND III)

4.2.1 Symptoms of food hypersensitivity

At four years of age, 11% of the children participating in our study were reported to exhibit at least one specific symptom of food hypersensitivity (FHS) elicited by a certain food. The most commonly reported symptom of FHS was eczema (50%), followed by vomiting/diarrhoea (39%), urticaria (30%), facial oedema (26%) itchy eyes/nose (18%) and, finally, asthma (6%). Approximately half of all of the children with eczema or vomiting/diarrhoea were reported to demonstrate only a single symptom, whereas almost all of the children with food-related asthma or rhino-conjunctivitis were reported to show multiple symptoms of FHS.

The food items most commonly reported to cause symptoms of FHS at four years of age were cow's milk and citrus fruits (32% for both), peanuts (27%), tree nuts (25%), eggs (24%), fruits with pips or stones (22%), chocolate (17%) and fish (11%). All other food items were reported to elicit symptoms in only a few percent of the cases.

4.2.2 Sensitization to food and levels of IgE antibodies to food

Thirteen percent of all of the children were sensitized (i.e., had serum levels of IgE antibodies $\geq 0.35 kU_A/L$) to at least one of the foods tested (milk, eggs, fish, wheat, peanuts or soy beans). Among the children with FHS, 31% were sensitized to at least one of these food items, while the corresponding value for children without FHS was 11% ($p<0.001$). Table III documents the details concerning the sensitization of children with and without FHS to these food items.

	Total (n= 2,336)		Without FHS (n=2,052)		With FHS (n=284)	
Food items						
			Prevalence of sensitization			
	n	**%**	**n**	**%**	**n**	**%**
Any of the six foods tested	305	13	218	11	87	31
Foods of animal origin:						
Cow's milk	197	8	151	7	46	16
Hen's eggs	112	5	70	3	42	15
Cod fish	17	1	7	0	10	4
Foods of plant origin:						
Peanuts	125	5	63	3	62	22
Soy beans	70	3	31	2	39	14
Wheat	88	4	54	3	34	12

Table III. Prevalence of sensitization to common food items among 4-year-old children with and without food hypersensitivity (FHS) in the BAMSE cohort. Sensitization was defined as the presence of serum levels of IgE antibodies to food ≥0.35 kU_A/L.

The relationship between the food reported to cause symptom and sensitization to this same food is presented in Figure 5. Two-thirds of children with reported peanut-related FHS and half of all those with egg-related symptoms were sensitized to the offending food. In the cases of the other food items reported to cause FHS, only one third or fewer of the children were sensitized to the offending food.

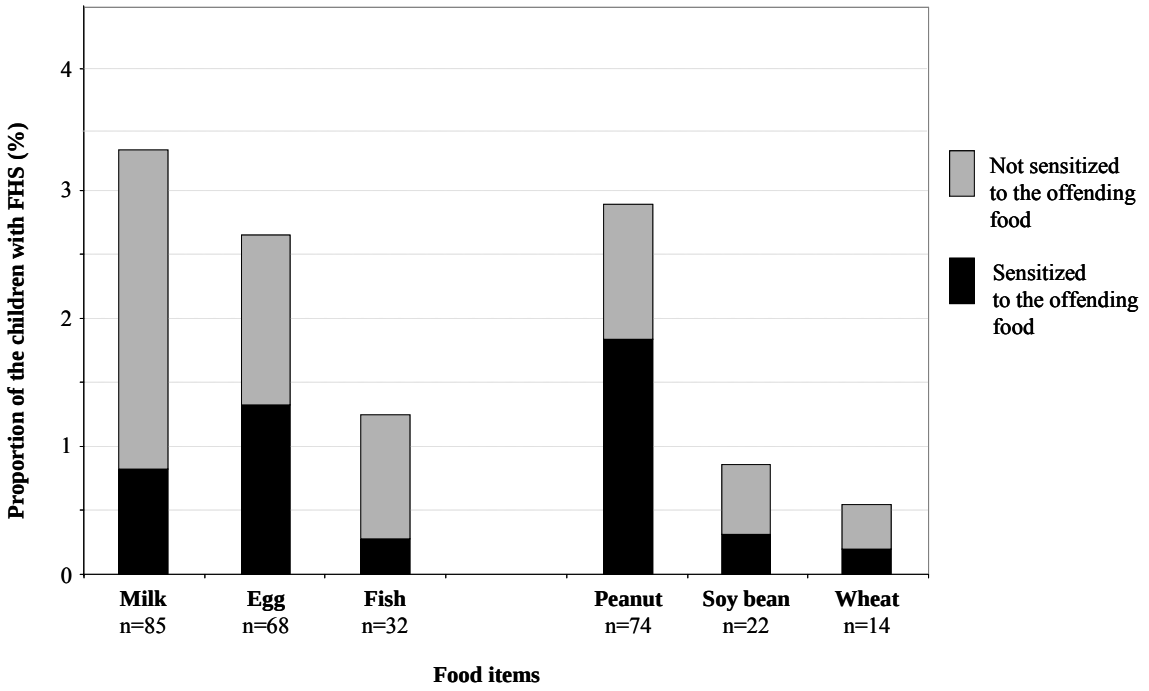


Figure 5. The proportions of children with parent reported symptoms of FHS related to a food item and sensitization to this same food.

The relationship between reported symptoms and sensitization to the foods tested is depicted in Figure 6. Less than half of all children with eczema or vomiting/diarrhoea were sensitized to the offending food. In contrast, two-thirds of those with urticaria or facial oedema and almost all children with rhino-conjunctivitis or asthma were sensitized to the offending food.

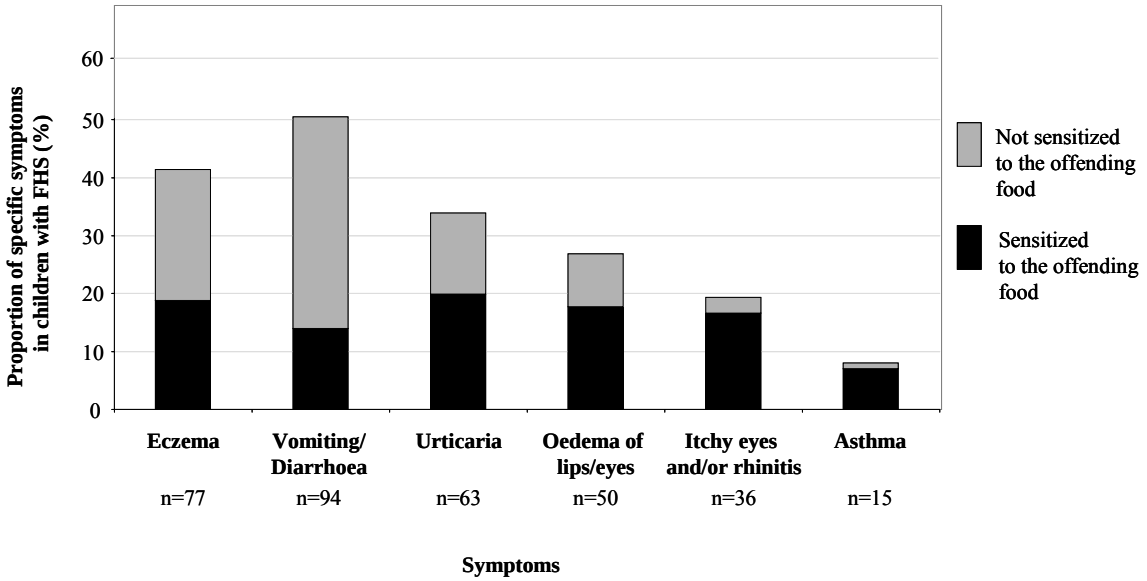


Figure 6. The proportion of children with different symptoms of FHS sensitized to at least one offending food. Only children with symptoms of FHS reported to be caused by any of the six foods tested (177/266) were taken into consideration in this analysis (Paper II).

4.2.3 Sensitization to food; quantitative approach

The relationship between the quantitative levels of IgE antibodies to food in the serum and the presence of reported symptoms related to the same item of food was also analyzed (Fig. 7). A serum level of IgE-antibodies to milk of 22 kU_A/L was associated with 90% probability for milk-related symptoms, and the corresponding value for eggs was 13 kU_A/L. The same probability for reported development of fish-related symptoms was observed at a much lower level of IgE antibodies to fish-allergens, (i.e., 4.7 kU_A/L), but it is noteworthy that only 17 of the children were sensitized to fish.

In the case of food allergens of plant origin the relationship between higher levels of IgE antibodies and reported symptoms was weaker. Thus, even with a serum level of IgE antibodies to peanuts of 100 kU_A/L, there was only a 63% probability for reported peanut-related symptoms. Among the 26 children exhibiting levels of IgE antibodies to peanuts $\geq$50 kU_A/L, one was reported to have never tasted peanuts, 15 as having peanut-related symptoms, and the remaining 10 children as not having any symptoms of FHS at all, not to any food. At the highest level of IgE antibodies to soy bean measured (44 kU_A/L), there was only a 40% probability of reported soy-related symptoms and, furthermore, 63 of the children sensitized to soy beans were also sensitized to peanuts. Only five of the 88 children sensitized to wheat were reported to exhibit wheat-related symptoms and the probability for such reported symptoms at a

serum level of IgE antibodies to wheat equal to 100 kU_A/L was 89%. The relevant probability curves, along with the 95% CIs, are depicted in Figure 7.

Analyses of the ORs for symptoms caused by the specific foods in relationship to the serum level of IgE antibodies directed towards the same food were performed employing a logistic regression model. A significant increase in the OR with increasing serum levels was seen for all of the foods tested, except for soy beans. However, the 95% CIs in the case of fish and wheat were very broad and must be interpreted with caution (Fig. 7). Moreover, as mentioned above, very few of those sensitized to wheat reported any wheat-related symptoms, and these children presented with wheat-allergen specific IgE antibody levels ranging from 0.47-100 kU_A/L.

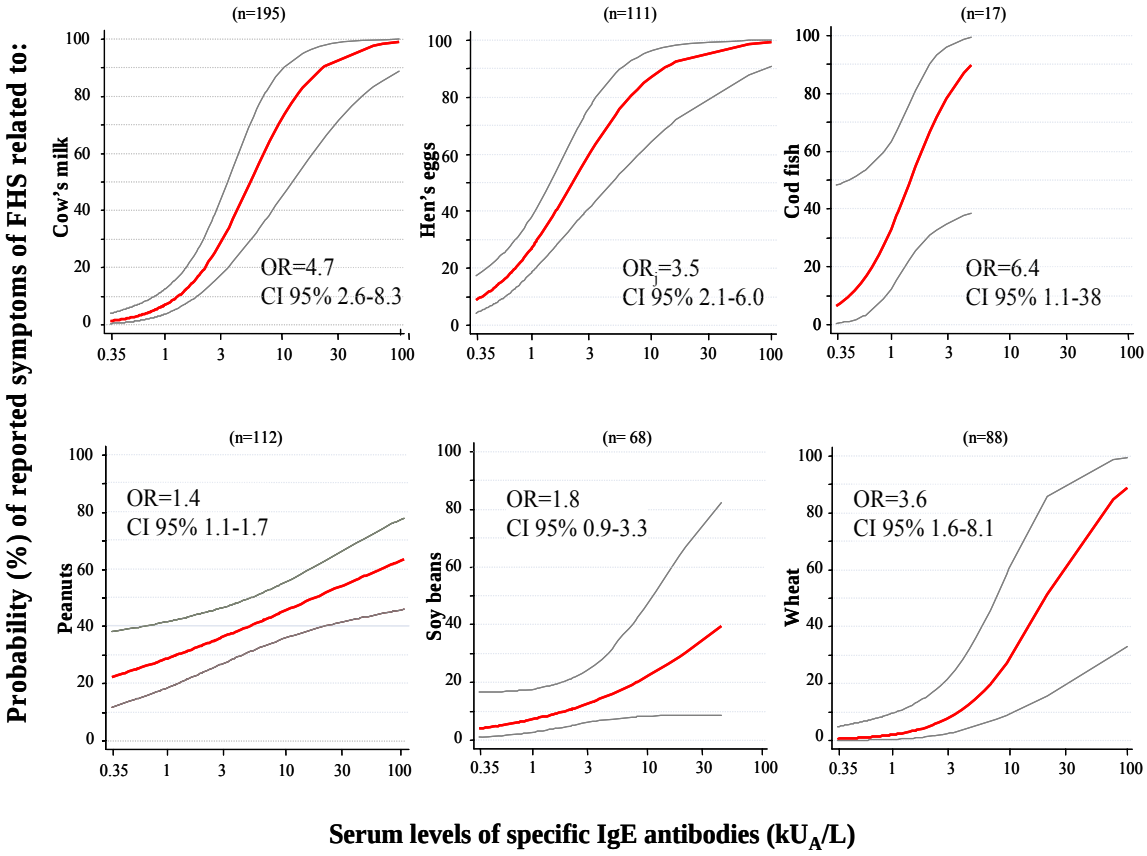


Figure 7. Relationships between increasing serum levels of IgE antibodies to specific food-allergens and symptoms reported to be caused by the same item of food. The relationships are shown with red curves and the 95% CI with black curves. The odds ratios (OR) are also indicated.

4.2.4 Major findings

Eczema and vomiting/diarrhoea were the most frequently reported symptoms of FHS and approximately half of the children with one of these symptoms had no other symptom of FHS. In contrast, the children with food-related asthma, rhino-conjunctivitis or facial oedema almost all suffered from multiple symptoms of FHS.

Among the children with FHS, 31% were sensitized to food. Peanut was the most commonly sensitizing allergen (Tab. III), with two-thirds of all the children reported to demonstrate peanut-related symptoms being sensitized to peanuts (Fig. V). Furthermore, half of all of the children with egg-related symptoms were sensitized to eggs (Fig. 5). With the other four items of food reported to cause symptoms a minority was sensitized to the offending food.

The OR for symptoms reportedly related to a given food increased with increasing serum levels of IgE antibodies towards this same food, with the exception of soy beans. We also determined the serum levels of IgE antibodies to milk, eggs or fish

associated with a 90% probability for reported symptoms related to the corresponding item of food. However, 10 out of the 26 children who exhibited very high serum levels of IgE antibodies to peanut had no reported symptoms related to peanuts.

4.2.4.1 Comments

The dichotomized relationship between symptoms caused by a certain item of food (i.e., "sensitized or not") is rather weak as has also been described earlier by other investigators.[62,149] Accordingly, establishment of sensitization provides information of little value in connection with diagnosing suspected food hypersensitivity. In this context, more nuanced information concerning the quantitative serum levels of IgE antibodies to food appears to be of importance.

As expected, IgE antibody levels for a 90% probability of symptoms were somewhat higher than corresponding levels found in studies based on patient-material and with symptoms after an oral challenge as the endpoint.[57,91,93,94,150]

About 20% of children with reported milk-related symptoms were sensitized to milk, but with higher levels of IgE antibodies to milk there were a close relationship to milk-related symptoms. Similar patterns were seen for egg and fish, i.e. high levels of IgE antibodies towards milk, egg and fish seem to be closely related to symptoms elicited by these foods, not only in patient-based materials as shown before, but also in a population-based sample of four-year-olds. [57,91,93,94,150]

A probability of 63% for symptoms related to peanut was reached at an IgE antibody level to peanuts of 100 kU_A/L or more. This implies that sensitization to peanut in this age group may occur, even with rather high IgE antibody levels, without association to symptoms to peanut. However, we cannot be certain that these children really had ingested a sufficient amount of peanut to experience peanut-related symptoms. Thus, a positive outcome at an oral challenge for some of these children can not be excluded. To our knowledge there has been no study so far where challenges have been performed in children with sensitization to peanut but with no suspicion of peanut-related reactions. In studies where the relationship between levels of IgE antibodies to peanuts and clinical reactivity has been assessed a cut-off value of approximately 15 kU_A/L for IgE antibodies to peanuts has been suggested.[91,150,151]

The relationship between reported reactions related to soy bean or wheat and IgE antibodies to those foods was utterly limited in our study. At the highest level of IgE antibodies to soy bean, 44 kU_A/L, a probability for soy-related reactions of only 40% was seen and 100 kU_A/L or more of IgE antibodies to wheat was needed to reach the maximum probability of 89% for reactions to wheat. Similar findings for soy bean and wheat have been reported by others.[91,97,150,152,153]

4.3 IMPACT OF FOOD HYPERSENSITIVITY ON HEALTH-RELATED QUALITY OF LIFE

4.3.1 Child Health Questionnaire - Parental Form 28

Comparison of three different groups of children revealed that children with FHS demonstrated scores on the Role/social limitations – physical (RP), General health (GH) and Physical functioning (PF) subscales of the generic instrument Child Health Questionnaire Parental Form 28 (CHQ PF28) that were significantly lower than the corresponding scores for children with allergic diseases other than FHS. In addition, the parents to children with FHS also scored significantly lower on the three subscales above as well as on the Role/social limitations – emotional (REB), Bodily pain (BP), Mental health (MH) and Parental impact – emotional (PE) subscales, than did parents with children with no allergic disease.

4.3.2 CHQ-28 in relation to symptoms of FHS

Children exhibiting food-related symptoms involving the lower airways, food-related symptoms at least once each month and/or at least two different food-related symptoms were defined as having pronounced (n=126) as opposed to mild (n=82) FHS. In five cases the frequency of symptoms was not available. In comparison to children with other allergic diseases, children reported to develop food-related symptoms involving the lower airways and/or children with frequent food-related symptoms were scored lower on six of the thirteen subscales in CHQ PF28, while those with two or more different food-related symptoms were scored lower on seven subscales.

4.3.2.1 Sensitization to food

Data concerning sensitization to food was available for 170 (80%) of the 212 children with FHS. Neither the presence of such sensitization nor being diagnosed with food allergy by a physician was associated with any lowering of the subscales of the CHQ PF28. However, children with serum levels of IgE antibodies to food (fx5®) that were above the geometric mean of ≥5.34 kU_A/L were scored lower on the Mental health (MH) and General health (GH) subscales.

4.3.3 FHS Disease specific questions

The parents who reported that their children had FHS were also asked to respond to disease-specific questions concerning limitations in daily life, emotional impact and consequences for both the child him/herself and the entire family. The details about some of these questions are presented in Table IV.

	Responses	
	Total number of responses	Positive[a] (%)
Questions		
Items concerning the child		
Ponders over her/his food hypersensitivity*	202	70
Feels sad about being food-hypersensitive*	203	48
Receives special meals at school	205	47
Experiences anxiety about developing acute symptoms	203	38
Feels that she/he is different than other children	202	15
Feels restricted in everyday life*	201	14
Does not eat out at restaurants	206	10
Cannot eat meals at the homes of friends*	205	7
Cannot participate in school outings	206	6
Items concerning the parents or entire family		
Experience difficulties in interpreting the list of ingredients on food items[b]	179	64
Prepare different meals for the child and for the rest of the family*	206	42
Adjust the diet of the entire family to be suitable for the child with FHS	205	32
Feel anxious about the child developing acute symptoms	208	31
Experience conflicts within the family over how to deal with the child's FHS*	201	17
Feel concerned about the future health of the child being affected negatively	203	15
Feel concerned about the child not receiving all the nourishment she/he needs*	203	13
Often abandons/changes plans and/or activities/vacations*	208	13
Do not feel secure that school personnel can care for the child properly if she/he should develop symptoms of FHS at school	205	14
Experience limitations in relationships to friends*	204	5
Express concerns about how to teach the child what food she/he should avoid	203	8

Table IV. FHS-specific questions concerning limitations in daily activities, emotional impact and consequences for both the child him/herself and the entire family. [a] Proportion of answers that where positive, i.e. "yes, sometimes/often/always" or "agree partly/completely". [b] Only parents who stated that they usually read the lists of ingredients and food items were asked to answer this question. For questions marked with * a significantly greater proportion of parents to children with report of pronounced FHS answered positively as compared parents to children with report of mild FHS.

4.3.4 Major findings

The health-related quality of life (HRQL) of children with reported FHS is impaired in comparison to that of healthy children, as well as of children with allergic diseases other than FHS. As assessed employing the generic instrument CHQ PF28, pronounced FHS appears to influence the HRQL more negatively than mild FHS.

Children sensitized to food did not have a worse HRQL in comparison to children without such sensitization, but children with high levels of IgE antibodies to food had a further impairment of FHS. However, responses to our disease-specific questions indicate that the severity of disease is not the only factor that affects HRQL negatively. Certain issues were reported to be a problem in a larger proportion of families with a child with pronounced FHS such as different aspects of social limitations and feelings of sadness in the affected child. On the other hand there were no differences in the proportion of parents to children with pronounced FHS as compared to the proportion of parents to children with mild FHS who reported that they or their child were anxious about developing acute symptoms (approximately one third in both cases).

4.3.4.1 Comments

In this investigation on the impact of food hypersensitivity on health-related quality of life, we chose to utilize a broad definition of FHS, because we hypothesize that the mere perception of food hypersensitivity may lead to dietary restrictions and other practical limitations and emotional consequences in daily life. The severity of the disease does, indeed, seem to exert an additional negative impact on HRQL. However, our results suggest that children with low grade of sensitization to food and/or a physician's diagnosis of food allergy do not have a greater negative impact on HRQL than do other children with FHS.

5 DISCUSSION

5.1 PHENOTYPES OF FHS AND DIAGNOSTIC PROCEDURES (PAPER I)

The overall aim of this thesis has been to investigate the relationship between perceived FHS and diagnosis of food allergy by a physician, allergic sensitization to items of food and, finally, HRQL. The discrepancy between the prevalence of reported FHS and diagnosis of food allergy observed is in agreement with numerous previous investigations [2,62,131,154-156] There may be several explanations for this discrepancy, but parents may act on their own personal beliefs concerning their child's FHS regardless of the advice given by the physician. Thus, approximately 25% of the children who show no response to an oral food challenge are still kept on a restricted diet by their parents.[4,5,93,94,103-105, 142,152,157-163]

Few studies have addressed these issues with an approach similar to that employed in Paper I. In one such population-based cohort study performed on the Isle of Wight in the United Kingdom (UK), in which, children were classified as exhibiting persistent or transient sensitization to various food allergens on the basis of positive SPT.[164] The majority of children found to be sensitized to food at four years of age (28/33, 85%) remained sensitized to food at the age of ten years, i.e., were persistently sensitized. Furthermore, children sensitized to food and/or aeroallergens at both these ages exhibited an enhanced risk for atopic dermatitis, asthma and/or rhinitis at various ages. In addition, the risk of asthma was greater among children with persistent sensitization.[164]

These findings from the UK are consistent with our own. Thus, we report that sensitization to food was significantly more common among children with report of persistent FHS than among those with transient FHS. Moreover, the children with persistent FHS demonstrated significantly higher levels of circulating IgE antibodies to food. Furthermore, all of our subjects with FHS, and especially those with the persistent phenotype, exhibited a risk for asthma, rhinitis and/or atopic dermatitis at eight years of age that was significantly higher than for children never reported to have FHS.

Similar observations have been made in two recent studies. In one German cohort study, the investigators concluded that sensitization to food allergens early in life is a predictor of later sensitization to inhalants.[165] In another study from Germany, children with persistent sensitization to food allergens run an increased risk for later development of allergic rhinitis and/or asthma.[66] In addition, Niggemann and co-workers reported that children with transient food allergy have lower levels of IgE antibodies than do children with persistent food allergy.[166]

Moreover, in a Finnish study children with persistent egg allergy were found to exhibit IgE antibodies to eggs directed specifically towards more sequential and conformational epitopes of ovomucoid and ovalbumin and consequently, determination

of these epitopes was proposed as a method for distinguishing between persistence and development of tolerance in such children.[167]

Another important finding documented in Paper I is that reported hypersensitivity to two or more items of foods at two years of age was associated with a significantly increased risk for persistent FHS. Thus, children reported to have FHS and who are not sensitized at four years of age (or who are sensitized, but have low levels of IgE antibodies), or whose symptoms at an early age are associated with only a single item of food appears to have a relatively good prognosis, both with respect to FHS and other allergic diseases. This is a novel observation.

5.2 FOODS AND SYMPTOMS

As described by others, the items of foods most commonly reported to cause FHS among our children at four years of age were milk and citrus, followed by peanuts and tree-nuts (Paper II).[3,149] However, symptoms related to certain vegetables and fruits were more frequently reported in these previous publications. This difference is probably mainly explained by cross-reactivity to pollen since these other studies involved older children, (i.e., 0-17 years and 2.5-14 years of age).[3,149]

In agreement with reports from Germany and France, the symptoms most commonly reported here were eczema and gastrointestinal symptoms followed by urticaria, facial oedema and symptoms from the airways.[3,149] In approximately 50% of our children, eczema or gastrointestinal disturbances were the only symptoms reported. Furthermore, the association between these symptoms and the presence of IgE antibodies to food was weak. This may indicate that, unless they occur in combination with other allergic responses, these symptoms are not IgE-mediated.

This suggestion is supported by the findings of Niggemann and co-workers that 10% of the positive food challenges in children with atopic eczema are not mediated by IgE antibodies.[107] Furthermore, young children with food-related allergic gastroenteritis/proctocolitis, often caused by milk, rarely have circulating IgE antibodies to food.[4,168] Responses to food items that cause the release of histamine, such as tomatoes, citrus fruits and strawberries, spinach and shellfish are other examples of FHS not mediated by IgE antibodies.[169]

Other symptoms of FHS observed included urticaria, facial oedema, rhino-conjunctivitis and asthma (Paper II). The majority of children with any of these symptoms present with multiple symptoms and are also sensitized to food. This group of children, who apparently suffered from complicated forms of FHS, seemed more prone to develop persistent allergic disease than children who exhibited only a single symptom of FHS.

5.3 THE ASSOCIATION BETWEEN SENSITIZATION TO FOOD AND REPORTED SYMPTOMS

The observation that the overall association between symptoms and sensitization to the offending food was rather weak may have several explanations (Papers II and III). In the first place, since the children were already four years old, the clinical symptoms of some of those with mild or moderate food allergy, particularly to milk or eggs, might have gone into remission even though they remained sensitized. Other children may have been in the process of becoming sensitized to certain foods without yet presenting symptoms. This may be true particularly for peanuts.

We found that children may have IgE antibodies towards certain items of food without reported symptoms or vice versa. In those with symptoms of FHS but no sensitization (as screened with fx5®), a food allergy mediated by IgE antibodies is not likely to have been present, since the food allergens included in the fx5® are responsible for 90-95% of all food allergies in preschool children.[4,170] Furthermore, less than half of all the children with eczema or gastrointestinal symptoms were sensitized to the offending food, whereas the majority of children exhibiting urticaria, facial oedema or symptoms from the airways were sensitized.

High levels of IgE antibodies towards milk, eggs or fish were found to be closely associated with symptoms reported to be caused by the same item of food. In the case of peanuts, soy beans and wheat, such a relationship was less clear. Some of the children who were highly sensitized to peanuts demonstrated no reported symptoms related to this food item. This indicates that the diagnosis of peanut allergy based on levels of IgE antibodies to food alone is problematic, at least in this age group. Thus, this approach of diagnosing allergy to peanuts, soy beans or wheat in preschool children must be questioned.

5.4 HEALTH-RELATED QUALITY OF LIFE

5.4.1 CHQ-PF28

HRQL in relation to a certain disease is important to investigate in clinical research. In this context, generic instruments are widely used. However, specific issues and concerns related to the investigated condition or diagnose cannot be captured by such an instrument alone and, therefore, disease-specific instruments also have been developed for many diseases. Use of these two approaches in combination increases the probability of being able to draw more precise conclusions of relevance for clinical practice.[140]

The majority of studies that have reached the conclusion that food allergy in children exerts a negative impact on HRQL have been based on hospital settings.[115,116,118,119] From the present investigation with a population-based design, we have come to similar conclusions (Paper IV). Sicherer and co-workers employed a longer

version (CHQ-PF50) of the same instrument chosen here.[119] They compared different aspects of HRQL in children with food allergy with the HRQL in a general American population and found that food allergy has a negative influence on General health (GH), Parental impact – emotional (PE) and Family activities (FA). In our own study, children with FHS had parental-reported lower scores on the subscales GH, Role/social limitations- physical (RP) and Physical functioning (PF) than children with other allergic diseases or no allergic disease. In comparison with children with no allergic disease children with FHS had lower scores on the subscales Role/social limitations – emotional (REB), Bodily pain (BP), Mental health (MH) and PE.

The fact that we and Sicherer *et al.* found somewhat different subscales to be affected can be explained by several factors: In the first place, our group of children was probably more heterogeneous with respect to severity of symptoms. Moreover, the subjects in the study by Sicherer *et al.* had all received a diagnosis of food allergy. In addition, we compared children with FHS to children with other allergic diseases, as well as to children with no allergic disease at all, whereas the reference group chosen by Sicherer and co-workers was a general population. Although it was not possible for us to compare our findings with Swedish normative values, as such data do not exist for the CHQ-PF28, our population-based design allows us to assume that the children and parents included were relatively representative.

This study showed that children with high levels of IgE antibodies to food or report of pronounced symptoms of FHS, in particular children with food-related symptoms from the lower airways, had an especially poor HRQL, reflecting an association with the severity of FHS and the HRQL. The negative impact of FHS on the HRQL, is in agreement with other reports.[116,119,171] However, although it can be assumed that children who had been diagnosed with FHS or food allergy had more severe symptoms, the HRQL of these children was not more impaired than that of other children with FHS. This indicates that there are components other than severity of disease that also affect the HRQL. There are only a few studies concerning the psychological characteristics on individuals with perceived FHS. In one of these studies the investigators conclude that in individuals who probably have FHS the psychological and general health did not differ from those with possible/unlikely FHS.[8] This is in contrast with findings in another study where self-reported allergies appears to be associated to mood and anxiety disorders.[172]

5.4.2 Disease-specific questions

One of the main findings from our disease-specific questions was that it was common for the child with FHS to eat dishes that were different from what the rest of the family ate and/or for the rest of the family to adjust their diet to suit the child. This clearly indicates that the families took their children's symptoms seriously. Bollinger and co-workers found that for many families of children with FHS planning meals was a major issue and grocery shopping a problem.[116] Two-thirds of our respondents stated that they had difficulties in interpreting lists of ingredient, a finding similar to that of Joshi *et al*.[173] One can assume that many families where no one has FHS also have such difficulties, but that they will not have such a negative influence on daily life and,

consequently, on the HRQL as when mistake in interpretation of labelling can affect a child's health negatively. An interesting difference between our subjects and those studied by Bollinger's group was that only a minority of our participants (6%) stated that the child could not participate in school outings, while 59% considered this issue to be problematic in the American study.[116] This difference could be explained by the fact that children in Bollinger's study had a more severe disease, but probably also by cultural differences.

Another observation made here was that approximately one-third of all the parents involved were anxious about the possibility that their child might develop acute symptoms of FHS and the same proportion reported that their children were themselves anxious about developing acute symptoms. Interestingly, no difference in this respect was seen between children with pronounced and mild FHS, indicating again that the severity of disease is not the only factor that exerts an impact on the HRQL[110,111] Parental concern and the concern of the child him/herself is likely to have a great impact in this respect, but little is known about this at present.[8,130]

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5.5 GENERAL DISCUSSION AND CLINCIAL IMPLIMENTATION

5.5.1 The use of measurements of quantitative IgE antibodies to food

A number of valuable articles on the relationship between sensitization and verified food allergy have been published in recent years.[3,4,57,62,63,94,107,149,174-177] Levels of IgE antibodies to different foods above which an oral food challenges can be considered unnecessary have been proposed. This is an important question, since food challenges are time-consuming and expensive, and therefore not included routinely in all clinics that care for children with FHS. However, the relationship between levels of IgE antibodies to food and symptoms has not been thoroughly investigated in the general population, and especially not in larger homogenous age groups.

5.5.1.1 Interpretation of allergy tests: can sensitization to a certain item of food precede/predict symptoms?

We could show that presence of IgE antibodies to food was rather common at four years of age with no reported FHS. For food allergens of animal origin, the association between symptoms and increasing levels of such antibodies was reasonably good, but this was not the case for food allergens with plant origin. Our subjects included ten children who were sensitized to peanuts with serum levels of IgE antibodies to peanuts $\geq 50 kU_A/L$ but had no reported FHS. It is possible, perhaps probable, that at least some of these children would react to a challenge with peanuts. Nonetheless, this finding indicates that the general population contains a number of individuals, at least at four years of age, who are highly sensitized to food without demonstrating any clinical allergic symptoms. Perhaps, despite current sensitization, a certain amount of a food item must be consumed over time before an association between levels of circulating IgE antibodies to food and adverse reactions to the item of food in question becomes evident. Another explanation could well be that sensitization could precede the development of symptoms. One could ask if parents whose child is sensitized to peanuts, but does not demonstrate peanut-related symptoms, should be given this information. However, by doing so, there is a considerable risk of causing unnecessary anxiety in both parents and children.

5.5.2 The need for better diagnostic tools

New and improved tools for diagnosis of food allergies are presently under development, but meanwhile, we should use and interpret levels of IgE antibodies to food with care. In order to avoid unnecessary dietary restrictions and anxiety, it is important to establish the absence as well as the presence of FHS or food allergy. One of the more refined and reliable diagnostic tools that will certainly become available in the future will probably be based on recombinant allergen molecules. Such molecules can be tailor-made to identify the epitope that elicits symptoms, thereby allowing more specific quantification of IgE antibodies.[158,178-180] Furthermore, epitope recognition patterns and the affinities of IgE antibodies are determinants of the severity and

duration of food allergy,[179,181] and assessment of such parameters can also be of value in connection with future food-allergen immunotherapy.[180,182,183]

5.5.3 Oral food challenges

Oral food challenges are generally considered to be the gold standard for diagnosing FHS or food allergy, but routine use of a food challenge to establish or rule out food allergy in patients found to be sensitized for the reasons mentioned above is, of course, unrealistic. At the same time, interpreting the results of other tests now in use is a tricky and delicate task. There are at present too few paediatric allergologists, at least in Sweden, even to manage children with severe symptoms of FHS or food allergy. It seems highly likely that not all general practitioners (and paediatric general practitioners as well, for that matter) are fully aware of the difficulties involved in interpreting serum levels of IgE antibodies to food. Being diagnosed with food allergy on the basis of non-specific symptoms in combination with sensitization to food is probably not an uncommon occurrence in most countries.

5.5.4 HRQL and FHS

Children with pronounced FHS were reported significantly more often by their parents to be restricted from eating at friends' homes or restaurants and to feel restricted in everyday life in other ways as well, in comparison to children with mild FHS. These related findings and other findings indicate an increased risk for segregation and other negative effects of FHS on the social life and development of the child. Moreover, approximately two-thirds of the children with reported FHS in our study were reported by their parents to be concerned about having FHS, which may exert a substantial influence on their daily lives. In recent years assessments of HRQL has been considered to be of great importance in both clinical practice and research, but little is yet known within this area. It is extremely important to improve our knowledge in this area and to offer children with FHS and their families support in coping with their situation. This approach would certainly have positive effects for the afflicted individuals and probably also improve health-care for allergy.

5.6 STRENGTH AND WEAKNESSES OF THE PRESENT INVESTIGATIONS

The large number of participants, the prospective and longitudinal design, and population-based approach are obvious strengths of the studies of this thesis. Furthermore, the response rate in connection with the BAMSE study has been very high. The questionnaires were sent out to families living in three different areas in and around Stockholm that were chosen as representative of the general population.[136]

The procedures commonly used for diagnosing of FHS and food allergy include either SPT and/or measurement of serum levels of IgE antibodies to food.[91,184-187] We

consider the choice of the latter approach in the BAMSE study to be a strength. The method involved has been standardized, the results obtained are reproducible and the quality of the data is independent of sample size and of the number of the different antibodies measured. To our knowledge, ours is the only investigation where serum samples from as many as 2600 children have been analyzed for IgE antibodies to food at two different ages.

At an early stage in our study, the proportions of young mothers and of smoking parents among the non-responders were slightly larger than among the participants. In addition, among the families who dropped out between four and eight years of age, the proportions of parents with less education and of children with allergic disease at four years of age were slightly larger. However, if these biases have any affect on our findings, it would be to attenuate the differences observed. The definitions of atopic eczema, rhino-conjunctivitis and asthma employed here have all been used in other peer-reviewed studies.[17,22,35,43,69,143,144,188]

Our first questionnaire, sent to the parents when their children were 2 months old, was designed to evaluate their current situation in terms of education, living conditions, life-style, etc. The questionnaires sent out at one, two and four years of age included questions concerning symptoms of allergy/hypersensitivity exhibited by the child during the past 12 months. In these cases there was, of course, a risk for misclassification of outcome, but since the information on exposures was collected prior to that on outcomes, any such misclassification should be non-differential.[189]

The disease-specific questions included in the evaluation of HRQL have not yet been validated. Nonetheless, the answers to these questions provided interesting information. An article in which the psychometric properties of these questions are evaluated is presently under preparation.

It is also important to stress that we have examined the parents' perception of the child's HRQL, rather than the perception of the child him/herself. Evaluation of the children's own perception would have been optimal, but we thought it was questionable to ask children with a mean age of nine years to answer a rather complicated and extensive questionnaire sent by mail, since reading capacity varies widely at this age.

As already pointed out, our findings on reported FHS cannot be compared directly to studies on food allergy verified by a food challenge. We decided not to perform food challenges for ethical and practical reasons. The majority of children sensitized to food had no report of food-related symptoms and to ask their parents to allow these children to be subjected to a food challenge might have caused unnecessary anxiety in both the parents and children, as well as making them more reluctant to participate in the BAMSE project in the future.

6 SUMMARY AND CLINICAL IMPLICATIONS

6.1 SUMMARY

- The presence of symptoms of FHS during the first two years of a child's life appears to be associated with an increased the risk of developing asthma, allergic rhinitis and/or atopic dermatitis at eight years of age.
- The proportion of FHS and DFA in children increases between the ages of one and eight as a consequence of the development of symptoms related to peanuts, tree nuts and fruits.
- At four years of age serum levels of IgE antibodies to food are lower in children with transient than with persistent FHS.
- The majority of children exhibiting urticaria, facial oedema or asthma as symptoms of FHS at four years of age have multiple symptoms and are sensitized to food, i.e., they appear to suffer from FHS of a more severe phenotype.
- Quantitative measurement of IgE antibodies directed to milk, eggs or fish is useful for the evaluation of IgE-associated FHS in preschool children, whereas, in contrast, levels of IgE antibodies to soy beans not can be used as a diagnostic tool for allergy to soy bean. Measuring levels of IgE antibodies to wheat and peanut seems to be of limited diagnostic value, at least in a population of preschool children.
- Parental perception of FHS in 9-year-old children exerts a negative impact on the parents' perception of the child's HRQL, an impact which is particularly pronounced for children reported to have food-related symptoms associated with the lower airways, as well as for children with high serum levels of IgE antibodies to food.

6.2 CLINICAL IMPLICATIONS

- A child reported to have FHS with only a single symptom at four years of age has a favourable prognosis.
- Reported FHS in the absence of sensitization to food or sensitized with low levels of IgE antibodies to food (fx5®) is another sign of a favourable prognosis.
- High levels of IgE antibodies specific for cow's milk, hen's eggs or fish are closely associated with symptoms reported to be evoked by these items of food, whereas in the case of sensitization to soy beans wheat or peanuts, this association is weak.
- Even pronounced sensitization to peanuts at four years of age is not always associated with peanut-related symptoms, an observation that emphasizes the necessity of diagnosing FHS or food allergy on the basis of solid criteria other than the test results alone. Furthermore, young asymptomatic individuals with high levels of IgE antibodies to peanuts should perhaps be more closely followed for the later development of peanut-related symptoms.

- Our findings concerning the reduction of HRQL illustrate how important it is that health-care personnel identify children and families in need of extra support.
- Severe FHS is likely to exert a more pronounced negative impact on the HRQL than mild symptoms of FHS do, but the severity of this condition is not the only factor of importance in this context.

6.3 FUTURE PERSPECTIVES/UNSOLVED ISSUES

In connection with future follow-ups of the BAMSE cohort, our characterization of the natural course of FHS of different phenotypes will be continued. Information on food hypersensitivity/allergy that has been verified by an oral food challenge will also be obtained. The current procedures for diagnosing food allergy are far from optimal, since those children who will continue to display mild symptoms or even go into remission cannot be distinguished from those who will later develop a more severe form of this disease. Testing with recombinants and components of allergen proteins should provide a more reliable diagnosis.

Additional studies on the impact of FHS on HRQL are required, with the aim of developing a short, validated disease-specific questionnaire concerning HRQL which might be useful both in clinical practice and in research.

In recent years numerous investigations have focused on various aspects of the development of tolerance to allergenic foods. Serum levels of IgE antibodies to milk are significantly lower in children who develop tolerance than in those with persistent allergy to milk.[190] In connection with the continuation of the BAMSE study the relationship between the development of tolerance and serum levels of specific IgE antibody levels will be examined.

7 POPULÄRVETENSKAPLIG SAMMANFATTNING

Födoämnesöverkänslighet, som innefattar födoämnesallergi, drabbar cirka 6% av alla barn under 3 år och cirka 2% av vuxna. Definitionen på födoämnesallergi är att symtomen förmedlas av immunförsvaret. Bland barn med födoämnesöverkänslighet reagerar 90-95% med symtom utlösta av mjölk, ägg, fisk, jordnöt, vete eller soja. Dessa födoämnen innehåller allergen, d.v.s. proteiner som kroppen kan komma att uppfatta som farliga. Då produceras antikroppar, s.k. IgE-antikroppar, mot allergenet.

Att diagnostisera födoämnesöverkänslighet är i många fall svårt och kräver en viss vana att tolka symtom på överkänslighet kombinerat med vana att tolka resultaten på de allergitester som finns att tillgå. De vanligaste allergitesterna innebär att man på olika sätt mäter förekomst av IgE-antikroppar mot olika födoämnen. Testmetoderna är bra hjälpmedel vid utredning av födoämnesöverkänslighet men räcker inte alltid till som enda underlag för att ställa diagnos. De bör ofta kompletteras med att patienten får prova små mängder av det misstänkta födoämnet. Denna metod kallas för födoämnesprovokation och bör utföras på mottagningar där det finns stor vana med metoden. Detta medför att diagnostiken av födoämnesöverkänslighet är förenad med betydande svårigheter.

Vidare finns endast ett fåtal studier där man undersökt hur den hälsorelaterade livskvaliteten påverkas hos barn med någon form av födoämnesöverkänslighet. De flesta av dessa befintliga studier är baserade på patienter som regelbundet går på uppföljning vid allergimottagningar. Det finns endast en annan studie där man liksom vi har studerat hälsorelaterad livskvalitet vid födoämnesöverkänslighet hos ett tvärsnitt av befolkningen.

Denna avhandling avsåg att belysa olika aspekter av relationen mellan symtom på rapporterad överkänslighet mot födoämnen och förekomst av IgE-antikroppar mot vissa födoämnen, men också att studera hur sjukdomen utvecklas över tid beroende på vilka symtom som finns under de första levnadsåren. Syftet var vidare att undersöka hur födoämnesöverkänslighet påverkar risken att utveckla andra allergiska sjukdomar samt att undersöka hur barns och familjers hälsorelaterade livskvalitet påverkas av födoämnesöverkänsligheten.

I den första studien sågs att barn med födoämnesöverkänslighet under de första 2 åren hade en större risk än andra för att ha astma, atopiska eksem eller allergisk snuva vid 8 års ålder. De barn som hade födoämnesöverkänslighet, men endast uppvisade ett symtom samt de som inte hade IgE-antikroppar mot vanliga födoämnen, hade en god chans att tillfriskna helt och hållet. *Resultaten betyder att antalet symtom och förekomsten av IgE-antikroppar kan användas som prognostiska faktorer. Detta är viktig information till barnet och dess föräldrar, men det har också betydelse för hur uppföljning och fortsatt utredning av barnet ska utformas.*

I studie 2 visades att hälften av alla 4-åriga barn med födoämnesöverkänslighet hade eksem eller symtom från mag/tarmkanalen som enda tecken på

födoämnesöverkänsligheten. Endast en minoritet av dessa barn hade IgE-antikroppar mot något födoämne. De barn som uppvisade något av symtomen nässelutslag, svullnad av läppar/ögon, besvär från ögon/näsa eller astma hade i regel flera symtom i kombination. De flesta av dessa barn hade också IgE-antikroppar. *Dessa iakttagelser i kombination med resultaten från studie I talar för att barn som vid 4 års ålder har födoämnesöverkänslighet men som endast har besvär i form av mag/tarmsymtom eller eksem har god prognos och i de flesta fall inte heller utvecklar någon annan allergisk sjukdom.*

I den tredje studien kunde ett samband påvisas mellan stigande nivåer av IgE-antikroppar mot mjölk, fisk och ägg och sannolikheten för att ha symtom mot dessa födoämnen. Sambandet mellan höga nivåer av IgE-antikroppar mot vete eller jordnöt och rapporterade symtom orsakade av dessa födoämnen var inte lika tydligt. Inget samband sågs mellan höga nivåer av IgE-antikroppar mot soja och rapporterade soja-relaterade symptom. *Dessa resultat innebär att värdet av att mäta IgE-antikroppar med dagens teknik mot soja måste ifrågasättas. Det innebär också att ställa någon av diagnoserna jordnötsallergi eller veteallergi enbart baserat på förekomst och/eller nivå av IgE-antikroppar mot dessa födoämnen är vanskligt, åtminstone på barn i förskoleåldern. Barn med allergiantikroppar mot soja i första hand, men kanske också mot vete eller jordnöt, kan alltså bli felaktigt diagnostiserade som födoämnesallergiker och bli rekommenderade specialkost med de konsekvenser det kan medföra,*

I studie 4 konstaterades att barn med födoämnesöverkänslighet bedömdes av sina föräldrar att ha sämre hälsorelaterad livskvalitet i jämförelse med friska barn och också jämfört med barn med andra allergiska sjukdomar. Barn som hade höga nivåer av IgE-antikroppar eller mer uttalade symtom på födoämnesöverkänslighet, d.v.s. symtom minst en gång per månad, flera olika symtom och/eller symtom från luftvägarna, hade en ytterligare försämring av livskvaliteten. Många födoämnesöverkänsliga barn fick specialkost i skolan och i många familjer lagades särskild mat till barnet med födoämnesöverkänslighet. Det framkom också att en majoritet av barnen hade funderingar till och från över sin sjukdom. Vissa kände sig också annorlunda jämfört med andra barn och en del upplevde begränsningar i sitt dagliga liv. *Dessa resultat illustrerar att födoämnesöverkänslighet hos barn för många har en påverkan på det dagliga livet och också utgör en stor del av såväl barnens som deras familjers vardag.*

Sammanfattningsvis visar resultaten från studierna att sambandet mellan IgE-antikroppar mot födoämnen och födoämnesöverkänslighet är varierande beroende på vilket födoämnesallergen som avses. Mätning av IgE-antikroppar mot soja, men kanske också mot vete och jordnöt, förefaller ha begränsat värde om inte stark misstanke om symtom mot dessa födoämnen finns. Det finns ett inte helt litet antal individer med höga nivåer av IgE-antikroppar mot olika födoämnen, från fram för allt växtriket, som inte har några kända symtom på födoämnesöverkänslighet. Det innebär att analys av förekomst av IgE-antikroppar som metod för screening i befolkningen i förskoleålder och med dagens teknik inte förefaller rimlig. Bland barn där stark misstanke om överkänslighet finns fyller dessa mätningar alltjämt en viktig funktion, men utveckling av förbättrade diagnostiska metoder är angeläget. Resultaten illustrerar också svårigheterna med att tolka testresultaten. Det innebär att det är av största vikt att säkerställa kompetensen hos de personer inom barnsjukvården som har till uppgift att

handlägga födoämnesöverkänslighet, en vanlig sjukdom under barnaåren. En förbättrad diagnostik skulle kunna bidra till att enklare kunna identifiera de som har födoämnesöverkänslighet, men också till att minimera överdiagnostisering. Det sistnämnda är angeläget inte minst med kännedom om vilka konsekvenser födoämnesöverkänslighet har för de drabbade barnen och deras familjers hälsorelaterade livskvalitet.

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