Children's hypersensitivity to cow's milk

Public health aspects and impact on families

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To Alan, Viana and Miranda

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ABSTRACT

Background and aims: Diet during childhood can have lifelong consequences for health. Cow's milk is regarded as a basic food item in Sweden, but is also the most usual cause of adverse reactions during the first years of life. Parental education is crucial in order to prevent less adequate diet and malnutrition. This is especially important in children in need of special diet. Nutritional treatment affects the child's health and development and the family's daily life. Knowledge concerning affected children and their families is required in order to improve care.

Methods: Study I is a cross- sectional study in which compliance with nutrition recommendations was evaluated retrospectively. The focus was on introduction of cow's milk in the diet of healthy children, both with and without heredity for atopic diseases. Study II is an intervention describing the process leading to the development, evaluation and follow-up of nutritional therapy in groups for families with children with cow's milk allergy. In Study III, an instrument was developed to measure the perceived impact on daily life in families with children with cow's milk allergy, exclusively or in combination with other food allergy. Study IV assesses the change in perceived impact over time on families with children with food allergy, following the child's and the food allergy's development.

Results: I) most parents seem to follow recommendations given by the Child Health Centers. However, families with children at risk of atopic disease require attention; otherwise, preventive measures will be less effective. II) The establishment of a milk allergy school substantially improved access for families with affected children. It met the families' need for information, was

appreciated according to the evaluation, entailed few administrative routines and was timesaving. The milk allergy school has become permanent and its implementation is increasing. III) A reliable, valid and sensitive instrument was created, showing that affected families are impacted negatively by the child's food allergy, compared to families with children not requiring a special diet. IV) The impact on affected families changed over time, following the development of the child and the cow's milk allergy.

Conclusions: Preventive information should be updated and communication needs to be improved. Continuous monitoring is necessary to prevent complications among affected children, including after the development of tolerance.

SAMMANFATTNING PÅ SVENSKA

Bakgrund: Kostvanor under barndomen kan ge livslånga konsekvenser för hälsan. I Sverige betraktas komjölk som ett baslivsmedel samtidigt som komjölksprotein är den vanligaste orsaken till överkänslighetsreaktioner under de första levnadsåren. Föräldrautbildning är av central betydelse för att förebygga att mindre lämplig kost introduceras och att näringsbrist uppstår. Speciellt viktigt blir detta för barn i behov av specialkost. Kostbehandling påverkar barnets hälsa och utveckling men även familjens vardag. Kunskapen om drabbade barn och deras familjer behöver öka för att förbättra vård och behandling.

Metoder: Delstudie I) är en tvärsnittstudie där följsamheten till gällande rekommendationer om spädbarns kost undersöktes retrospektivt. Tonvikt lades på komjölksintroduktion till barn med, respektive utan hereditet att utveckla atopisk sjukdom. Delstudie II) är en intervention som beskriver processen som ledde till skapande, utvärdering och långtidsuppföljning av en mjölkallergiskola, en arbetsmetod för kostbehandling av barn med komjölksallergi. I delstudie III) konstruerades ett instrument avsett att mäta grad av påverkan på vardagen för familjer med barn med komjölksallergi, enbart eller i kombination med andra livsmedel. Delstudie IV) studerar påverkan över tid för familjer med barn med födoämnesallergi i förhållande till barnets utveckling och till födoämnesöverkänslighetens utveckling.

Resultat: I) De flesta föräldrar verkar följa rekommendationer som barnhälsovården ger. Familjer med risk att utveckla atopiska sjukdomar behöver dock uppmärksammas särskilt, annars finns det en risk för att resultaten av förebyggande åtgärder blir mindre lyckad. II) Skapandet av en mjölkallergiskola ökade avsevärt tillgänglighet till kostbehandling för drabbade familjer. Den möter familjernas behov av information, är uppskattad enligt utvärdering, innebär få administrativa rutiner och är tidsbesparande. Mjölkallergiskolan permanentades och dess användning ökar III) Ett tillförlitligt och känsligt instrument skapades som visade att drabbade familjer påverkas negativt av barnets födoämnesallergi jämförd med familjer med barn utan behov av specialkost. IV) Påverkan förändrades över tid till följd av barnets och födoämnesallergins utveckling.

Slutsatser: Preventivt information behöver uppdateras och spridningen kan förbättras. Kontinuerlig uppföljning av barn med födoämnesallergi är nödvändig för att förebygga komplikationer, även bland barn som utvecklat tolerans.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Mikkelsen, A., Rinne-Ljungqvist, L., Borres, M.P., van Odijk, J. Do Parents Follow Breastfeeding and Weaning Recommendations Given by Pediatric Nurses? A Study With Emphasis on Introduction of Cow's Milk Protein in Allergy Risk Families. J Pediatr Health Care 2007; 21: 238-244.

II. Mikkelsen, A., Lissner, L. Borres, M.P. Milk allergy school: Nutritional therapy in group for parents of children with cow's milk allergy/intolerance in Primary Health Care. Pediatr Allergy Immunol 2005; 16: 86-90

III. Mikkelsen, A. Borres, M.P., Björkelund, C., Lissner, L., Oxelmark, L. The Food hypersensitivity famiLy ImPact (FLIP) questionnaire-development and first results. Pediatr Allergy Immunol 2013; 24: 574-81

IV. Mikkelsen, A., Mehlig, K., Borres, M.P., Oxelmark, L., Björkelund, C., Lissner, L. Monitoring the impact of cow's milk allergy on children and their families with the FLIP questionnaire – a 6-month follow-up study. Manuscript in preparation.

CONTENT

ABBREVIATIONS

AAP	American Academy of Pediatrics
AAAAI	American Academy of Allergy, Asthma and Immunology
ACAAI	American College of Allergy, Asthma and Immunology
ASCIA	Australian Society of Immunology and Allergy
BLF	Swedish Paediatric Society, affiliated with the Swedish Medical Association
CHC	Child health centers. May also be referred to, in publications, as well-baby clinics (1), see primary health care under brief definitions
CM	Cow's milk
CMA	Cow's milk allergy
CMH	Cow's milk hypersensitivity
CMP	Cow's milk protein
CMPA	Cow's milk protein allergy
CMPI	Cow's milk protein intolerance
CMPH	Cow's milk protein hypersensitivity
DBPCFC	Double blind placebo-controlled food challenge
DRACMA	Diagnosis and Rationale for Action against Cow's Milk Allergy, working group in the World Allergy Organization
EAACI	European Academy of Allergy and Clinical Immunology
ESPGHAN	European Society for Gastroenterology, Hepatology and Nutrition

FA	Food allergy
FH	Food hypersensitivity
FLIP	Food hypersensitivity famiLy ImPact questionnaire
ICC	Intra-Class Correlation Coefficient
IgE	Immunoglobulin E; a type of immunoglobulin, implicated in allergic reactions
OFC	Open food challenge
OI	Overall importance
SD	Standard deviation
SPSQ	Swedish Parental Stress Questionnaire
SPT	Skin prick test
WAO	World Allergy Organization
WHO	World Health Organization

BRIEF DEFINITIONS

Allergen	Substance that induces the hypersensitive state of allergy and stimulates the formation of antibodies in some individuals (2).
Atopy	Type of hypersensitivity characterized by an immediate physiological reaction, with movement of fluids from the blood vessels into the tissues, upon exposure to an allergen. Atopy occurs mainly in individuals with a familial tendency to allergic disease (3).
Food allergy, food hypersensitivity	Any adverse reaction to food, divided into immune-mediated reactions, i.e. IgE-mediated (food allergy), and non-immune-mediated reactions, i.e. non-IgE- mediated (food intolerance) (3).
Health-related quality of life (HRQL)	The component of quality of life that pertains to an individual's health and consists of an individual's physical, mental and social well-being (4).
IgE-mediated and non-IgE-mediated reaction	Classification of reactions, according to whether IgE antibodies are produced in response to an allergen or not (5).
Parental stress	The conflict between parental resources and demands connected to the parental role (6).
Primary health care	In Sweden primary health care is defined as the part of public health that should, without delimitation regarding diseases, age or patient group, reply to the populations' need of such medical treatment, care, preventive work and rehabilitation that does not require the hospitals' medical or technical resources or other special competence" (7). Within

	primary health care, there are child health centers (CHC) dedicated mainly to prevention. Families attend CHC for health checkups, vaccinations, counseling regarding parenting, accident prevention, nutrition education, etc. Some primary health care organizations also have pediatric clinics, e.g. West Götaland, where families seek help when they suspect a disease in their children.
Quality of life (QoL)	Individuals' perception of his/her position in life in the context of the culture and value systems in which the individual lives and in relation to his/her goals, expectations, standards and concerns (4).
Reliability	Refers to the reproducibility of an instrument, i.e. its ability to produce the same or similar results when re-administered. In health measurement scales, e.g. questionnaires, it is usually assessed by calculation of internal consistency and test-retest reliability (8).
• Internal consistency	It describes the degree to which the items of a questionnaire relate to each other and to the total questionnaire. It is most commonly assessed by calculation of Cronbach's α, where $\alpha \geq 0.70$ indicates good internal consistency (9). Calculation of Cronbach's α is a way of assessing the homogeneity of a scale (8).
• Test-retest reliability	It is usually evaluated by the intra-class correlation coefficient (ICC) which is an estimate of the reproducibility of the questionnaire over varying elapsed time. The questionnaire is administered to the same population on two occasions after controlling that no change in the condition/situation has taken place. Test-retest reliability is considered to be

	good at an ICC ≥0.70 (9).
Validity	Describes an instrument's ability to measure what is intended. It is considered that there are several types of validity (8).
• Internal validity	Is considered to be the internal structure within a questionnaire and is usually assessed by factor analysis, inter-item correlation and floor and ceiling effects (9).
• Factor analysis	A statistical method commonly used to reduce the number of items with relevance to be included in an instrument. Factor analysis may also aid the development of subscales by revealing eventual underlying structures in the study responses (8).
• Inter-item correlations	It is a coefficient of the correlation between items in a questionnaire and in scales. This is a way of assessing an instrument's appropriate length. If the coefficient is greater than 0.85 it indicates that there is redundancy, i.e. there are items that can be excluded (9).
• Floor and ceiling effects	These are assessed by calculation of the percentage of respondents with minimal or maximal score on a questionnaire, respectively. Floor and ceiling effects should be minimal, preferably under 15% (9). Too many participants scoring lowest or highest possible effect would impede the detection of any improvement or detriment as measured by a scale (8).
• External validity	Indicates the relationship between an instrument and other instruments assessing the same or similar dimensions and is usually assessed through face, content, convergent/discriminant and construct validity (9).
• Face validity	This is a subjective judgment that an

		instrument appears reasonable. It is usually done by allowing experts to inspect the instrument, for instance subjects assumed to be affected by a specific condition or disease targeted by the instrument (8).
•	Content validity	Closely related to the concept of face validity. It is an assessment of whether all domains, or important content, are sampled in the instrument. As with face validity, it is usually assessed by allowing intended respondents to review the instrument (8).
•	Convergent and discriminant validity	The extent to which a new instrument correlates and does not correlate with a similar instrument to assess a similar condition. This type of validity is considered more rigorous than face and content validity (9). Usually assessed by administering the new and an existing, validated instrument measuring the same or similar condition and by calculating correlations between both instruments. An instrument's variables should correlate with similar, related variables from another instrument (convergent validity) and there should not be any correlation with dissimilar variables (discriminant validity). Convergent validity correlations should fall in the range of 0.4-0.8 (8).
•	Construct validity	Is considered to be the most rigorous type of validity. It refers to an instrument's ability to measure the theorized attributes of a construct. It can be assessed by the correlation of the instrument to an independent measure or outcome related to the condition or disease under study or by administering the measure to different

	groups, e.g. affected or not by the condition or disease, i.e. cases and controls or different degrees of a condition or disease (8, 9).

1 INTRODUCTION

Feeding practices during infancy have short- and long-term health implications. The most appropriate source of nourishment for infants is breast milk or, when lactation is not possible, infant formula. In due time, the infant is weaned to the family's diet, following a gradual transition from a liquid-based diet to a variety of food, through a learning process following the child's development. The aim of weaning is to provide for the increasing nutritional needs of the growing infant. Nutrition recommendations provide rationale for the advice that health care providers should give families with infants and children. Nutrition education is central in the primary health care in order to prevent nutritional deficiencies, inadequate weaning and nutrition-related disease.

Assessing families' compliance with recommendations is necessary in order to evaluate their effect on the methods applied by health workers. Evaluation leads to improvements in the development and adaptation of nutrition education to the evolving needs of both health workers and consumers in a changing society.

Nutrition guidelines regarding prevention of atopic diseases focus on commonly allergenic food(s), such as cow's milk (CM). A basic food in infant and child nutrition worldwide, CM is also the most usual offending food allergen in infancy and childhood. In an attempt to prevent food allergy (FA), families with atopic heredity are recommended to avoid CM during the infants' first months of life (primary prevention). Despite preventive efforts, a considerable, and possibly increasing, number of infants and children develop cow's milk allergy (CMA). Attention should be devoted to the nutritional treatment of diagnosed cases, preventing short- and long-term consequences of elimination diets as well as further development of atopic disease (secondary prevention) and in order to maintain good health despite the presence of disease (tertiary prevention). The child's nutritional status, growth and development may be jeopardized. The development of eating skills and eating behavior may be disrupted at a vulnerable age if a special diet is required. It is thus of paramount importance to increase access to appropriate information for affected families as well as to others involved in the child's daily life. These tasks present a challenge to parents and public health; the latter must also meet demands for cost-efficiency. Children affected by adverse reactions to food constitute one of the largest patient groups for dieticians.

The limitation of food and the constant vigilance required in cases of FA affect not only the child but also the families, extended families and others involved in his/her daily life, e.g. kindergarten staff. Identifying and measuring this impact can help adapt, develop and allocate appropriate resources to improve the care offered to affected families. Improved support and nutrition education to families with healthy children as well as those with children affected by diseases that can compromise normal growth and development will result in benefits in health, quality of life and finances to the individual, society and public health.

2 BACKGROUND

2.1 Cow's milk allergy

Nutrition-related issues are among the most common cause of consultations in public health. As a basic food item, CM is often the object of concern and suspicion, related to adverse reactions in children. Normal parental stress concerning diet may increase in cases of nutrition-related disease (10-12). Shortcomings in the clinical management of CMA have been identified in primary health care, such as significant under-diagnosis, delayed diagnosis, incorrect diagnosis, incorrect choice of replacement formula and inadequate or insufficient dietary counseling (13).

2.2 Weaning

Weaning has been defined as the gradual introduction of beverages and foods other than breast milk or infant formulas (14). The rationale for weaning recommendations are to 1) meet the nutritional requirement of the growing infant, e.g. body iron stores are usually depleted by approximately 6 months of age, 2) encourage the infant's motor skills, as well as its natural curiosity, 3) enhance further development and maturity in the digestive tract to handle foods other than breast milk or formula and 4) take advantage of the lower risk of developing food allergies or celiac disease when introduction is gradually done while ongoing breastfeeding (15, 16). The main reason for delaying weaning until the age of six months is to prevent microbial contamination from milks and foods other than breast milk, especially in developing countries. The timing of weaning is partly motivated by a risk assessment balanced between maintaining adequate growth and ensuring a low infection risk (17, 18). However, the age of introduction has been debated. Several European authorities consider that an age of introduction between ages four and six months is safe (19).

Weaning is not merely the provision of energy and nutrients to the growing infant; meals, one of the most central activities for any individual, are of essential meaning in the socialization process and represent important occasions both in family life and social life (20, 21). There is significant evidence of the consequences of feeding patterns in infancy and childhood for health and for long- and short-term disease prevention (22). FA is a common public health concern and its prevention and management are targeted by an increasing body of research and interventions (23-25).

At the time of Study I, i.e. spring of 1999 to the summer of 2001, the weaning advice given to the parents during the child's first year (26, 27) were:

- Breastfeeding for 6 months of age or longer
- Introduction of solids between four and six months of age
- Avoidance of spinach and beet due to the high nitrate content
- Avoidance of rhubarb due to the high oxalate content
- Avoidance of honey due to the risk of infection with *Clostridium botulinum*
- Introduction of gluten similarly as for other weaning foods, i.e. in small amounts, increasing with age
- Additional advice addressing prevention of atopic disease was given to families with children considered at risk, defined as having both parents, alternatively a parent and a sibling with chronic atopic disease requiring treatment:
  - When breastfeeding is not possible or additional feeding is necessary, CMP-containing formula should be avoided until the age of three-four months. Instead, an extensive hydrolyzed formula should be used if needed to delay or prevent allergic disease. Parents were also advised to introduce CM-based formula gradually from the age of three-four months when required. No dietary restrictions were recommended for the pregnant or lactating mother for any period of time, or for infants above four-six months of age
  - Recommendation to delay introduction of fish and egg until 12 months of age were removed in 2001.
  - Mothers of children at risk of developing atopic disease were advised to avoid peanut during breastfeeding. This recommendation was also removed after 2001.

Breastfeeding was considered short if it lasted 0-3.9 months and long if lasting four months or more. Breastfeeding was considered exclusive when including possible trial of weaning foods for a fully breastfed infant; all other regimes were defined as partial breastfeeding. Since 2001 nutrition guidelines have been modified, breastfeeding has been defined as exclusive when nothing other than breast milk is provided, except possibly vitamin supplements and medicines. If formula or other foods are introduced,

breastfeeding is now considered to be partial. Avoidance of rhubarb, spinach and beet is no longer considered necessary. Parents with infants at risk of developing atopic disease are no longer advised to delay the introduction of fish and egg. Lactating mothers are advised not to follow any special diet (15, 26, 28, 29).

2.3 Prevention of food hypersensitivity and cow's milk allergy

CMA is the most usual FH in children, often associated with other hypersensitivity (30, 31). The guidelines presented previously are shared by the American Academy of Pediatrics (AAP) (32); the Australian Society of Clinical Immunology and Allergy (ASCIA) (33); the American College of Allergy, Asthma and Immunology (ACAAI) (34); the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (15); the European Academy of Asthma, Allergy and Clinical Immunology (EAACI) (35) as well as the Paediatric Allergy section of the Swedish Paediatric Society (26). Dietary advice to prevent atopic disease previously focused on avoidance. However, recent research has yielded evidence that early and varied introduction of solids during lactation might promote the development of tolerance (36), leading to an acknowledged change in paradigm (24, 37). Nonetheless, previous recommendations, such as avoiding the introduction of solids until age six months or avoiding fish and egg during the first year, survive in different media and present a challenge to the information efforts in public health (15, 27).

2.4 Cow's milk in human diet

The use of dairy products in the weaning of infants is a uniquely human trait, with a few exceptions, such as the use of other milk to aid survival of the offspring of animals of interest for human nutrition (38). Archaeological research has revealed the use of fresh milk since prehistoric times, as well as of extensive processing of ruminant milk (39). Processing milk into yoghurt, fermented milk and cheese provided the benefit of storage, creating a buffer against famine (38, 39). It has been hypothesized that milk was also added to processed cereal and sundried for storage, creating an ideal weaning food (40, 41).

Like most mammals, the vast majority of human beings are capable of digesting lactose into glucose and galactose during infancy, by the action of an enzyme (lactase) residing in the mucous membrane of the small intestine. This ability gradually disappears in approximately 70-80% of the population

with age. There is major individual variation in the age at which lactose intolerance becomes clinically relevant, as it is determined by the individual genotype (42). When not digested, lactose continues its passage through the digestive tract to the large bowel where it is fermented by the action of bacteria, causing bloating, distension pain and diarrhea. There are North-to-South and West-to-East gradients, with increasing prevalence of lactose intolerance in populations further south and east. Processed milk products, such as innumerable varieties of fermented milk and cheese, contain lower amounts of lactose than fresh milk, if any. This is the reason for the widespread use of dairy products despite the high prevalence of lactose intolerance (38, 39, 42). A diet with lower lactose content, according to individual tolerance, based on persisting lactase activity, is usually enough to avoid symptoms.

Regardless of genotype, lactose intolerance is extremely unusual among infants and children, except due to secondary damage of the mucosa, as in gastroenteritis or undiagnosed celiac disease. Human breast milk contains higher doses of lactose than CM or other mammals' milk. Lactose plays an important role in the development of brain (43) and normal gut flora in the newborn human infant. Approximately 20% of the lactose ingested by the infant passes undigested into the large intestine, where it promotes the proliferation of *Bifidobacteria* and *Lactobacilli* (44), preventing the growth of potentially harmful *Clostridia* (45, 46). Restricting lactose intake, for example with lactose-free formula or gruel, is seldom justified. It is also advised against for children with gastroenteritis (47). Regular feeding should not be disrupted and lactose-containing formulas are considered appropriate in the vast majority of cases (48). The development of lactose persistency, i.e. the ability to digest lactose beyond lactating age, in some groups is considered to be one of the most highly selected gene variants in humans. This may provide an evolutionary asset (49), a powerful selective advantage resulting in a positive calcium balance and an important source of vitamin D in an environment with reduced sunlight, such as Northern Europe and Scandinavia (42). In summary, lactose intolerance seldom restricts dairy product consumption.

In addition to lactose, CM contains fat, proteins (whey and casein), vitamins, minerals and water, and has high nutritional value at a reasonable price (50). The addition of dairy products or the wide variation of byproducts improves the nutritional quality of foods, as well as other qualities, such as texture or palatability (51, 52). The use of CM is spreading to less obvious foods, such as meringues, and to non-edible products such as hygiene products and textile fibers (53, 54). As in most of Scandinavia and Northern Europe, dairy products are a basic ingredient in the traditional cuisine, accounting for a

considerable amount of energy and nutrients. Dairy contributes approximately 22 % of the caloric intake in children's diet. CM provides about a third of the requirements of protein and fat, almost 70% of the recommended intake of calcium, almost half of the recommended intake of riboflavin and considerable amounts of other nutrients such as vitamin B12, zinc and selenium (5, 55, 56). Worldwide, CM is the preferred source of energy and nutrients in the composition of infant formula and specific infant food such as porridge, gruel and follow-on milks (5).

The guidelines for CM introduction to the infant's diet recommend the use of adapted CM-based products, i.e. with lower protein and salt content, and the addition of iron as a minimum requirement. Consumption of non-age-adapted dairy products is advised to be delayed until age 10-12 months (57). There is evidence of a negative effect of CM consumption on iron status which, however, is apparently limited to the period before 12 months of age. The benefit of dairy products adapted to infant needs has not been confirmed beyond age 12 months (58).

Consumption of dairy products in Sweden is high, compared to other countries, but there has been a decreasing trend during the last decades (Fig 1) (55). Worldwide, dairy production and consumption are increasing, e.g. in Asia (59), whereas trends in Europe vary (60, 61).
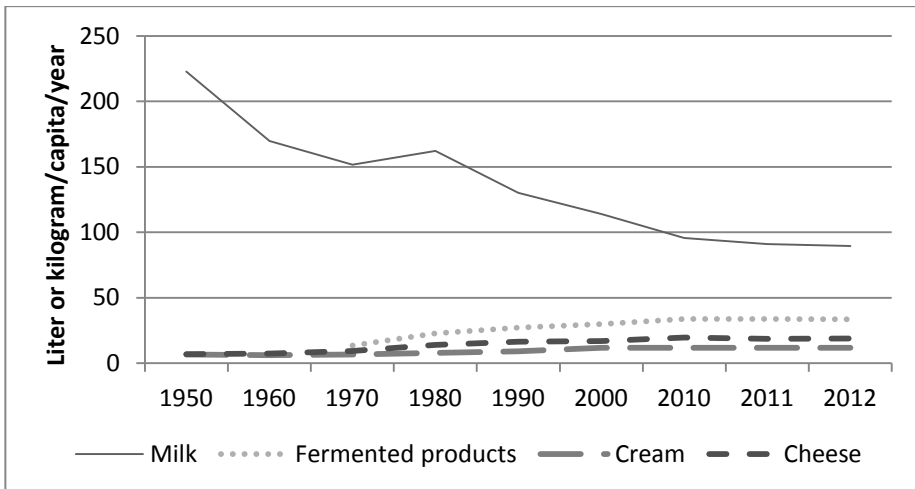

Figure 1. Consumption of dairy products in Sweden in liters or kilos (cheese) per capita and year, 1950-2011 (55).

Epidemiological data suggest that protein intake in children in the Nordic countries exceeds recommended levels, with dairy as a major contributor.

Albeit limited, the evidence suggests that increased intake of protein from animal sources in childhood, especially from dairy products, may be associated with negative health effects, such as earlier puberty and increased risk of obesity later in life. Experts thus suggest an upper limit of 15% protein contribution to energy intake at age 12 months (62).

CM consumption is continuously debated and hypotheses concerning its benefits versus harmful effects have been presented. Exorphines identified in casein and in gluten have, for instance, been hypothesized as having opioid effects on the brain, affecting individuals with autism spectrum disorders negatively. Despite the fact that this has never been confirmed, there are still widespread misunderstandings concerning CM's effect on autism spectrum disorders, e.g. the standard treatment in the USA is a gluten- and CM-free diet. Moreover, a potentially diabetogenic effect of CM when consumed during the first eight to nine months of life has been explored, but is as yet unconfirmed (58). These aspects are beyond the scope of this thesis and will not be discussed further. Instead, this thesis focuses on adverse reactions to CM protein, i.e. allergic and non-allergic hypersensitivity in children, the frequency of which is uncontroversial (63).

2.5 **Adverse reactions to cow's milk protein**

CMA is defined as abnormal reactions, immunologically or non-immunologically mediated, to CM protein (Fig 2) (63). However, other terms are also used: cow's milk protein hypersensitivity, cow's milk protein allergy (CMPA), cow's milk protein intolerance (CMPI), sometimes combined as CMPA/I (3, 30, 64). The main allergens in CM are from the casein and whey fractions. The whey allergens are alpha-lactalbumin (*Bos d 4*); beta-lactoglobulin (*Bos d 5*, absent in human milk); bovine serum albumin (*Bos d 6*) and bovine immunoglobulins (*Bos d 7*). The casein allergens, collectively known as *Bos d 8,* consist of four different proteins (alpha$_{s1}$, alpha $_{s2}$, beta, and kappa casein) (65, 66). Patients are most often sensitized to alpha (100%) and kappa caseins (92.7%) (5).
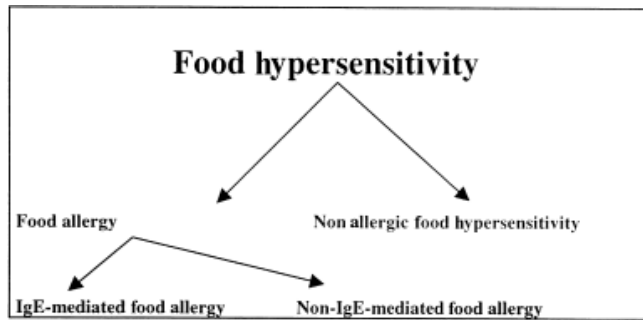
Figure 2. Nomenclature of food hypersensitivity (63).

2.5.1 Prevalence

CM protein (CMP) is the most common allergen, causing reactions in 2-7% of infants in most studied countries around the world, depending on recruitment methods, age distribution of the studied population and diagnostic criteria (5, 30, 58). The condition is less common in adults, affecting less than 0.5% of the population (67). However, many authors caution that study results must be regarded as estimates. Definitions, methods and population characteristics potentially limit comparisons between studies. Many of the prevalence studies referred to are based on self-reports or, in the case of children, on parental reports. Furthermore, many individuals with complaints have not been tested, making diagnosis confirmation difficult. Despite mixed reports on prevalence trends in CMA, evidence of an increase, as noted for other atopic conditions, is regarded as convincing but is as yet unconfirmed by studies (68). The World Allergy Organization's (WAO) working group for the Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) (5) estimates that 1.9-4.9% of children suffer from CMA (69). Self-/parental report of CMA usually indicate higher prevalence than when diagnosis is confirmed by appropriate tests (5, 70).

2.5.2 Symptoms

Depending on the interval to reaction onset after ingestion, CMA is categorized as immediate- or delayed- onset. Reactions occur within minutes to an hour in the former case and a day, days or weeks after CM intake in the latter case. CMA may present with a wide variety of symptoms, reflecting different pathological mechanisms. Combinations of symptoms from several organs or organ systems are common (3, 5). The table below provides an overview of common CMA symptoms.

Table 1. *Type of common reaction to CMA according to World Allergy Organization's working group for the Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) (5), when others are not indicated.*

Type of reaction	Organ system	Symptoms
Immediate onset reactions, IgE-mediated	Skin	Angioedema (swelling of lips and/or eyelids)
		Urticaria
		Itching
		Irritation
		Atopic eczema
	Airways	Runny nose, nasal congestion
		Asthma/wheeze, dyspnea
		Laryngoedema/stridor
		Chronic coughing
	Gastrointestinal tract	Oral allergy syndrome
		Nausea, vomiting, pain, flatulence and diarrhea
	Cardiovascular system	Anaphylactic reaction
Delayed onset reactions, non-IgE mediated	Gastrointestinal tract	Oral allergy syndrome
		Colic (71)
		Constipation, chronic constipation, unresponsive to routine therapy (72, 73)
		Anal fissures (74)
		Diarrhea
		Failure to thrive, i.e. lower weight gain than expected for age
		Repetitive, projectile vomiting
		Iron deficiency anemia, unresponsive to traditional iron supplementation therapy, especially in combination with hypoproteinemia due to malabsorption (75).
		Regurgitation
		Food refusal

2.5.3 Diagnosis

The general approach to diagnosis of CMA include medical history and physical examination, elimination diets, specific IgE measurements and SPT according to guidelines (5).

The double-blind placebo-controlled food challenge (DBPCFC) is considered to be the "golden standard", especially in adults. Open food challenge (OFC) is usually preferred in pediatric care but allergists appear to avoid performing challenges due to risk, cost and time (76).

However, The WAO states, in its 2010 position paper, that there are no studies targeting the optimal duration of the elimination diet (5). The length of elimination is individually adjusted to the type of symptoms. Follow-up challenge procedures are usually performed at 6-12 months intervals, depending on symptom severity. For breastfed infants, elimination is accomplished by advising the mother to adopt a CM-free diet (5).

2.5.4 Prognosis

The prognosis of CMA is usually favorable. About two thirds of all infants with CMA outgrow this condition by the age of two. The prognosis seems to be better for children with non-IgE-mediated, than with IgE-mediated, CMA (77) (Fig. 3). Approximately 2-5% of children have been found to have persisting CMA in adulthood (30, 78). This may be due to either residual allergy, especially in cases of casein IgE-mediated allergy (79), or to partial resolution of CMH (80).

Approximately half of the children with IgE-mediated CMA develop other FA early in life, further challenging their nutritional status, growth and development. Although FA may disappear with age, new atopic diseases such as rhino-conjunctivitis or asthma can occur in affected children (30, 31). This process is usually referred to as the atopic march (81) and is the target of secondary and tertiary prevention efforts.
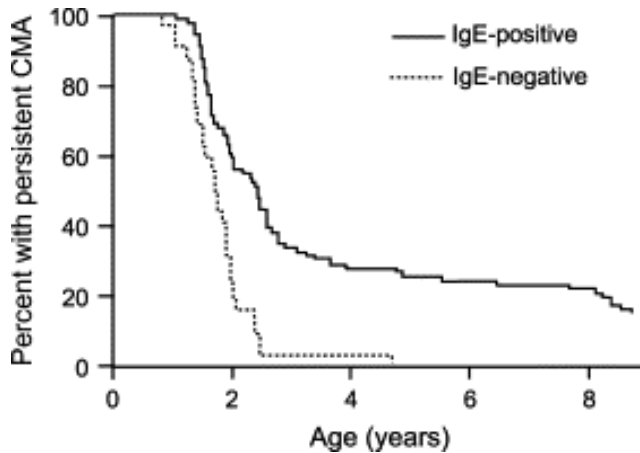
Figure 3. Proportion of children with persistent CMA, IgE-positive (n = 86) and IgE-negative (n = 32) types (p = 0.001 at 2.0 years and p <0.0001 at 3.0, 4.0, 5.0, 6.0 7.0, and 8.6 years) (77).

2.5.5 Nutritional risks of cow's milk–free diets

Eliminating a basic food item such as CM generates concerns about the nutritional consequences. Studies investigating CM-free and CM-restricted diets have shown serious macro- and micronutrient deficiencies and, more seriously, growth retardation (82-85). It is not uncommon that the child diagnosed with CMA has a varying degree of malnutrition, usually manifesting as lower weight gain than expected for age, especially in children with malabsorption (86). In cases of underweight, special considerations are needed. In the absence of specific guidelines for children with CMA, existing guidelines for children with malnutrition published by the World Health Organization/Food and Agriculture Organization of the United Nations/United Nations University (WHO/FAO/UNU) have been suggested to be useful (86). According to the WHO guidelines for wasted (low weight for age) children, the optimal formula for catch-up growth should contain 1 kcal/ml and have a protein/energy ratio of between 8.9% and 11.5%, depending on the desired rate of catch-up growth (87). Despite often higher nutritional needs in children with CMA, available CM-free formulas follow composition guidelines for healthy children (88). Careful, individual consideration is needed when choosing the appropriate alternative. Furthermore, additional adjustments and complementary food(s) may be needed to achieve acceptable caloric and nutrient intake and optimal catch-up growth (89).

The nutritional adequacy of CM-free diets in the treatment of CMA has led to concern and professional counseling has been recommended in this context (5, 83, 86, 90). Depending on the symptoms, there may be increased

requirements for energy and nutrients, for instance due to skin lesions and/or ongoing gut inflammation (91, 92). CMA affects mainly children at a vulnerable stage in life. During the first year of life, children are normally expected to triple their birth weight (93), an exceptional accomplishment; catch-up is difficult to achieve after this age (70, 86). Children requiring special diets may have disrupted eating development and feeding difficulties are often reported by parents, apparently partly due to children associating food with discomfort (94). Parents of affected children naturally develop increased awareness of reactions as they learn to manage the FA (95). At the other end of unfavorable development spectrum, recent research suggests that obesity can occur in this population (96).

2.5.6 Treatment of cow's milk allergy

The goals of the nutritional treatment in infants and children are to achieve symptom relief by excluding the offending food(s); prevent inadvertent exposure and unnecessary avoidance; support normal growth and development for age and gender; provide an adequate, healthy, nutritionally dense and balanced diet with appropriate alternatives to the excluded food allergens and minimize the impact on quality of life (86).

Regardless of the pathology of CMA, once the diagnosis has been established the treatment is strict and complete avoidance of CM, at least initially. Exclusion of CM results in alleviation of symptoms, however to a fluctuating degree in some children. Additional treatment, such as individually tailored cutaneous therapy in children affected by skin symptoms, is usually necessary. At the same time, residual symptoms may affect appetite and absorption of nutrients, making adjustment of nutritional intake necessary in order to meet the individual's needs (82-86) .

2.5.7 The exclusively breastfed infant – the nursing mother

The evidence on the preventive effects of breastfeeding for atopic diseases in children is not conclusive. However, the benefits of breastfeeding for the child's health and well-being are uncontroversial, and are encouraged for all mothers. Breastfeeding trends in Sweden have been decreasing during the last decade with a tendency to stabilize since 2011 (Fig. 4) (97).
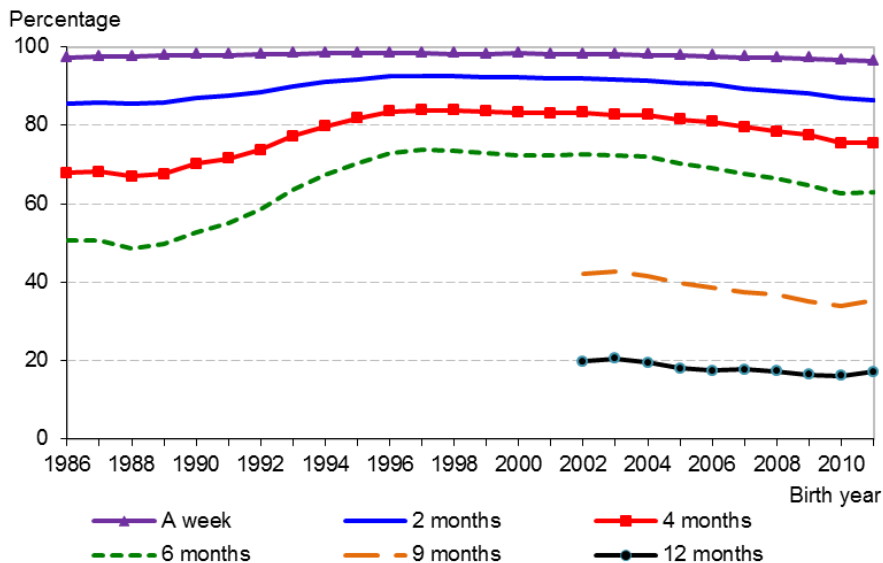
Percentage

Figure 4. Exclusively and partially breastfed children born 1986-2011, percent (97).
Note: Data collection for breastfeeding at 9 and 12 months of age started in 2002.

When reactions occur during exclusive breastfeeding, the nursing mother is advised to eliminate CM from her own diet and should be offered nutritional counseling. There are no guidelines concerning the treatment of breastfeeding mothers recommended a CM-free diet, except recommendations concerning calcium and vitamin D supplementation (89).

2.5.8 The partially breastfed infant

When symptoms arise following occasional feeds with CM-based infant formula in the otherwise breastfed infant, continuation of breastfeeding is ideally recommended, according to guidelines issued by the WHO (95). No elimination should be advised in the maternal diet since breast milk has been well tolerated previously by the infant (91). In many cases, small amounts of CM are tolerated, allowing for a CM-reduced diet which may be less challenging. However, the level of dairy product intake considered safe in the nursing mother's diet is individual and must be assessed in each infant (91).

2.5.9 Choice of substitute

2.5.9.1 Formula

DRACMA has issued guidelines for the choice of formula (5). Amino acid based-formula is preferable for children considered to be at risk of anaphylaxis, while extensively hydrolyzed casein- or whey-based formula is

recommended for those without this risk. Differences in palatability may make introduction troublesome for older children who might have developed a taste memory regarding breast milk and/or formula (98). Additional methods may be required to achieve optimal catch-up growth (86). Soy-based formulas are considered easier to introduce due to higher palatability; they are also more economical, yet another consideration when choosing an appropriate formula. However, soy-based formulas are not available in Sweden due to several considerations, including soy's potential allergenicity (5, 99), its aluminum content and its hormonal effect (90). According to the ESPGHAN (2012), soy-based formula can be introduced from the age of six months under the condition that soy allergy is out ruled (90). Nursing mothers on a CM-free diet are, however, usually allowed to consume soy products. DRACMA also discusses hydrolyzed rice-based formulas available in some parts of the world. CM-free formula alternatives vary around the world and choice is guided by availability, appropriateness, costs and other concerns. In Sweden, the available CM-free formulas are based on hydrolyzed whey or casein, or on amino acids and available at pharmacies. CM-free formula is usually prescribed by a physician or dietician and subsidized by the national health insurance. In other countries, reimbursement for costs for substitutes used to treat CMA varies greatly (100).

While affirming that breast milk is always the first choice, the infant food industry has recently developed CM-free products, such as CM-free porridge and gruel. These products are age-adapted and enriched with vitamins and minerals, according to guidelines for baby foods (5). The expert panel at DRACMA has not taken alternatives in different countries into consideration, recommending that this issue be addressed in national guidelines.

2.5.9.2 Other substitutes

Other mammalian milks are advised against, due to the risk of cross-reactivity (101, 102). Products based on almonds, hazelnuts, cashews, sesame seeds, etc. are usually not considered alternatives in children's diet due to their potential allergenicity (80, 81).

Fruit juice is also a common choice, often with detrimental effect on energy and nutrient intake, as well as on dental health (103).

Alternative dairy-like substitutes derived from oats, rapeseed, rice, coconut and other sources are being developed and attracting increasing interest. The nutritional quality varies widely and they are generally not suitable replacements for breast milk. Case reports have shown that some of these alternatives have contributed to fad diets and caused severe malnutrition

(104, 105). However, these products might be considered for occasional use, e.g. when the child is weaned to the family's diet and might have otherwise shared dairy-containing dishes. At this age, the child may be able to consume a wider range of foods, in addition to baby food, and careful reading of ingredient labeling is thus necessary.

2.5.10 Ingredient labeling

Parents with children with FA must read ingredient labels carefully. According to European Union guidelines, ingredients must be listed in descending order according to weight, in the national language or in a language that can be read understandably in the country, such as Norwegian in Sweden. The Swedish National Food Agency issues recommendations for food labels. The environmental authorities in each municipality in Sweden supervise implementation of and compliance with regulations (106, 107).

Over the years, the information provided by ingredient labels has been improved and become more reliable. The EU has agreed on a list of common allergens that must be mentioned when present in any food item, even if the allergen is a confidential ingredient to a brand, e.g. in spice mixtures. CM is included in this list of compulsory declaration of ingredients (108). However, a new problem has arisen, as the food industry may not be able to guarantee the absence of allergens in products due to manufacturing processes, such as shared production lines or storage. Many manufacturers consequently warn consumers with so-called precautionary labeling, i.e. "may contain traces of..." leaving consumers to decide by themselves what risk to take. Products that individuals with FA may have consumed safely in the past became later subject to precautionary labeling and may thus be considered risky. Consumers have been found to disregard this precautionary labeling, thus endangering their health (109). Attempts have been made to improve this situation which is still under discussion and organizations and the food industry both aim at international consensus (107, 109, 110). Individual considerations might nonetheless be appropriate when counseling regarding consumption of specific products (111). There is currently no way to monitor the risk and the general recommendation is to heed these warnings. Case reports on reactions, some with fatal outcome, indicate that precautionary labeling should be taken seriously, especially in cases of simultaneous unstable or undertreated asthma (112).

2.6   Nutrition counseling

The responsibility for managing and monitoring disease falls on parents and other adults in the child's proximity. Children are dependent on the adults' capacity to educate themselves and others. This is crucial in order for the

children to be able to meet their nutritional requirements, grow and develop optimally, while avoiding adverse reactions (81).

The goal of guidelines is to provide rationale and evidence for making informed choices for different groups, e.g. infants and children. The WHO has defined public health as "The science of promoting health, preventing disease and prolonging life through the organized efforts of society" (113). The interpretation of this overall goal calls for adaptation according to the structure, resources and culture of the society, within which this defined public health system is organized. Historically, the Alma-Ata declaration, published in 1978 (114), stated progress towards "health for all" as a millennium goal. In 1986, the Ottawa charter further detailed how to achieve this goal through advocacy, enabling all people to achieve their fullest health potential and mediate between differing interests in society for the pursuit of health. Retrospective analysis and evaluations within and across countries have proven valuable in guiding resource allocation and development of working strategies. In this context, diet and nutrition have been fully recognized as playing an essential role at the forefront of public health policies and programs (113). The WHO issues and continuously updates recommendations and guidelines at the population level (87, 114).

2.6.1 Nutrition education: past, present and future

One of the most common definitions of nutrition education is "any set of learning experiences designed to facilitate the voluntary adoption of eating and other nutrition-related behaviors conducive to health and well-being" (115). Historically, nutritional work has addressed deficiencies resulting from shortage or low quality of available food, still a reality in many parts of the world. During the last decades, however, there is an increasing shift in target towards the prevention of diseases resulting from increased accessibility to food of varying quality, such as overweight, obesity, coronary heart disease and diabetes, in industrialized and developing countries alike (116). Compiled experience in nutrition education, often shared with other disciplines in the field of prevention (sex education, drug abuse prevention, etc.), exposes a diversity of pedagogical theories and didactic models (115-119). Research in the social psychology and health behavior fields has provided useful knowledge to improve nutrition education. More attention is being devoted to the importance of people's thoughts, motivations, values, and perceptions of the world, as well as social and cultural contexts and physical environment, in influencing behaviors and practices (120). There is dynamic interaction between these internal and external environmental factors that affect each other and behavior. This has led to the development of

a social ecological model in which several levels of nutrition education are included: firstly, the individual, family, and household levels; secondly, the institutional, organizational and community levels and finally, the social structure, policy and practice levels. It has been proposed that nutrition education be directed at self-reliance, building on participants' existing abilities, providing opportunities for self-directed learning and the development of social networks and social support (119).

Interactive education is gaining recognition in achieving desirable healthy nutrition behavior, with empowerment as a central concept. Paulo Freire (1921-1997), considered the founder of empowerment theory, dedicated his life to increasing literacy among farm workers in rural Brazil. Freire describes empowerment as a lifelong process through which individuals free themselves from personal and social boundaries that restrict them, through critical reflection followed by action. People become conscious of the fact that their lives and the world surrounding them can be changed. In this on-going cycle, communication between individuals is emphasized as crucial. In Freire's own words, liberating power can only develop in true communication, i.e. equal communication, in which both parties have the opportunity to express themselves and both parties' views are considered (121). Evaluations of nutrition education programs based on the empowerment model have been found to enhance participants' self-esteem, induce their capacity to take initiatives and increase their motivation to improve nutritional habits. For instance, facilitated group discussion led by dieticians who encourage participants to share their thoughts and experience, interjecting only to correct misinformation and keep the discussion on track, is considered a more meaningful way of engaging individuals towards healthy eating behavior (117). Most authors warn that no model can be applied universally. Instead, caregivers should be able to determine suitable models for different situations and consider alternatives when appropriate (115-119).

Evaluation of working methods should include caregivers' and care – consumers' satisfaction, measurement of health improvement, assessment of compliance with given advice and identification of barriers related to health providers and consumers. Evaluation should include the extent to which the ongoing work has led to significant improvements to public health and public finances (122-125).

2.6.2 Pediatric nutrition counseling

WHO guidelines include recommendations to all nations to organize the dissemination of accurate information for the promotion of healthy behaviors (113, 114). A diversity of health workers across the world promote public

health goals for infants and children, including dedicating attention to families with special needs, such as those with children at risk of developing atopic disease. Efforts have been successful in various areas such as accident prevention, where Sweden has the lowest childhood injury mortality in the world (126); decreased caries prevalence (127); and prevention of iron deficiency anemia and rickets, both rare in Sweden (128, 129). The Swedish national health program is implemented mainly through the CHCs. Their success is not merely a result of the CHCs own work, but also of their ability to cooperate with other agencies in the community, such as pre-schools (130). At the same time, health workers must continuously gather and update knowledge and expertise from researchers and specialists in order to meet arising challenges. As societies change, so do the targets for prevention and the challenge to reach out with preventive measures.

Most parents obtain and actively seek available nutrition information in a variety of ways. Many families seek confirmation of information or support from professionals such as primary health care workers (131). Disease prevalence and the relationship between disease and food intake often receive special attention. For example, the number of diagnosed cases of celiac disease increased in the late eighties (132-134). Because of this development gluten intake was intensely discussed, resulting in attempts to change feeding pattern, even before there was enough scientifically based knowledge on which to base guidelines (16, 133, 135, 136). Parental concerns regarding gluten, naturally, increased during this period. Likewise, parents often asked whether children, considered to be at risk to develop FA, should avoid fish and eggs. New recommendations are often subject to confusion, queries and disbelief before acceptance (27). In nutritional guidelines addressing healthy diet and prevention of specific diseases, certain foods, for example CM, receive special attention.

2.6.3 Nutritional therapy in groups

There is growing public awareness regarding possible adverse reactions to food (68). Official guidelines concerning the treatment of CMA acknowledge the importance of nutrition education (5, 90, 112, 137, 138). However, only two of these recognize the role of the dietician in the diagnosis and management of FA (90, 138). Non-compliance with elimination diets has been suggested to be the result of the absence of nutrition information from a dietician/nutritionist (139). The continuously growing demands for cost-efficiency and increasing accessibility, with unchanged and sometimes reduced resources, while maintaining and preferably increasing the quality of care, have led to the development of new working methods.

Facilitated group discussions, described earlier (2.6.1, p 18) (117), based on empowerment theories have proven beneficial in achieving healthy behavior goals. Initially, these projects had a generally preventive nature focusing on the general public, and often on socioeconomically disadvantaged groups (117, 140). However, these methods have also proven valuable in the treatment of various diseases, e.g. achieving optimal glycemic control in patients with type-2 diabetes (141), obesity treatment in children (142) and other diseases and conditions (143-145). When participants themselves are allowed to guide the content of the meetings, e.g. discussion of the need for constant vigilance and other concerns, awareness will probably increase and possible solutions to cope with daily situations will be identified (139, 146).

2.7   Parenthood, food and health

Parents are considered to be the most important actors shaping the eating behavior of their children, by transmitting their genes as well as their attitudes and beliefs about food and food consumption. Parents interactively provide for their children's welfare by conveying attitudes and behaviors (parenting style) and acting as providers, models and monitors (parenting practice) (147). Responsibility for decision-making with the welfare of the child in mind can be perceived as a burden. In this context, feeding has a special impact on the early parent-child relationship because of its psychological connotations. Food may be a source of stress in health and disease (148, 149).

2.7.1 Impact of food allergy on family life

When managed by elimination diet, FA may have scarce or no symptoms, making it less manifest than other diseases or disabilities. In cases of life-threatening anaphylaxis, quality of life can be dramatically affected and successful diagnosis, treatment and management are thus critical (150-153). Like most atopic diseases, FA often has an unstable pattern, requiring continuous monitoring and re-adjustment of treatment and coping strategies (154, 155).

In addition to the objectively measurable symptoms underlying FA diagnosis, individuals with allergies report symptoms such as sleeping problems, fatigue, poor concentration, thirst and headache, as well as irritability, frustration, impatience and embarrassment (156, 157). Families with children with FA have reported experiencing significant impact on general health, emotional impact and limitation of their activities (153). Additionally, while educating others involved in the child's everyday life, families encounter diverse reactions concerning how they treat their children

and handle problems. They are often accused of being overprotective and "hysterical". This multifaceted situation adds to the burden of caring for a child with FA, sometimes in combination with other atopic diseases, resulting in feelings of frustration, misunderstanding and distance from other people (158, 159).

Despite the fact that elimination diets are supported by rational and qualified evidence, elimination diets have serious social implications, in addition to the risks of undernourishment or malnutrition. Bullying is reported by children with FA and their parents, causing additional burden for affected families (160).

Most families struggle with worries about practical matters such as economy, household management and family responsibilities; however, for families with children requiring special diet, this burden may increase. At the same time, affected families must cope with doubt and uncertainty, together with a diffuse feeling of guilt without exactly knowing what they may have done wrong (161). The impact of FA on daily life has drawn growing attention in recent decades (162) and has been the focus of an increasing number of studies. Although the prognosis is usually good, with CMA disappearing during the first years of life, it affects children at a vulnerable age, of paramount importance to health, the development of eating skills and attitudes towards eating.

2.7.2 Measuring impact on daily life

The realization that physiological parameters are not enough to measure well-being in patients affected by disease has led to the development of instruments to measure impact on health-related aspects, such as perceived health, quality of life and impact on the daily life of patients, parents and caregivers. Methods to achieve this goal have been developed and improved in order to achieve precision and cultural appropriateness (163, 164). Reliability and validity have been defined for this subjective type of measurement. Reliability refers to an instrument's ability to produce similar results when re-administered. Validity is defined as the degree to which an instrument assesses what is intended. Several types of validity have been defined over the last decades and the highest degree of rigorousness has been attributed to construct validity (8, 165) (See under "Brief definitions").

Generic instruments allow comparison of experienced impact between patient populations affected by different diseases (166). However, generic questionnaires may contain items that are irrelevant to the disease under study and contribute unnecessary information, as well as being excessively

long (8). Recent interest on the effect of atopic diseases, such as asthma or atopic dermatitis, on everyday life has resulted in the development of specific questionnaires (156, 167, 168). They usually cover nutrition-related issues but generally in a limited number of questions, failing to provide detailed information regarding issues related to FA and its impact on the everyday life of children and their families. Generic, related questionnaires were used to aid validate these new specific instruments. One example is the Child Health Questionnaire- 28 items (CHQ-28), used in studies developing specific questionnaires measuring health-related quality of life in affected children and their parents (150, 169, 170). The first years of parenthood are characterized by dramatic changes in daily life and a certain amount of stress is normally expected (171), for instance: not being satisfied and confident as a parent, being primarily responsible for the child, struggling with the limited time available for oneself and feeling fatigued and drained (4). The SPSQ focuses on parents' experienced stress in relation to their own situation, originally targeting families with children aged 0-7 years (164). It has proven reliable and valid in measuring parental stress in relation to food-related diseases such as diabetes (165) and feeding disorders related to nutrition (137). Furthermore the SPSQ has proven capable of measuring change over time (172).

Early on, health was defined by the WHO as the absence of disease. Later definitions, however, acknowledge the fact that good health can be achieved despite the presence of disease, and contribute to maintaining a good quality of life (173). Food and meals are a daily recurrent component of everyday life typically occurring several times daily and playing an essential role in individuals' quality of life. This thesis attempts to contribute knowledge about mitigating the impact of FA on affected children and families and preventing future complications, in order to achieve normality and minimum impact on daily life.

3 AIMS

This thesis has the following major aims:

- To evaluate compliance with weaning recommendations at the time the study was performed (spring 1999 – summer 2001), with emphasis on the introduction of CM to the diet of infants with atopic heredity

- To develop nutritional therapy for families with infants and children with CMA

- To create an instrument to measure impact on families with children with CMA, exclusively or in combination with other FA

- To follow up the change in impact on families as the children grow and to follow the progression of the CMA using the Food hypersensitivity famiLy ImPact (FLIP) questionnaire

4 SUBJECTS

4.1 Study I

This was a population based convenience sample recruited from CHCs. Parent-child pairs were recruited from Gothenburg, the second largest city in Sweden, and two counties; Bohuslän and Dalarna, together comprising 10% of the population of Sweden. This sample was considered representative because almost all families attend CHC.

4.2 Study II

The participants in paper II, developing a method to increase access to treatment for families with children required to follow a CM-free diet, were recruited from all six pediatric clinics in primary health care in Gothenburg existing at the time.

4.3 Studies III and IV

All families participating in the different steps for the development of the Food hypersensitivity famiLy ImPact (FLIP) questionnaire had children on a CM-free diet, with CMA exclusively or in combination with other FA. They were recruited when attending the pediatric clinics in primary health care in Gothenburg, individually or in groups described in Paper II. At the validation stage, new clinics were involved: three pediatric clinics in primary health care in South Bohuslän, the Department of Pediatrics at Falun Hospital in Dalarna county and a private allergy clinic in Norrköping. A total of 10 units participated in the validation (two clinics in Gothenburg had merged into one in 2005). The same participants were followed up six months after baseline. Healthy controls were recruited from Gothenburg CHCs.

Participants included in the studies in this thesis are specified in table 2.

Table 2. *Participants and demographic characteristics.*

	Study I	Study II	Study III	Study IV
Participants, parents	n = 467	Baseline sample, n = 84; follow-up at 3 years, n = 74	Cases, n = 239; Item generation, n = 83; Clinical impact method, n = 50; Face and content validity, n = 12; Validation n = 94; Controls, n = 135	n = 82
Time of data collection	Spring of 1999 to summer of 2001	Baseline: Jan, 1999-Nov, 1999 Follow up: Nov, 2002	Baseline: Feb, 2008-Nov, 2009; Test re-test: Feb, 2008-May, 2008	Oct, 2008-Sept, 2009
Gender boys/girls	53%/47%	52%/ 48% (at baseline)	Cases, 59%/41%; Controls, 41%/59% (1†)	35%/65% (1†)
Mean age (Range)	12.3 m (10-21 m)	9 m (3m-5 yr)	Cases: 17.78 m (6 m-5 yrs); Controls: 23.22 (6 m-6 yrs)	26.23 (11 m-5.5 yrs)
Ethnicity	Non-Nordic (any or both parents) 12.4%	Not studied	Cases: Non-Nordic mothers, 16%; Non-Nordic fathers, 12% Controls: Non-Nordic mothers, 10%; Non-Nordic fathers: 16%	Cases: Non-Nordic mothers, 15%; Non-Nordic fathers, 10%
Family hypersensitivity	27%	Not studied	Cases: 49% mothers, 35% fathers, 22% siblings; Controls: not studied	Cases: 29% mothers, 17% fathers, 12% siblings;
Hypersensitivity in the child	17% according to parental report 11.3% reported food allergy	100 % at baseline and 22 % at 3-yr follow-up	Cases: 100% CMA at baseline; Exclusively, n = 55 CMA + other FA, n = 39	Outgrown CMA, n = 20; Persistent CMA + other FA, n = 57; Outgrown CMA, persistent other FA, n = 5

†: missing

4.4 **Ethics**

No approval was required for Study II as it was part of regular method development and quality assessment within the primary health care of Västra Götaland region. The Ethics committee at Gothenburg University, Gothenburg, Sweden, approved Study I. Approval for Studies III and IV was obtained from the Ethics Committee at the Sahlgrenska Academy at the University of Gothenburg and participants gave signed consent. When additional centers were included, an amendment was added and approved to the latter committee.

5 METHODS

5.1 Study I

Each nurse at every CHC in all three study areas (n = 287 nurses in total) distributed a questionnaire to two consecutive families. Parents visiting the CHC with their children for one-year health check-ups and vaccinations were asked to fill in a questionnaire before leaving. The questions covered breastfeeding and/or formula feeding and introduction of weaning foods, including CM, follow-on formula, CM-free formula, rhubarb, spinach, beets and honey. Breastfeeding was categorized into exclusive (fully breastfed, possibly with additional trial of weaning foods) or partial. Detailed questions about allergy, asthma, hypersensitivity and FA in the family and in the child were included (in this study termed family hypersensitivity), as well as questions about number of siblings, ethnic background and parental education. At the time of the study, breastfeeding was recommended, if possible, to at least six months of age. High-risk families were advised to avoid giving CM-based formula to their infants until the age of three-four months, and preferably replace breast milk with extensively hydrolyzed formula if required.

5.1.1 Analysis

Non-compliance with current dietary guidelines has been categorized as follows: i) introduction of solids before four months or after six months of age, ii) high-risk families introducing CM before four months of age and iii) introduction of rhubarb, spinach, beets or honey. Means, median, range, standard deviations (SD) and frequencies were calculated for continuous variables. Percentages were calculated for categorical variables. The chi ^{2} – test was used to analyze possible relationships between categorical data, for example compliance with advice to introduce CM (yes/no). Factors used to examine non-compliance to advice included ethnic background (Nordic vs. non-Nordic in the mother or both parents), parental educational level (low: one or both parents with nine-year elementary school; high: at least secondary school). Multiple regression analysis was used to analyze the following factors: time of introduction of foods in relation to family hypersensitivity (yes/no), ethnic background, number of siblings (no siblings/one or more) and parental education level (Table 3, Paper I, p. 241).

5.2 Study II

5.2.1 Organization and content of the group sessions

At the group sessions, the dietician encouraged participants to share experiences and solutions to daily problems arising from following a CM-free diet, addressed any misconceptions, such as confusion of CMA and lactose intolerance, and kept the discussion on track according to the working method for facilitated group discussion (113, 168). Practical exercises were also included, such as reading ingredient labels from a mixture of packages commonly found in a regular household. Participants were also given written instructions concerning the CM-free diet and recipe booklets prepared by the dietician and the manufacturers of the CM-free formula.

5.2.2 Evaluations

After conclusion, the milk allergy school was evaluated with a questionnaire to be completed at home and mailed back. Three years after participation, participants were interviewed by telephone, according to a structured protocol.

Access to therapy was evaluated by comparing the interval between diagnosis and access to nutritional therapy in three different periods, i. e. the year prior to starting the milk allergy school and during the milk allergy school's first and third years of operation.

5.2.3 Analysis

Percentages were calculated based on participants' answers to the evaluation questionnaire. Differences in time elapsed between diagnosis and access to nutritional therapy were calculated by the chi ^{2}-test (Table 3, Paper I, p. 241).

5.3 Study III

5.3.1 Construction of the questionnaire

The questionnaire was constructed based on input from families with children with CMA, exclusively or in combination with other FA, attending individual or nutritional therapy in group (n = 83, sample 1, Figure 1, Paper III, p. 575). The responses, transformed into statements, were submitted to new parents (Sample II, n = 50, Figure 1, Paper III, p. 575) for determination of item importance, in telephone interviews using the clinical impact method (169).

Items scoring highest overall importance (OI) were candidates for inclusion in a preliminary questionnaire which was scrutinized by 12 parents with affected children, two of the authors (MPB and AM), two pediatricians and two dieticians experienced in the field (face and content validity) (Sample III, n = 18, Figure 1, Paper III, p. 575).

New parents with children diagnosed at least three months previously (Sample IV, n = 94, Figure 1, Paper III, p. 575) received the questionnaire package, including an information letter, a background questionnaire, the FLIP and the SPSQ. A subset of these parents was asked to fill in the forms and questionnaires a month later for reliability purposes (Sample IV_R, n= 26, Figure 1, Paper III, p. 575). In order to test the FLIP's validity, correlations to the total SPSQ scores were calculated (construct validity). Families with children without FA (Sample V, Figure 1, Paper III, p. 575) were recruited as controls from CHCs from the same area and received a questionnaire package including an adapted information letter, the FLIP's nutrition-related questions, i.e. the non-disease-specific questions, and the SPSQ.

5.3.2 Analysis

Factor analysis was performed by principal component analysis with Varimax rotation on the FLIP, to reveal underlying structure and aid the construction of subscales (Sample IV, Figure 1, Paper III). The FLIP's reliability was assessed by calculating Cronbach's α. Reproducibility was assessed by calculation of the intra-class correlation coefficient (ICC) between test and retest one month later. The same tests were performed on the SPSQ. Several types of validity were studied for the FLIP (See "Brief definitions"). (i) The proportions of participants scoring the lowest, i.e. no effect, and the highest, i.e. always affected (floor-ceiling effects), were registered (8), (ii) as was the FLIP's sensitivity to differentiate within affected families according to age, birth order, number of FAs and number of ongoing or accidental symptoms (discriminative validity; Mann Whitney U Test in cases with two variables and Kruskal Wallis Test in cases with ≥ three variables). The total FLIP and SPSQ scores displayed normal distribution, but not the respective subscales; non-parametric tests were therefore chosen. Boys and girls in cases and controls were pooled for the analysis after having ruled out statistically significant differences in scores on the FLIP, the SPSQ or their respective subscales (results not shown). (iii) The degree to which the FLIP and the SPSQ measured similar constructs was assessed by comparison between total FLIP and subscale scores and total SPSQ scores in cases (Spearman's correlation coefficient) (Sample IV, Figure 1, Paper III, p 575), as well as between FLIP's nutrition subscale scores and total SPSQs scores in

cases (Sample IV, Figure 1, Paper III, p 575) and controls (Sample V, Figure 1, Paper III, p 575) (construct validity, Mann Whitney U Test) (Table 3).

5.4   Study IV

Families who had participated in the validation of the FLIP were approached six months after baseline. Parents were asked to fill in a form with related information, such as new examinations by the physician, clinical tests, re-introduction of food(s), etc. Missing details could be retrieved from medical records when necessary.

5.4.1 Analysis

The FLIP's internal reliability and construct validity were re-assessed at follow-up by calculation of Cronbach's α and the Spearman's correlation coefficient, respectively. Change over time was assessed with the paired samples t-test between both administrations (baseline and follow-up) of the FLIP and its subscales and the SPSQ and its subscales. The analysis was stratified by a variable describing the progression of CMA, i.e. outgrown or persistent, exclusively or in combination with other FA; or other FA excluding CM. In order to adjust for age, we used a linear mixed model to regress the scores of the FLIP and its subscales on age at baseline, progression status, time-point and the interaction between time point (baseline and follow-up) and progression status (Table 3).

5.4.2 Summary of statistical analysis used in the four studies

A compilation of the statistical analysis used in the four studies encompassed in the present thesis is summarized in table 3.

Table 3. *Compilation of statistical analysis used in the four studies.*

Statistical method	I	II	III	IV
Chi 2-test	x	x	x	
Cronbach's α			x	x
Factor analysis by principal component analysis with Varimax rotation			x	
Floor-ceiling effects			x	x
Intra-class correlation coefficient (ICC)			x	
Kruskal-Wallis in cases with three or more variables.			x	x
Mann-Whitney U-test in cases with two variables			x	x
Mixed linear model				x
Multiple regression analysis	x			
Paired-samples t-test				x
Spearman's correlation coefficient for FLIP and subscales' scores against SPSQ scores			x	

6 RESULTS

6.1 Study I

6.1.1 Hypersensitivity in the family and the child

Of 574 distributed questionnaires, 472 were returned (Gothenburg 138/170, Bohuslän 166/206, Dalarna 168/198). Five questionnaires were excluded because of low age (less than 6 months), leaving 467 analyzable questionnaires (82% response rate). Hypersensitivity of any kind in the family or the child was reported by 66%. According to the given definition (in this study termed family hypersensitivity), 27% (n = 125) were denoted high-risk families. The most common atopic disorder was rhinitis and eczema among parents and eczema and FA among siblings. In this group, 11.3% of the children were reported to have FA. CM was the most common offending food (5%).

6.1.2 Introduction of cow's milk

CM had been introduced in the infants' diet at 5.5 months of age (range = 0-12 months). Almost 40% of the group of high-risk infants (39%, 49/125) needed formula before the age of four months. Most of them (92%, 45/49) were given a formula containing CM, contradicting current recommendations. None of the 49 children classified as being high-risk and requiring supplementation were given CM-free formula as an allergy-preventive measure. Only five infants (10%, 5/49) in this group were given CM-free formula, but this was due to diagnosed CMA (Fig. 5). Over one-third of the non-risk infants required formula before the age of four months (35%, 118/342) and were given CM-based formula in most cases (89%).
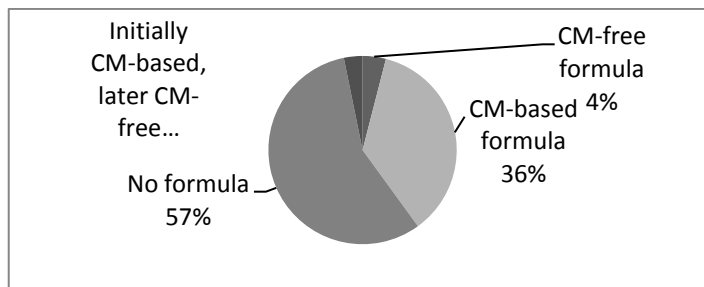

Figure 5. Proportion of children at risk of developing atopic disease (n = 125/467, 27%) and type of feeding.

6.1.3 Introduction of weaning foods, rhubarb, spinach, beets and honey

Most families (82%) introduced solids between four and six months of age, according to guidelines. Likewise, compliance with guidelines for the introduction of spinach, beets, rhubarb and honey was high (Fig. 6). Non-compliance with these guidelines did not differ between non-risk and high-risk children. Early introduction of weaning food was significantly related to non-Nordic background (p = 0.001), no/short breastfeeding (p = 0.001) and the absence of siblings (p = 0.02).
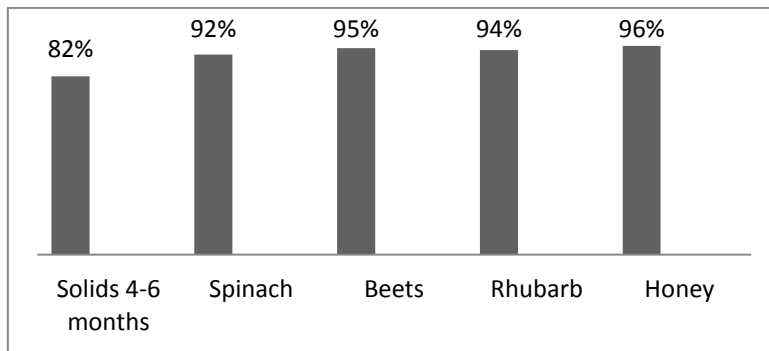
Figure 6. Proportion of parents introducing solids, spinach, beets, rhubarb and honey according to guidelines.

6.2 Study II

The majority of the families (84 families; 86%) invited to participate in the milk allergy school during the study period accepted. The average age of the children was nine months (range = 3 months-5 years) and more than 80% were below the age of one year. An average of seven families participated in each meeting.

6.2.1 Symptoms and diagnosis

The most common symptoms among the 84 children were skin problems (Table 1, Paper II, p. 88). Gastrointestinal and respiratory symptoms were less common. Skin prick test and/or specific IgE analyses for CM protein were positive in most cases (Table 1, Paper II, p. 88). In one case, the diagnosis was based solely on an elimination and challenge test. The majority of the children did not have adverse reactions to other allergens (n = 53). The rest of the children reacted to other foodstuffs, the most usual being egg (n = 16), red coloured fruits and/or vegetables (n = 5), other fruits (n = 2), peanut,

soy, tree nuts, fish, one respectively, or combinations of the foodstuffs mentioned (n = 4).

At the follow-up three years later, CMA was still present in twelve children (Table 2, Paper II, p. 88). The disease status was uncertain in four cases as it had almost disappeared in two children and the diagnosis was under re-evaluation in two. Half the group had developed other food allergies/intolerance (55%). The majority of the children (n = 58, 78%) were free of symptoms and able to consume dairy products. For this latter group, milk had been successfully introduced into the diet before three years of age, usually at the physician's initiative (n = 47). However, 11 families reported that they had introduced dairy products in their child's diet on their own initiative after the child was accidentally exposed to milk in the diet and no reactions were observed. The length of time for introduction of dairy products into the child's diet varied widely. Introduction lasted up to one month for 24 children, up to six months for 22 children and more than six months for two children. This very long introduction was attributed to dislike of dairy products. Nine families performed a gradual introduction of dairy products without specifying for how long a period of time and only in one case did the introduction occur immediately after advice by the physician.

6.2.2 Post-session evaluation

The majority of participants (72%) stated, at the end of the course, that they were satisfied with the content and presentation of information. More than half of the participants (56%) would have preferred to obtain information both individually and in group. A smaller group (13%) considered it sufficient to attend a milk allergy school, whereas only seven participants (8%) would have preferred individual information. The rest of the participants (23%) did not express an opinion. Positive aspects included quality of the information and support provided (38%), meeting other parents in the same situation (35%) or both (14%). The most common criticism concerned heterogeneous groups in terms of age and/or symptoms of the children (11%).

At the three-year follow-up, the participants' responses were more positive, including satisfaction with the information received in most cases (88%). Thirteen (18%) families expressed a need for additional follow-up.

6.2.3 Time between diagnosis and access to nutritional therapy

The interval between diagnosis and access to nutritional therapy with a dietician during the first two years since the milk allergy school was

introduced decreased, albeit not significantly. In 2003, the mean interval between diagnosis and nutritional therapy was 18 days (range: 0-90 days) during a comparable ten-month period (October 2002- June 2003) and 83% of the families participated within a month after diagnosis. The interval between diagnosis and nutritional therapy has significantly decreased since the pilot year of the study (Fig. 7).
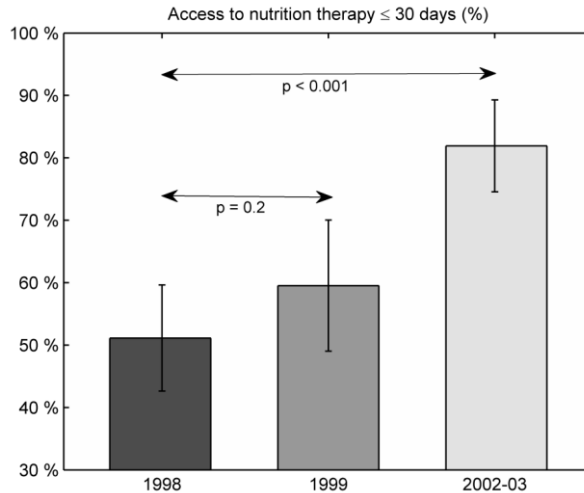

Figure 7. Time elapsed between diagnosis and access to nutritional therapy before the introduction of a milk allergy school, during the milk allergy school's pilot year and three years later.

6.3 Study III

6.3.1 Item generation and selection

A total of 68 statements related to the care of affected children were formulated, based on a review of the literature and input from 83 parents, one pediatrician and two dieticians. These statements were initially subject to a qualitative content analysis by two of the authors independently (LO and AM). Consensus regarding categorization was high (n = 48 statements, 71 % of concordance).

Items scoring the highest OI according to the clinical impact method (n = 50 mothers) were candidates for inclusion in the questionnaire.

6.3.2 Construction of the questionnaire

The FLIP's final version includes 19 questions answered on a seven-point Likert scale and a "non-applicable" alternative (See Appendix, paper III, p. 16).

6.3.3 Reliability

Complete questionnaires were returned by 94 families (82% response rate). Dropouts in the first (n = 4) and second (n = 6) administrations from the test-retest subset (n = 36) left 26 analyzable questionnaires. The FLIP showed good reproducibility for the whole scale (ICC = 0.71), the Health & Emotions and Everyday Life subscales (ICC = 0.73 and 0.83 respectively) but lower reproducibility for the Nutrition subscale (ICC = 0.40). Controls returned 135 (response rate 58%) complete questionnaires.

The FLIP showed high internal consistency totally (Cronbach's α = 0.90) as well as for all subscales at baseline and follow-up (Table 4).

Table 4. *Reliability assessed by Cronbach's α on the FLIP and subscales at baseline and 6-month follow-up.*

FLIP and subscales	Cronbach's α at baseline (n = 94)	Cronbach's α at follow-up (n = 82)
FLIP-total (n = 19 questions)	0.90 (3 †)	0.95 (1 †)
Nutrition (n = 5 questions)	0.69 (2 †)	0.83 (1 †)
Health & Emotions (n = 7 questions)	0.88	0.91
Everyday Life (n = 7 questions)	0.80 (1 †)	0.91

† Missing values

6.3.4 Validity

Factor analysis with Varimax rotation was performed on three, four and five factors, explaining 55%, 62% and 67% of the variance, respectively. The three-factor solution was considered to make the best sense and guided the grouping into the Everyday Life, Health & Emotions and Nutrition subscales. Additionally, the three-factor solution corresponded to the non-disease-specific questions administered to controls. No participants scored the highest possible effect and few scored no effect on the total FLIP (1%) or the Health & Emotions (2%), Everyday Life (2%) and Nutrition (4%) subscales. This

indicates a low risk of missing the targeted population or failing to measure change when re-administering the questionnaire (floor and ceiling effects).

The progression from the qualitative content analysis, through factor analysis and to the final questionnaire was consistent (Table 5). Following the three-factor solution chosen to guide the construction of the FLIP and its subscales, the domains Health and Emotions were combined into the Health & Emotions subscale. The domains Social and Practical concerns were combined into the Everyday Life subscale. Questions 5 ('In the past month, how often have you been troubled by your need to spend extra time preparing meals (i.e. label reading, extra time shopping, cooking extra meals, etc.) due to your child's food hypersensitivity?') and 17 ('In the past month, how troubled have you been by the food costs because of your child's food hypersensitivity?') were placed in the Health & Emotions subscale, according to the results of factor analysis. However, after discussion within authors (AM, LO and LL), these two questions were instead placed in the Everyday Life subscale, where they were considered to make better sense (face validity) and result in a more even number of questions within each subscale, marked in bold in table 5.

Table 5. *Qualitative content analysis and factor analysis of the final 19 questions included in the FLIP, construction of subscales.*

Domains	Qualitative content analysis	Four-factor solution	Three-factor solution	Final subscales
Nutrition	14,15,16	14,15,16	4,14,15,16, 19	4,14,15,16, 19
Health	6,7,13,19	5,6,7,9,11,12, 13,17,18	**5**[*],6,7,9,11,12, 13,**17**[*],18	6,7,9,11,12, 13,18
Emotions	4,11,12	4,19		
Social	8,9,10,18	1,2,3,8,10	1,2,3,8,10	1,2,3,**5**[*],8,10,**17**[*]
Practical	1,2,3,5,17			

* Questions marked in bold type were moved to another subscale in the final questionnaire.

6.3.5 Comparison among cases

Families registered higher impact in daily life, measured by the total FLIP scores, when they had older children (≥14 months of age); a second child or more (n = 28, 30%) (p = 0.02), especially in the Health & Emotions (p = 0.03) and Everyday Life (p = 0.001) subscales; and when the children had to avoid two or more foods (p = 0.003). The FLIP's total scores and subscales'

scores revealed statistically significant moderate correlations to the SPSQ's total scores (Spearman's correlation coefficient = 0.48, p = 0.01 and 0.4-0.5, p = 0.01, respectively) showing that both questionnaires concur in measuring similar phenomena (construct validity). However, all correlations are moderate demonstrating that the questionnaires measure a construct dissimilar enough to justify the use of our disease-specific questionnaire.

6.3.6 Comparison with controls

Cases showed statistically significant higher impact than controls on the FLIP Nutrition subscale (Md = 1.86, n = 92 and Md = 1.43, n = 135 respectively, p = 0.0001) and the total score of the SPSQ (Md = 2.38, n = 94 and Md = 2.24, n = 135 respectively, p = 0.02) (Fig. 8).
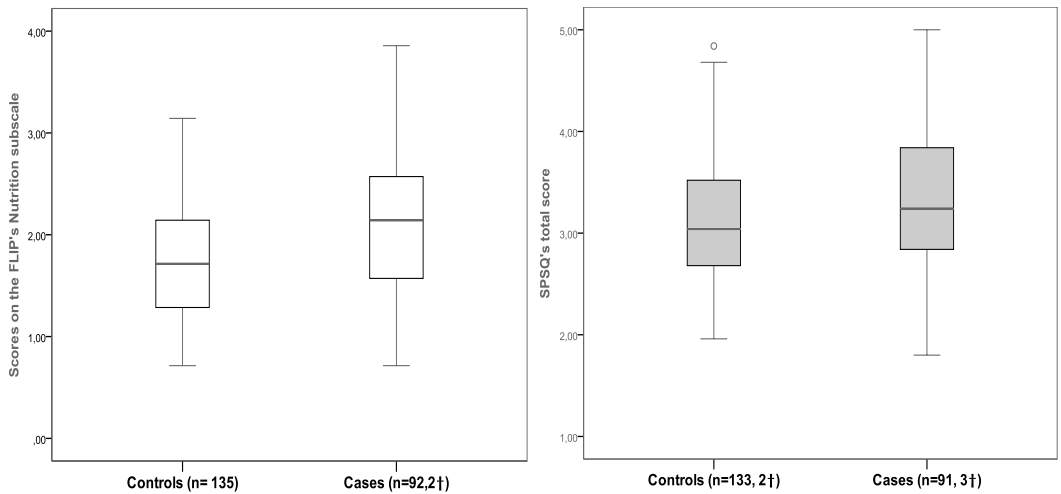
Figure 8. Comparison between scores from controls and cases on the FLIP Nutrition subscale (p = 0.0001) and the SPSQ total score (p = 0.02); scores' medians, 25th, 75th percentiles and ranges.
† Missing values.

6.4 Study IV

At follow-up, 82 of the original families participating at baseline (n = 94) returned complete questionnaires. A quarter of the children (n = 20, 24%) had developed tolerance and were no longer on a restricted diet. A few of the children in this group (n = 4) were in the process of re-introducing CM after having outgrown CMA, according to the physician's assessment. Five children had outgrown their CMA but still needed to avoid other food(s). The

details of the group at follow-up, including CMA status, reported symptoms and administered tests between baseline and follow-up are described in Table 1 (Paper IV, p. 13).

6.4.1 Psychometric properties of the FLIP at follow-up

Assessment of the internal reliability of the FLIP was evaluated in terms of the Cronbach's α coefficient, which took values between 0.95 (FLIP total score, 19 items), 0.84 (Nutrition subscale, 5 items), 0.93 (Health & Emotions subscale, 7 items), and 0.92 (Everyday Life subscale, 7 items). These coefficients were equal, or somewhat higher, compared to baseline (Paper III), and only minor changes were seen when excluding drop-outs from the baseline results. There was moderate correlation between the total score of the SPSQ and the total score of the FLIP (r = 0.40, n = 77, p = 0.001), for the Health & Emotions subscale (r = 0.42, n = 78, p = 0.001) and the Everyday Life subscale (r = 0.35, n = 78, p = 0.001); and small for the Nutrition subscale (r = 0.29, n = 77, p = 0.05). These results are also similar to the ones observed at the first administration (Paper III, p. 577).

6.4.2 Change in impairment over time following the progression of cow's milk allergy

Families with children who had outgrown the CMA (n = 20) revealed decreased impact on the FLIP, as well as on the Health & Emotions, and Everyday Life subscales at follow-up, compared to baseline. Scores were lower by at least 1.2 points, with the exception of the Nutrition subscale, which showed no decrease (Table 2, Paper IV, p. 14).

The greatest decreases in impact were registered on the items 'fear of reactions', 'fear the FA may not outgrow', 'worry about the child's health', 'feeling embarrassed by others' comments about the child's FA', 'visiting restaurants/cafes' and 'being burdened by the extra time spent on purchasing and preparing meals' (Appendix, Paper IV, p. 16). The analysis of the SPSQ showed no changes in perceived stress in this group (Table 2, Paper IV, p. 14).

Families whose children had persistent CMA (n = 57) scored as high as at baseline, and even increased impact according to the Everyday Life subscale (+0.5 points, p = 0.001) (Table 2, Paper IV, p. 14). Mixed linear regression analysis of the FLIP scores on age, progression of the CMA, time-point including their product term, i.e. between time-point (baseline and follow-up)

and progression status, revealed that families with older children scored higher on the total FLIP and on the Everyday Life subscale (p = <0.01).

Currently affected families reported the greatest increases in impact when 'planning holiday/vacations' (+0.9 points, p = 0.001), 'visiting restaurants/cafes' (+0.9 points, p = 0.001), and 'leaving the child at kindergarten or with babysitters' (+1.4 points, p = 0.0005) (Appendix, Paper IV, p. 16). Paired-samples t-test of the SPSQ detected no changes in stress in the group with persistent CMA (Table 2, Paper IV, p. 14), with the exception of one subscale measuring social isolation (p = 0.01) (results not shown).

Comparison of groups (outgrown versus persistent)

The results of the mixed model are summarized in Figure 1 (Paper IV, p. 15). Within groups, the results for the longitudinal change hardly differed from the results of the paired samples t-test in Table 2 (Paper IV, p. 14). As illustrated in Figure 1 (Paper IV, p. 15), the slope of the trajectories differed strongly between the two groups for the total FLIP scale (A, p < 0.0001), the Everyday Life score (C, p < 0.0001) and the Health & Emotions score (D, p < 0.0001). However, the corresponding difference in trajectory for the Nutrition subscale was much less dramatic (B, p = 0.04), indicating that the outgrown group showed only minor improvement compared to the group with persistent CMA.

7 GENERAL DISCUSSION

This thesis has contributed knowledge about assessment of compliance with nutrition guidelines (Paper I), the creation of a milk allergy school (Paper II), as well as an instrument to measure the impact of FA on daily life (Papers III, IV).

7.1 Nutrition guidelines for promoting a healthy diet and preventing atopic disease

Pediatric nutrition guidelines seem to be followed by most families, demonstrating the success of the CHCs' nutrition education efforts. However, Paper I highlighted some areas of concern: first-time parents and immigrant families that introduced solids too early and families with atopic heredity who did not comply with preventive guidelines concerning CM-free formula during the first months in life. The modern lifestyle and the wide access to information of varying quality, provided by a multitude of stakeholders, presents a challenge to parents wanting to make informed choices for the well-being of their children. Furthermore, the health care providers face an increasing number of patients, tasks and demands from the organization to "do more with less", reducing the available time for appropriate knowledge update, communication and reflection (130). The interval required for transmission of knowledge from researcher to clinician and for updating guidelines leads to delays. During transitional periods, obsolete guidelines sometimes linger and co-exist with new ones, increasing misinformation and confusion, undermining the credibility of the health care providers.

Critical evaluation of current programs suggests that the future success of nutrition education may depend on assessment of parents' motivation to make healthier choices. Understanding that this might be enhanced by emotion-based, rather than by knowledge-based approaches, could guide the development of appropriate educational strategies for the new generations of parents currently attending primary health care (118). Likewise, further development of communication techniques, such as web-based advice might increase interest and compliance (174). Health allies, on the other hand, could benefit from nutrition update activities, for which the specialized dietician is an appropriate leader. These strategies can be intensified as new guidelines are issued. Moreover, discussions should be regularly initiated to promote critical reflection, hopefully leading to increased awareness and compliance with nutrition guidelines.

7.2   Nutritional therapy in pediatric clinics

The introduction of the milk allergy school (Paper II) improved access to nutritional therapy provided by a dietician, proved to be a useful continuation of the public health's tradition of education and its use is increasing (175).

It has been suggested that diagnosed CMA is increasing. The natural course of CMA, i.e. being outgrown during childhood, may be changing to one with slower rates of resolution, resulting in a higher proportion than previously believed of children with CMA persisting into adolescence and adulthood (5, 76, 78). CMA and FA can be challenging and affect a significant number of people, increasing the need for knowledge and support to manage the special diet and possible reactions (112). Despite the fact that lactose intolerance seldom affects infants or preschoolers, it is often mistakenly confused with CMA, especially during the first year of life (176). This leads to both unnecessary limitations in the diet of individuals with lactose intolerance and the wrong choice of dairy substitutes for those affected by CMA. Parallel to preventive work, there is an ever-growing administrative demand for cost-efficiency and increased accessibility with unchanged or reduced resources, while maintaining and sometimes increasing the quality of care. The milk allergy school successfully met these needs. Since individual counseling was replaced by less time-consuming group counseling, the milk allergy school might have contributed to resources being made available for alternative use, for example for children with extensive FA and/or additional diagnoses, such as under-nutrition (70, 177).

7.3   Impact on daily life in families with children with cow's milk allergy

The milk allergy school participants raised issues that might compromise compliance with nutritional therapy or have negative consequences. The lack of guidelines for nursing mothers recommended a CM-free diet is a concern (83, 90, 178). Used to consume the diet of their choice, affected nursing mothers may have a restricted social life, affecting the intake of energy and nutrients, jeopardizing their health and the continuation of breastfeeding. The three-year follow-up revealed unnecessarily long re-introductions of normal diet for several children who had outgrown their CMA, while a briefer process would have alleviated the impact on their health and their families' daily life. Children affected by FA and their parents naturally develop increased awareness of adverse reactions. Repeated accidental exposure might lead to exaggerated caution, as well as conditioning attitudes towards food. These aspects may lead to limited food choices, suboptimal nutrition

and negative attitudes towards healthy eating (89, 94, 178). It became evident that exploring these issues could lead to increased awareness of factors that were essential to the compliance with and outcome of this therapy.

The initial qualitative and quantitative approaches in Paper III provided descriptive data on the impact on families with children with FA. However, factor analysis was considered to provide a more rigorous and robust base for construction of the questionnaire and therefore replaced the qualitative content analysis. Additionally, factor analysis made it possible to construct fewer subscales, in comparison with qualitative content analysis making the FLIP more manageable. Papers III and IV added knowledge on tangible, nutrition-related issues on affected families, remaining even after the onset of tolerance. Once identified, these concerns can be addressed by the primary health care.

This thesis has focused attention on the importance of nutritional aspects, both objectively from the families' perspective, and with important consequences for public health. Elucidating these aspects might lead to improvement in the quality of the care provided to affected children and their families, as well as prevent future complications, nutritional deficiencies and disrupted development of eating behavior. Additional monitoring of growth and development is essential in order to detect signs of deviant feeding/eating behaviors. Administrating the FLIP at follow-up may help identify families at risk, as well problematic areas that are targets for treatment and support.

7.4   **Limitations**

In Paper I, atopic heredity was registered according to parental report, which explains the somewhat high prevalence, in comparison with epidemiological data. This discrepancy may be due to today's parents overestimating their burden of atopic disease, or to a selection bias. However, CHC nurses were informed that the study's focus was on breastfeeding and weaning practices and not on atopic disease (27). Additionally, the study population was considered to be representative, compared to the national breastfeeding statistics (97).

The implementation of the milk allergy school (Paper II) can be regarded a small natural experiment. It was developed with a convenience sample of subjects and there was no control group undergoing alternative treatment, for example individual treatment. However, when asked, only few participants expressed a desire for individual treatment. Most participants stated that they were satisfied with the group therapy alternative or would have preferred both individual and group treatment if given the choice.

The FLIP questionnaire (Paper III) was sensitive to the disease burden, measured by the number of FAs. However, it failed to discriminate according to the number of symptoms, i.e. disease severity. This might have been a consequence of including a relatively small number of participants. However, patients with increased symptom severity, e.g. at risk of anaphylaxis, are more often treated at specialized clinics. A larger study, including patients at different care levels, would have improved the validity of the FLIP regarding disease severity.

Paper IV reports a six-month follow-up. Further follow-ups, continuing until and after all children had outgrown their FA might create knowledge of the long-term consequences of CMA and FA and help develop preventive strategies.

Throughout the studies included in this thesis, especially Papers II-IV, it proved difficult to recruit families with immigrant background, an experience shared by other researchers (179), making the group of non-Swedish parents too small to permit meaningful analysis and conclusions. These families may face special difficulties, as immigration affects diet, and poor language skills might impair the ability to comply with an elimination diet. Attention must thus be devoted to the special situation in this group (180) and researchers should endeavor to include families with different backgrounds, reflecting modern multicultural society.

8 CONCLUSIONS

Breastfeeding and weaning recommendations seem to be followed by most families. However, there was no compliance with preventive guidelines for children at risk of developing atopic disease. Routines should be created for the distribution of information about weaning, in order to reach families with special needs; otherwise, implementation of current recommendations and preventive strategies will be less successful (Paper I).

The development of a milk allergy school significantly increased access to nutritional therapy. The milk allergy school seems to meet the families' needs for information, is appreciated according to evaluations, has few administrative routines and is timesaving. This school has become permanent and is being increasingly implemented (Paper II).

The process leading to the construction of the FLIP questionnaire has shed light on the situation of families with children on a CM-free diet. The FLIP is a reliable, valid and sensitive instrument and can be valuable both clinically and in research. The results confirm the need for continuous and updated nutritional therapy and support for families with young children with FA (Paper III).

The FLIP is sensitive to changes following the development of FA. There is a sustained impact on affected families. Despite developed tolerance, nutritional effects in the families with children who no longer must exclude food(s) remain a concern. Families with children with persistent and outgrown CMA would benefit from preventive measures targeting not only the development of atopic disease but also nutrition-related conditions such as eating disorders (Paper IV).

9 FUTURE PERSPECTIVES

9.1 Implications for public health

As new generations of parents attend primary health care updated knowledge and improved education and communication skills in health care providers will be required in order to meet new demands (28, 181). Feeding practices should be followed up periodically in order to assess current conditions, compliance and guide nutrition education strategies. New guidelines will test the staff's competence. For instance, the latest nutrition guidelines encourage exclusive breast feeding until six months of age when possible, as well as avoidance of fewer specific food items, in comparison to previous guidelines. Likewise there is a paradigm shift since recent years concerning the prevention of atopic disease and FA, i.e. from delayed introduction of common food allergens during the first six months of life to unrestricted introduction, preferably during ongoing lactation. Some of these advices are causing a great deal of confusion and, sometimes, controversy (24, 28, 136, 182-184).

Dieticians may be the most appropriate nutrition professionals to facilitate regular updates of information about current guidelines and the latest research and help prevent the dissemination of obsolete advice (185, 186). Open and trusting dialogue would promote the exchange of knowledge and experience between health care professionals and dieticians and encourage mutual mentorship (117, 119, 187). Furthermore, this strategy could be a neutral counterpart to the information offered by the food industry and other stakeholders.

Consequences at the organization level will encourage cooperation and coordination of efforts between policy and implementation of strategies, with relevant agencies such as preschool, schools and different care levels. This will in turn improve access to preventive information, treatment and help cope with increasing numbers of patients (130, 188). This is especially important in the case of primary health care organizations that lack pediatric clinics or pediatricians. General practitioners, district nurses and other health workers in most of primary health care in Sweden and other European countries must provide nutrition education, diagnose and manage affected children themselves. Knowledgeable providers that can implement effective working methods will contribute to the quality of care (70, 181).

Being at an advantageous front line position, primary health care has a unique opportunity to promote healthy behavior, where nutrition is crucial to health. Primary health care has a long and solid experience of nutritional counseling and treatment in a wide diversity of settings, to groups with different needs, and under more or less favorable conditions. The compiled experience over the last decades has contributed to develop a working philosophy to improve health (120, 188, 189). Continuous innovation of working methods and cooperation across various disciplines, while paying attention to the impact of disease on individuals and their families, might contribute to achieve the goal of health for all (114, 181). Primary health care has succeeded in meeting challenging issues in the past and should be able to find inspiration to develop working methods adapted to demands in the times ahead, while striving towards equity, sustainability and participation (190). For instance, information and communication technology is rapidly evolving and it is a constant challenge to utilize existing tools and develop new ones to reach out to population that gets much of their health information from the internet (191).

The use of dairy products provides human beings with a beneficial and effective source of energy and nutrients and aids the survival of infants when breastfeeding is not possible. The use of dairy products is increasing, probably a consequence of their palatability and the globalization of the economy. The advantages and disadvantages of CM on traditional local diets and its impact on the health of various populations have yet to be evaluated (59, 192, 193).

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Appendix

1. Food hypersensitivity famiLy ImPact (FLIP) questionnaire in Swedish
2. FLIP Nutrition subscale for healthy controls in Swedish and English

Appendix 1 FLIP in Swedish

Kod:_____

Var god och svara på **varje fråga** genom att sätta ett kryss i lämplig cirkel. Kryssa bara i ett svarsalternativ för varje fråga.

1. Om Du och Din familj planerade en resa/semester, hur mycket skulle valet av semester bli begränsad på grund av Ditt barns matöverkänslighet?

Extremt mycket	Mycket	Ganska mycket	Något	Mycket lite	Nästan inte	Inte alls	*Ej aktuellt*
o	o	o	o	o	o	o	□

2. Om Du och Din familj skulle äta på restaurang, hur mycket skulle Ditt val av restaurang bli begränsad av Ditt barns matöverkänslighet?

Extremt mycket	Mycket	Ganska mycket	Något	Mycket lite	Nästan inte	Inte alls	*Ej aktuellt*
o	o	o	o	o	o	o	□

3. Om Du och Din familj planerade att delta i sociala aktiviteter som innefattar mat tillsammans med andra t.ex. fester, hur begränsad skulle Din förmåga att delta vara på grund av Ditt barns matöverkänslighet?

Extremt mycket	Mycket	Ganska mycket	Något	Mycket lite	Nästan inte	Inte alls	*Ej aktuellt*
o	o	o	o	o	o	o	□

4. Har Du någonsin upplevt svårigheter att lära Ditt barn att äta?

Extremt mycket	Mycket	Ganska mycket	Något	Mycket lite	Nästan inte	Inte alls	*Ej aktuellt*
o	o	o	o	o	o	o	□

5. Under den senaste månaden, hur ofta har Du känt Dig besvärad av att behöva lägga ner extra tid på att handla mat dvs. läsa ingrediensförteckningar, gå i flera affärer och laga extra måltider på grund av Ditt barns matöverkänslighet?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

6. Under den senaste månaden, hur ofta har Du varit orolig på grund av rädsla att Ditt barn ska få en reaktion orsakad av matöverkänsligheten?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

7. Under den senaste månaden, hur ofta har Du varit orolig över att Ditt barn inte ska "växa ifrån" sin matöverkänslighet?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

8. Under den senaste månaden, hur oroad har Du varit över att lämna/låta Ditt barn vara hos andra på grund av matöverkänsligheten?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

9. Under den senaste månaden, hur ofta har Du upplevt svårigheter att få andra att förstå vikten av att utesluta de livsmedel Ditt barn inte tål?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

10. Under den senaste månaden, hur ofta har Du upplevt otrygghet i att låta Ditt barn vara på "dagis" eller hos dagmamma på grund av matöverkänslighet?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

11. Under den senaste månaden, hur ofta har Du varit ledsen på grund av Ditt barns matöverkänslighet?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

12. Under den senaste månaden, hur ofta har Du varit orolig att Ditt barn inte ska ha en normal uppfostran pga. mat överkänsligheten?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

13. Under den senaste månaden, hur ofta har du känt Dig orolig over Ditt barns hälsa på grund av matöverkänsligheten?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

14. Under den senaste månaden, hur ofta har Du upplevt att Ditt barns mat är varierad?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

15. Under den senaste månaden, hur ofta har Du upplevt svårigheter att komma på vad Du ska tillaga/servera till Ditt barn?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

16. Under den senaste månaden, hur ofta har Du upplevt att Ditt barns mat är näringsriktig?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

17. Under den senaste månaden, hur ofta har Du upplevt att matkostnaderna varit högre på grund av Ditt barns matöverkänslighet?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

18. Hur ofta under den senaste månaden, har Du känt Dig besvärad av omgivningens kommentarer om Ditt barns matöverkänslighet?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

19. Under den senaste månaden hur ofta har Du känt att Ditt barn är nöjt och belåtet?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

Appendix 2. FLIP-Nutrition subscale in English

The Food hypersensitivity famiLy ImPact (FLIP) questionnaire[1]- Nutrition subscale

Please answer **every question** by drawing a cross in the right circle. Choose only one answer for each question.

Code:_____

1. Have you ever experienced any difficulties in teaching your child to eat?

All the time	Almost all the time	Often	Sometimes	A little	Almost never	Never	Not relevant
o	o	o	o	o	o	o	□

2. In the past month, how often have you experienced lack of variation in your child's diet?

All the time	Almost all the time	Often	Sometimes	A little	Almost never	Never	Not relevant
o	o	o	o	o	o	o	□

3. In the past month, how troubled have you been about planning what to cook or serve to your child?

All the time	Almost all the time	Often	Sometimes	A little	Almost never	Never	Not relevant
o	o	o	o	o	o	o	□

4. In the past month, how often have you felt concerned about the nutritional content in your child's diet?

All the time	Almost all the time	Often	Sometimes	A little	Almost never	Never	Not relevant
o	o	o	o	o	o	o	□

5. In the past month, how often have you experienced that your child is happy and satisfied?

All the time	Almost all the time	Often	Sometimes	A little	Almost never	Never	Not relevant
o	o	o	o	o	o	o	□

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[1] This questionnaire was originally developed in Swedish, translated to English and back-translated to Swedish according to the guidelines of the World Health Organization.

FLIP-Nutrition subscale in Swedish

Kod: _____

Var god och svara på **varje fråga** genom att sätta ett kryss i lämplig cirkel. Kryssa bara i ett svarsalternativ för varje fråga.

1. Har Du någonsin upplevt svårigheter att lära Ditt barn att äta?

Extremt mycket	Mycket	Ganska mycket	Något	Mycket lite	Nästan inte	Inte alls	*Ej aktuellt*
o	o	o	o	o	o	o	□

2. Under den senaste månaden, hur ofta har Du upplevt att Ditt barns mat är varierad?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

3. Under den senaste månaden, hur ofta har Du upplevt svårigheter att komma på vad Du ska tillaga/servera till Ditt barn?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

4. Under den senaste månaden, hur ofta har Du upplevt att Ditt barns mat är näringsriktig?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□

5. Under den senaste månaden hur ofta har Du känt att Ditt barn är nöjt och belåtet?

Hela tiden	Nästan hela tiden	Ofta	Ibland	Lite	Nästan aldrig	Aldrig	*Ej aktuellt*
o	o	o	o	o	o	o	□