Kaisa Pyrhönen

FOOD ALLERGIES AND HYPERSENSITIVITIES AMONG CHILDREN IN SOUTH KARELIA

OCCURRENCE, INHERITANCE AND SEASONALITY
KAISA PYRHÖNEN

FOOD ALLERGIES AND HYPERSENSITIVITIES AMONG CHILDREN IN SOUTH KARELIA
Occurrence, inheritance and seasonality

Academic dissertation to be presented with the assent of the Faculty of Medicine of the University of Oulu for public defence in the Auditorium of Kastelli Research Centre (Aapistie 1), on 15 April 2011, at 12 noon

UNIVERSITY OF OULU, OULU 2011
Abstract

The aim of the South Karelian Allergy Research Project (SKARP) was to quantify the occurrence of children’s food allergy and food-associated hypersensitivity symptoms and their associated factors. The study population comprised all children born between April 2001 and March 2006 and living in the province of South Karelia, in the south-eastern part of Finland. The questionnaire survey was conducted in cooperation with the child health clinics in the area in 2005–2006. Concurrently with but independently of the questionnaire study, the results of allergy tests regarding the same child population were collected from patient records.

The participation rates in the questionnaire study were 54% (644/1194) among the newborn infants and 69% (3308/4779) among the children aged 1 to 4 years. The lifetime prevalence of parent-reported food allergies was 9% and that of parent-perceived food-associated hypersensitivity symptoms 21% by the age of 4 years. In addition, another 19% of children adhered to an elimination diet without previous symptoms associated with any food items. The prevalence of children with such diets decreased by age. Up to the age of 4 years, 19% of the participants had undergone a food allergy test and 8% of the participants had obtained a positive result in these tests. Physician-diagnosed food allergies and food allergies based on the tests were more common for milk, egg and cereals than for other food items. The tested children and those with a positive test result were only slightly overrepresented among the participants. Allergic manifestations in either biological parent doubled and in both biological parents tripled the incidence of a positive food allergy test. The spring season coinciding with the end of the first trimester of pregnancy predicted sensitisation to food items in the children.

In early childhood, food allergies and food hypersensitivities were found to be common in a child population. New population-based knowledge regarding the inheritance of these conditions was obtained. Additionally, an association was observed between the timing of the 11th gestational week in spring and the sensitisation to food items, the detailed reasons and immunological mechanisms of which must be confirmed in further studies.

Keywords: child, cohort, diagnostic test, epidemiology, food allergy, food hypersensitivity, heredity, participation rate, population, seasonal, the SKARP
Pyrhönen, Kaisa, Ruoka-allergiat ja yliherkkyydet lapsilla Etelä-Karjalassa. 

Esiintyvyys, periytyvyys ja vuodenaikaisuus

Oulun yliopisto, Lääketieteellinen tiedekunta, Terveystieteiden laitos, PL 5000, 90014 Oulun yliopisto; Oulun yliopisto, Luonnontieteellinen tiedekunta, Matemaattisten tieteiden laitos, PL 3000, 90014 Oulun yliopisto; Tampereen yliopistollinen sairaala, Lastentautien vastuualue, Lastentautien tutkimuskeskus, Lääketieteet, 33014 Tampereen yliopisto; Etelä-Karjalan sosiaali- ja terveyspiiri, PL 24, 53101 Lappeenranta; Oulun yliopistollinen sairaala, Yeiläääketieteen yksikkö, PL 5000, 90014 Oulun yliopisto


Tiivistelmä


Asiasanat: diagnostinen testi, EKAT, epidemiologinen, kohortti, lasten, osallistumisaste, periytyvyys, ruoka-allergia, ruokayliherkkyys, vuodenaika, väestö
To all children and their families living in the province of South Karelia, Finland
Acknowledgements

In April 2002, Emeritus Professor of Dermatology Matti Hannuksela gave me the idea to design a questionnaire for parents regarding food allergies in their children. I promptly began developing the first questionnaire and the study plan. I am extremely grateful to Professor Hannuksela for the inspiring idea and for his skilfull and encouraging supervision in the beginning of this project.

The material for this academic dissertation was collected and the SKARP was carried out and conducted in collaboration with the Institute of Health Sciences, University of Oulu, Finland. I would like to thank the director of the Institute of Health Sciences, Professor Sirkka Keinänen-Kiukaanniemi for her support and positive attitude towards the SKARP study, which enabled me to finish my academic dissertation.

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statistician at the Steno Diabetes Centre, Denmark, for the R-script used in the harmonic analyses.

I am extremely grateful to Adjunct Professor of Clinical Allergology Erkka Valovirta and Professor of Epidemiology Markku Koskenvuo for reviewing my academic dissertation, as well as for their constructive comments on it.

The questionnaires were translated and each original paper was edited for language by Mr. Malcolm Hicks before the first submission to the journal, and the summary of this academic dissertation was edited for language by Ms. Aino Halme. Many thanks to both of them for their friendly cooperation in aiming at an exact way of reporting the results.

I am grateful to the staff of the Institute of Health Sciences, University of Oulu, Finland. I especially want to thank Mr. Markku Koiranen for his assistance in data management and for his help in many ways regarding the questionnaire survey. I also owe my warm thanks to Mr. Martti Lampela and Ms. Ritva Mannila for their cooperation and great help in sending and receiving the questionnaires. I am very grateful to Mr. Martti Lampela for his careful work in revising the final layout of this summary of the academic dissertation. I also wish to thank Ms. Piia Hiltunen, Mr. Mikko Katiska, Ms. Riitta Kokko and Ms. Sinikka Lihavainen for their careful work in sending, receiving and recording the questionnaires.

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Kiitossanat


Kiitokset appivanhemmilleni Raili ja Jorma Pyrhöseille ja veljelleni Matille perheineen sekä kaikille muillekin sukulaisille, jotka ovat kannustuksestaan antaneet voimia työhöni. Erityiskiitokset vanhemmilleni Leena ja Heikki Lähepellolle henkisestä tuesta, rinnalla kulkemisesta ja aidosta kiinnostuksesta tutkimusaiheettani kohtaan. Lämpimät kiitokset aviopuolisolleni Ollille ja rakkaille lapsillemme Ainolle, Laurille ja Eevalle ymmärtämyksestä, kasvusta ja myötäelämisestä vierelläni väitöskirjatyöni jokaisena hetkenä.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>Confidence intervals</td>
</tr>
<tr>
<td>DBPCFC</td>
<td>Double-blind placebo-controlled food challenge</td>
</tr>
<tr>
<td>FA</td>
<td>Food allergy</td>
</tr>
<tr>
<td>FHS</td>
<td>Food hypersensitivity</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
</tr>
<tr>
<td>IgE-tot</td>
<td>Total immunoglobulin E</td>
</tr>
<tr>
<td>Kela</td>
<td>Social Insurance Institution of Finland</td>
</tr>
<tr>
<td>kUA/L</td>
<td>Kilounits of antibody per litre</td>
</tr>
<tr>
<td>NA</td>
<td>Missing information</td>
</tr>
<tr>
<td>OFC</td>
<td>Open food challenge</td>
</tr>
<tr>
<td>PIC</td>
<td>Personal identity code</td>
</tr>
<tr>
<td>PPT</td>
<td>Proportion of positives out of tested subjects</td>
</tr>
<tr>
<td>PPTR</td>
<td>Proportion of positives out of the test results</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>RR</td>
<td>Relative rate</td>
</tr>
<tr>
<td>sIgE</td>
<td>Specific immunoglobulin E</td>
</tr>
<tr>
<td>SKARP</td>
<td>South Karelian Allergy Research Project</td>
</tr>
<tr>
<td>SPT</td>
<td>Skin prick test</td>
</tr>
<tr>
<td>SU/ml</td>
<td>Standardized units per millilitre</td>
</tr>
</tbody>
</table>
List of original publications

This academic dissertation is based on the following original publications, which are referred in the text by the Roman numerals I-V.


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1 Introduction

More than 50% of children in industrialised countries have been estimated to have an allergic condition or asthma (Valovirta 2009), constituting a major public health problem and imposing a burden on society and health care system. Therefore, the nationwide Finnish Allergy Programme 2008–2018 was recently launched with the aim of decreasing the prevalence of difficult symptoms of allergic diseases and the resulting burden on the society (Haahela et al. 2008a, 2008b). Although food allergies (FA), food hypersensitivities (FHS) and food-associated symptoms are assumed to be common diseases, population-based knowledge on their occurrence and risk factors is scarce (Cochrane et al. 2009, Rona et al. 2007). In early childhood, FA is often the first manifestation of allergic diseases (Kjaer et al. 2009, Sicherer 2002). Information on their occurrence and associated factors in the general population is needed for planning and arranging diagnostic protocols and treatments, making comparisons between population groups and finding preventive measures (Björkstén 2005). The multinational EuroPrevall project has collected epidemiological data on the occurrence, risk factors and costs of FA in many countries across Europe (Keil et al. 2010, Kummeling et al. 2009, Miles et al. 2005, Mills et al. 2007).

The South Karelian Allergy Research Project (SKARP) was initiated to address the occurrence of food-associated hypersensitivity symptoms and physician-diagnosed FAs in early childhood, as well as their associated factors in the general population of a geographically defined area in the south-eastern part of Finland. The data were compiled by means of questionnaires and interviews and by collecting relevant allergy test results from the patient records of the entire study population. As information on allergy testing was equally available for both the respondents and non-respondents to the questionnaire survey, it was possible to estimate the occurrence of allergy testing in the entire child population of this age and also to assess the validity of the questionnaire data and the degree of bias related to possibly selective participation.

This academic dissertation presents a detailed documentation of the data collection process in the SKARP study and the results of the study pertaining to the following research topics: (1) the occurrence of FHSs and FAs based on parental reports in the questionnaire survey, (2) the occurrence of FA testing and positive test results, and (3) the season of the crucial gestational period predicting sensitisation to food items and (4) parents’ allergic phenotype as a risk factor for a positive FA test result.
2 Review of the literature

This review of the literature is based on a comprehensive literature search mainly between April 2002 and October 2003, preceding the SKARP study. The literature search was focused on studies reporting occurrences of FA and their risk factors in general child populations.

In the beginning, the original research reports on FAs were searched for among the titles of articles published in several volumes of the journals available; BMJ, Lancet, Allergy, and Annals of Allergy. As a result of the literature search between August 2002 and 2003, a sensitive key word (‘food allergy’) yielded 2129 references from PubMed and 1300 from Ovid Full Text. In addition, 300 references were found in EbscoHost. All the titles and abstracts of references were read and relevant research reports, meta-analyses and reviews were tabulated according to the following topics: occurrence, risk factors, diagnostics, patophysiology, treatments, clinical features, consequences (growth, psycho-social etc.) and co-morbidity (asthma, rhinoconjunctivitis, atopic eczema) of FAs. The total number of references (above) also included case reports, experiments on animals and surveys concerning adults or adolescents only, the full texts of which were not retrieved and were excluded if these exclusion criteria were evident from the title or the abstract. All relevant full texts were ordered and read. The reference lists of the papers were checked to find further relevant research reports. The search was repeatedly updated also by using additional explanatory factor such as ‘season’ as a key word.

In the final phase, only the original research reports on population-based surveys concerning the occurrences, determinants and risk factors of FA in children up to the age of four years were included. In recent years, four reviews on prevalence studies of FAs or FHSs have been published (Chafen et al. 2010, Osterballe 2009, Rona et al. 2007, Zuidmeer et al. 2008).

2.1 Definition of terminology pertaining to food allergies

The word hypersensitivity has been recommended by the European Academy of Allergy and Clinical Immunology (EAACI) to cover allergic and non-allergic reactions with non-identified immunological mechanisms (Johansson et al. 2001, 2004). Thus food hypersensitivity (FHS) covers both Immunoglobulin E (IgE)-mediated and non-IgE-mediated FAs.
IgE-mediated sensitisation to food allergens has been explained to develop as a result of a contact with the food item. The specific IgE-antibodies (sIgE) and positive reactions in Skin Prick Tests (SPT) to food items indicate IgE-mediated sensitisation to food items (Eller et al. 2009, Metclafe et al. 2003, Niggemann & Beyer 2005). However, an IgE-mediated sensitisation does not necessarily indicate clinical FA (Hill et al. 2004, Metclafe et al. 2003).

Food allergy is defined as a disease, in which allergic symptoms have been caused by eating a certain food item and an immunological reaction has been identified (Johansson et al. 2001). The European Academy of Allergy and Clinical Immunology (EAACI) has recommended restricting the use of atopy only for the reactions, in which an IgE-mediated mechanism has been documented by SPTs or sIgEs. Allergy is not as strictly defined as atopy, but it is used to signify the reactions caused by IgE-mediated immunological mechanisms, too (Johansson et al. 2001, 2004). The FA diagnosis has been considered easy, when severe symptoms appear immediately and sIgE-antibodies for a suspected food items are high and/or SPTs are clearly positive (Wüthrich 1996). However, a systematic review (Chafen et al. 2010) demonstrated the prevalence of FA being greatly limited by a lack of uniformity for criteria for making a diagnosis.

In 2004, a working group established by the Finnish Pediatric Society published a guideline for diagnosis and treatment of FA to be applied in clinical practices for children (Pediatric Society of Finland 2004). The guideline defined FA pragmatically; causal association between symptoms and a food item is considered sufficient, and the identification of immunological mechanism is not required for the diagnosis of FA.

2.2 Feasibility of food allergy tests for epidemiological studies

Food-specific immunoglobulin E tests

 Specific immunoglobulin E antibodies for a great number of different food items can be measured by a method indicating these antibodies in the serum of a blood sample. The blood test is not painless, and both the sensitivity and the specificity of IgE-antibodies vary according to age, delay-time to the appearance of FA symptoms, and food item (Appendix 1). The results of an IgE test must be classified as positive by different cut points depending on the method; Magic Lite >1.43SU/ml and CAP (Pharmacia & Upjohn, Uppsala, Sweden) >0.35kU/L
(Kjaer et al. 2009, Kleine-Tebbe et al. 1992). In addition, the need for food challenges can be reduced by setting higher cut points for sIgEs (Hill et al. 2001, 2004), but these cut points are known neither for infants, for different populations nor for all different food items.

Skin prick tests for food items

A greater threshold for the diameter of the urticarial weal of skin reaction in SPTs has been demonstrated to decrease the need for the food challenges as well. In one study, a 99% positive predictive value (PPV) for a positive food challenge was reached at the cut points of 17–18mm for milk and egg (Verstege et al. 2005), while in another study of children aged less than 2 years, 100% PPV was reached by a diameter of 6mm for milk, 4mm for nut and 5mm for egg (Hill et al. 2004). Variation in the sensitivity and specificity of SPTs occurred depending on cut points in different food items and also in different age groups (Appendix 2). Therefore further information is required about these especially in young children (Eigenmann et al. 2008). However, a systemic reaction has also been induced by altogether 3/10 000 of skin tests according to a previous study (Valyasevi et al. 1999).

Food challenges

The double-blind placebo-controlled food challenge (DBPCFC) has been considered a gold standard for an FA diagnosis (Bindslev-Jensen et al. 2004, Caffarelli & Petroccione 2001, Reibel et al. 2000, Sicherer 1999). In DBPCFC, neither the physician nor the parents or the child are aware of the food item the child is obtaining and eating. In the first years of life, the open food challenge (OFC) has been considered an adequate method of confirming an FA diagnosis (Bindslev-Jensen et al. 2004). As food challenges include a risk of systemic reaction, conducting them for research purposes in such a large population of children having no indication of FA symptoms and some of whom had previously suffered a severe reaction to food items, would be both unethical and unfeasible. In a survey of retrospectively evaluated DBPCFCs in Germany (Reibel et al. 2000), 51% (178/349) of all performed challenges (for 204 children) were positives. Some medication was needed in connection with 67% (120/178) of positive DBPCFCs, and 35% (42 challenges) of these needed emergency treatment and parenteral medication. In Finland, a serious reaction was reportedly
caused in 36 (1.3%) out of 2848 OFCs (Kaila et al. 2000). Therefore, health care staff must be trained and prepared to treat a possible life-threatening generalized reaction due to food challenges (Bindslev-Jensen et al. 2004, Reibel et al. 2000, Sicherer 1999).

In epidemiological studies based on unselected and relatively large child populations, OFC or DBPCFC should be performed on each child testing numerous food items. This would be very expensive. The subjects are obviously selected depending on the parents’ consent, which might be affected by different parental characteristics, e.g. occupation, socio-economic circumstances and/or place of residence (distance from hospital), because one DBPCFC includes both a challenge with a food item and a placebo, therefore taking 1 to 2 days (Bindslev-Jensen et al. 2004). Moreover, it is recommended that all negative challenges be confirmed by eating natural food items (Caffarelli & Petroccione 2001). False positive reactions to DBPCFCs in as many as 13% of healthy children have been found to be a problem as well (Vlieg-Boerstra et al. 2007).

In Finland, 4 out of 24 hospitals advised to confirm all FA diagnoses in their Pediatric Departments by OFCs, and 14 hospitals advised to confirm most FA diagnoses by OFC (Kaila et al. 2000). The DBPCFC was used in seven hospitals, although none of them employed it routinely (Kaila et al. 2000). A positive history of symptoms and high sIgE values were associated with the need for parenteral medication (Reibel et al. 2000). In Italy, almost all health care units reported performing SPT and two thirds performed sIgEs prior to an OFC (Martelli et al. 2005).

### 2.3 Occurrence of food hypersensitivity, sensitisation and allergy

Low participation rates or missing information on participation have often been found to be a problem in observational epidemiological studies (Morton et al. 2006, Sandler 2002). In a recent meta-analysis of prevalence studies on FA, low response rates were thought to cause bias due to the non-respondents probably having a lower prevalence of FA and a different socioeconomic profile (Rona et al. 2007). The participation rates have varied from 31% to 92% (Tables 1–2, Appendix 3). The proportion of parents who did not give their consent to perform food challenges for scientific purposes was relatively high (56% to 86%) in a previous study (Venter et al. 2008). The participants had more stringent eligibility criteria in the studies including clinical investigations than in the questionnaire surveys, for example not planning to move out of the city, birth weight, or only

More than one fourth of children have been reported to have some food-associated symptoms by the age 2 years (Table 1). Almost two thirds of the symptoms were associated with fruit, milk and vegetables and two thirds of the symptoms had disappeared after 6 months (Eggesbø et al. 1999). The point prevalences of FHS symptoms are lower (2–8%) than the cumulative incidences of FHS symptoms, except in a German study (Roehr et al. 2004), in which a high prevalence of FHS symptoms (62%) might be explained by a relatively low response rate.

A low participation rate, a small proportion of tested subjects and a relatively small number of cases with a positive test result cause difficulties in evaluating and comparing the prevalence estimates of positive sIgEs for food items as well (Table 2, Appendix 3). In a Danish study (Jøhnke et al. 2006, Osterballe et al. 2005), the high incidence of a positive sIgE for any food item may be explained by a selection bias caused by the low participation rate (Osterballe 2009). In the previous studies, the occurrence of a positive SPT for any food item ranged from 1% to 6%, but was also based on relatively small numbers of cases (Table 2). This variation may have been caused also by the different eligibility criteria of tested subjects, by the different proportion of tested subjects out of the target population or by the duration of the follow-up time. On the Isle of Wight, the point prevalences of positive SPTs for a food item were found to be quite stable in ten years of two separate cohorts (Table 2).
Table 1. Previous reports on the occurrences of self-reported food hypersensitivities for any food item in childhood.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study area</th>
<th>Years of birth</th>
<th>Age (years)</th>
<th>Participants/Target population</th>
<th>Response Rate</th>
<th>Methods</th>
<th>Prevalence % (n)</th>
<th>Incidence % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bock 1987</td>
<td>Fort Collins (USA)</td>
<td>1980</td>
<td>0-3</td>
<td>480/520</td>
<td>92</td>
<td>Questionnaire</td>
<td>28 (133)</td>
<td></td>
</tr>
<tr>
<td>Eggesbø et al. 1999</td>
<td>Oslo</td>
<td>1992-3</td>
<td>2</td>
<td>3486/6400 (complete 2803)</td>
<td>54</td>
<td>Questionnaire</td>
<td>35 (992)</td>
<td></td>
</tr>
<tr>
<td>Kristjansson et al.1999</td>
<td>Sweden1</td>
<td>1994-5</td>
<td>1.5</td>
<td>328/361</td>
<td>91</td>
<td>Questionnaire</td>
<td>28 (91)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iceland2</td>
<td></td>
<td></td>
<td>324/411</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Madrigal et al. 1996</td>
<td>Mexico</td>
<td></td>
<td></td>
<td>291/NA</td>
<td></td>
<td></td>
<td></td>
<td>4 (12)</td>
</tr>
<tr>
<td>Iikura et al. 1999</td>
<td>Japan</td>
<td></td>
<td>&lt; 6</td>
<td>1336/1548</td>
<td>86</td>
<td>Questionnaire</td>
<td>13 (168)</td>
<td></td>
</tr>
<tr>
<td>Roehr et al. 2004</td>
<td>Berlin</td>
<td></td>
<td>&lt;18</td>
<td>739/2354</td>
<td>31</td>
<td>Questionnaire</td>
<td>62 (455)</td>
<td></td>
</tr>
<tr>
<td>Jørnke et al. 2006,</td>
<td>Odense</td>
<td>1999-2002</td>
<td>3</td>
<td>486/1095</td>
<td>44</td>
<td>Questionnaire</td>
<td>15 (74)</td>
<td></td>
</tr>
<tr>
<td>Osterballe et al. 2005</td>
<td>central Israel</td>
<td>2001</td>
<td>0-2</td>
<td>9070/NA</td>
<td>NA</td>
<td>Questionnaire</td>
<td>2 (150)</td>
<td></td>
</tr>
<tr>
<td>Dalal et al. 2002</td>
<td>the Isle of Wight</td>
<td>2001-2</td>
<td>1</td>
<td>969/1063</td>
<td>91</td>
<td>Telephone 7 (65)</td>
<td>26 (250)</td>
<td></td>
</tr>
<tr>
<td>Venter et al. 2006,2008</td>
<td>Hong Kong</td>
<td>2000-5</td>
<td>2-7</td>
<td>3677/4576</td>
<td>80</td>
<td>Questionnaire</td>
<td>8 (298)</td>
<td></td>
</tr>
</tbody>
</table>

1 Health care centres of Ekholm and Johannelund in Lindköping, 2 Health care centres of Hafrarfjórdur and Gardabaer
Table 2. Previous reports on the occurrences of IgE-mediated sensitisation for food items based on a positive result in specific immunoglobulin E tests (sIgE) and in skin prick tests (SPT).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study area</th>
<th>Years of birth</th>
<th>Age (years)</th>
<th>No. of tested subjects/ participants</th>
<th>Food item</th>
<th>Positive result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SPT % (n)</td>
</tr>
<tr>
<td>Bock 1987</td>
<td>Fort Collins (USA)</td>
<td>1980</td>
<td>0-3</td>
<td>43 (480)</td>
<td>Any</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Kristjansson et al. 1999</td>
<td>Sweden1, Iceland2</td>
<td>1994-5</td>
<td>1.5</td>
<td>14 (328)</td>
<td>Any</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Dalal et al. 2002</td>
<td>central Israel</td>
<td>2001</td>
<td>0-2</td>
<td>102/6070</td>
<td>Any</td>
<td>1 (78)</td>
</tr>
<tr>
<td>Venter et al. 2006, 2008</td>
<td>the Isle of Wight</td>
<td>2001-2</td>
<td>1</td>
<td>763/969</td>
<td>Any</td>
<td>2 (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>642/891</td>
<td></td>
<td>5 (29)</td>
</tr>
<tr>
<td>Julge et al. 1997, Júge et al. 2001</td>
<td>Tartu</td>
<td>1993-4</td>
<td>0.5</td>
<td>92/173</td>
<td>Milk</td>
<td>12 (11)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>116/220</td>
<td></td>
<td>21 (24)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>120/229</td>
<td></td>
<td>26 (31)*</td>
</tr>
<tr>
<td>Saarinen et al. 2000</td>
<td>Helsinki</td>
<td>1994-5</td>
<td>0-2</td>
<td>239-233/6209</td>
<td>Milk</td>
<td>2 (101) 2 (144)</td>
</tr>
<tr>
<td>Eggesbo et al. 2001a, 2001b</td>
<td>Oslo</td>
<td>1992-3</td>
<td>2.5</td>
<td>103/2721</td>
<td>Milk</td>
<td>&lt;1 (4) &lt;1 (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>41/2721</td>
<td>Egg</td>
<td>&lt;1 (17) &lt;1 (18)</td>
<td></td>
</tr>
<tr>
<td>Kull et al. 2006, Wickman et al. 2002</td>
<td>Stockholm</td>
<td>1994-6</td>
<td>4</td>
<td>2614/7221</td>
<td>Fish</td>
<td>&lt;1 (18)</td>
</tr>
</tbody>
</table>

* The number of subjects with a positive result were estimated according to reported prevalence estimate

1 Health care centres of Ekholmen and Johannelund in Lindköping, 2 Health care centres of Hafnarfjördur and Gardabaer
The occurrence estimates of FA vary between <1% to 8% (Table 3) when the FA diagnosis has been verified by a food challenge, but these estimates are based on small numbers of tested subjects and subjects with a positive test result, too. Among the children aged more than 2 years, the prevalence estimates of physician-diagnosed FA based on parental reports, on a ‘good clinical history’ or ‘clear convincing clinical history’ were 5–6% (Table 3). In a Finnish survey (Kajosaari 1982), the high prevalence estimates of FA for any food item may partly be explained by the challenges performed at home (Table 3).

### Table 3. Occurrences of FAs for any food item based on food challenges or physician diagnosis in early childhood.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study area</th>
<th>Year of birth</th>
<th>Age (years)</th>
<th>Tested subjects/Participants</th>
<th>Methods</th>
<th>Positives % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kajosaari 1982</td>
<td>Helsinki</td>
<td>1979</td>
<td>1</td>
<td>NA/261</td>
<td>OFC at home</td>
<td>19 (50)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1978</td>
<td>2</td>
<td>NA/202</td>
<td>OFC/Blind FC</td>
<td>22 (44)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1977</td>
<td>3</td>
<td>NA/200</td>
<td>Blind FC</td>
<td>27 (54)*</td>
</tr>
<tr>
<td>Bock 1987</td>
<td>Fort Collins (USA)</td>
<td>1980</td>
<td>0-3</td>
<td>29/480</td>
<td>OFC/Blind FC</td>
<td>8 (37)</td>
</tr>
<tr>
<td>Hikino et al. 2001</td>
<td>Fukuoka City (Japan)</td>
<td>1993-4</td>
<td>1.5</td>
<td>21766</td>
<td>Physician-dg</td>
<td>11 (2381)</td>
</tr>
<tr>
<td>Venter et al. 2006, The Isle of Wight 2001-2</td>
<td>1</td>
<td>Physician-dg</td>
<td>4 (39)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>23+47/969</td>
<td>OFC</td>
<td>4 (35)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>9+15/969</td>
<td>DBPCFC</td>
<td>2 (15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>21/969</td>
<td>Physician-dg</td>
<td>6 (58)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>1/969</td>
<td>DBPCFC</td>
<td>&lt;1 (7)</td>
<td></td>
</tr>
<tr>
<td>Leung et al. 2009</td>
<td>Hong Kong</td>
<td>2000-5</td>
<td>2-7</td>
<td>3677</td>
<td>Physician-dg</td>
<td>5 (170)</td>
</tr>
<tr>
<td>Kristjansson et al. 1999</td>
<td>Sweden</td>
<td>1994-5</td>
<td>1.5</td>
<td>14/328</td>
<td>SPT/DBPCFC</td>
<td>2 (6)</td>
</tr>
<tr>
<td></td>
<td>Iceland</td>
<td></td>
<td></td>
<td>14/324</td>
<td></td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

* The number of tested subjects were estimated according to the prevalence estimates reported

1 Two health care centres in Lindköping, 2 Two health care centres in Reykjavik

In a large Japanese cohort (Hikino et al. 2001), the lifetime prevalence of physician-diagnosed FA based on questionnaire survey was surprisingly higher at the age of 1.5 than 3 years (11% vs. 9%). The cumulative incidence of OFC-confirmed milk allergy was estimated to be 2% in Helsinki, when the prevalence estimates of milk allergy were <1% in Oslo and Odense (Table 4).
Table 4. Occurrences of FAs for specified food items based on food challenges or physician diagnosis in early childhood.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Year of birth</th>
<th>Age (years)</th>
<th>Tested subjects/Participants</th>
<th>Methods</th>
<th>Food item</th>
<th>Positives % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eggesbø et al. 2001a, 2001b</td>
<td>Oslo</td>
<td>1992-3</td>
<td>2.5</td>
<td>54/2721</td>
<td>Physician-dg DBPCFC</td>
<td>Milk</td>
<td>1 (31)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Physician-dg DBPCFC</td>
<td>Egg</td>
<td>&lt;1 (22)</td>
</tr>
<tr>
<td>Saarinen &amp; Savilahti 2000</td>
<td>Helsinki</td>
<td>1994-5</td>
<td>0-2</td>
<td>247/6209</td>
<td>OFC</td>
<td>Milk</td>
<td>2 (118)</td>
</tr>
<tr>
<td>Osterballe et al. 2005</td>
<td>Odense</td>
<td>1999-2002</td>
<td>0-3</td>
<td>54/486</td>
<td>OFC</td>
<td>Milk</td>
<td>&lt;1 (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Egg</td>
<td>Peanut</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>

Table 5. Point prevalences of elimination diets for different food items in previous studies on the occurrences of food allergies in early childhood.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Year of birth</th>
<th>Age (years)</th>
<th>N</th>
<th>Egg %</th>
<th>Fish %</th>
<th>Citrus fruit %</th>
<th>Any %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kajosaari 1982</td>
<td>Finland</td>
<td>1979</td>
<td>1</td>
<td>261</td>
<td>21</td>
<td>14</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1978</td>
<td>2</td>
<td>202</td>
<td>9</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Venter et al. 2006</td>
<td>the UK</td>
<td>2001-2</td>
<td>1</td>
<td>969</td>
<td>Not known</td>
<td></td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Leung et al. 2009</td>
<td>Hong Kong</td>
<td>2000-5</td>
<td>2-7</td>
<td>3677</td>
<td>Not known</td>
<td></td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

2.4 Elimination diets

The point prevalences of elimination diets in early childhood may comprise a remarkable proportion of children, because children have never tasted all food items in early childhood. Among these children the information on both tolerance and FA for the food items in question is missing. In Table 5, none of the studies reported any reason for avoiding a food item or whether a food item had previously been tasted or not. In day care centres in Helsinki, the prevalence of some special diets was 14% in 1996 (Juntunen-Backman & Korppi 1999, 2002); 9% had FA, with other reasons for special diets being celiac disease, diabetes, lactose intolerance or religious reasons. The prevalences of different elimination diets were food items which are commonly known to cause FA symptoms in 5%, milk in 1%, egg in 2%, cereals in 0.2% and to several essential food items in 0.6% of children.
2.5 Risk factors for food allergies

Risk factors have been more thoroughly studied for other allergic manifestations than for FA (Cochrane et al. 2009), although FA is often the first manifestation of the ‘atopic march’ (Hikino et al. 2001, Kjaer et al. 2009, Sicherer 2002, Spergel & Paller 2003, Wahn 2000). The annual prevalences of sensitisation to food allergens were observed to decrease in a German cohort and those to inhalant allergens to increase from the age of 1 to 6 years (from 10% to 3% and from 1.5% to 8%, respectively) (Kulig et al. 1998, 1999).

In the cohort studies from the Isle of Wight and Japan (Tariq et al. 1998, Hikino et al. 2001), boys had a higher risk for FA than girls, whereas a higher prevalence of FAs was found among girls in a Swedish study population of older children (3 to 15 years of age) (Hjern et al. 2001). In the Japanese cohort (Hikino et al. 2001), the prevalence of FA was lower in infants with a lower birth weight (8%, <2500g vs. 11%, >2500g), but no difference was found based on the duration of pregnancy.

2.5.1 Inheritance

The inheritance of FA has remained largely unknown (Cochrane et al. 2009), although it has been suspected in Finland for more than a hundred years (Cedercreuz 1909), and FA is often the first manifestation of allergy in early childhood (Sicherer 2002).

Paternal and maternal history of adverse reactions to food was associated with parent-reported adverse reactions to food among pre-schoolers in Hong Kong (Leung et al. 2009). Atopic mothers report symptoms of allergic diseases in their infants more commonly than non-atopic mothers (Venter et al. 2009). Two previous studies provide evidence for the heritability of peanut allergy (Hourihane et al. 1996, Sicherer et al. 2000). Higher frequencies of certain HLA types have been found among patients with nut allergy, and particular genetic polymorphisms are more common among patients with either nut or any FA than other patients with atopy or participants without an FA, respectively (Amoli et al. 2002, Cambos Alberto et al. 2008, Hand et al. 2004, Liu et al. 2004, Woo et al. 2003), but it would be necessary to replicate these findings in other populations (Lack 2008).
2.5.2 Season of birth

No previous knowledge was available on the season of birth as a risk factor for FAs in population-based studies. Therefore the available literature concerning other study designs was also searched and considered.

A previous Swedish study on 209 participants (Nilsson et al. 1997), born in 1970’s, found higher prevalences of sIgE antibodies to egg white, milk and wheat in children born in autumn or winter than those born in summer. Among 369 Japanese child patients with atopic dermatitis, higher values for egg specific IgEs were found in those born in winter than those born in other seasons (Kuzume & Kusu 2007). A Dutch study comprised results of the diagnostic sIgEs for egg in 78 000 and for milk in 89 000 children younger than 4 years (Aalberse et al. 1992). The highest prevalence of a strongly positive egg or cow milk specific sIgE was associated with birth season in autumn or winter. FA was also found to be more common among child patients in Boston, who were born in the fall and winter seasons (Vassallo et al. 2010). In another Swedish study (Kihlström et al. 2002), sensitisation to birch pollen appeared more commonly in children born in a spring of exceptional high exposure to birch pollen grains than in children who were exposed to lower amounts of birch pollen at their first months after the birth in another spring (17% vs. 9%, respectively OR 2.4;95% CI 1.2–4.6). The cumulative incidence of food-associated symptoms was highest in the children born in the spring of highest pollen exposure (16%;31/197 vs. 12%;24/195). At the age of 4 years, the prevalence of positive SPT for hazelnut was also highest in the children exposed to the highest pollen concentration in the first 3 months after the birth (11%;21/197 vs. 7%;13/194).

Time to developing atopy during gestation has remained a controversial issue (Bønnelykke et al. 2008, Hertz-Picciotto et al. 2008, Jones et al. 2000). The 11th gestational week has been considered critical to the development of the immune system (Hertz-Picciotto et al. 2008). The association between maternal and fetal IgEs against food allergen has been taken an evidence for the prenatal development of atopy (Pfefferle et al. 2008).

A central regulator in the development of allergy has been considered a cytokine interleukin-10 (Akdis & Blaser 2001), a low level of which has been associated with a low concentration of vitamin D (Zittermann et al. 2004). A low intake of vitamin D during pregnancy has been associated with asthma and allergic rhinitis in the child (Erkkola et al. 2009). Vitamin D deficiency in children born in winter, or delayed effects of winter darkness during early
pregnancy (Lamberg-Allardt et al. 2001), may interfere with the development of sensitisation. Lower cytokine responses of cord blood have previously been measured in the offspring of allergic than non-allergic parents (Gold et al. 2009). The responses were higher in those born in spring or summer than in those born in autumn or winter (Sullivan Dillie et al. 2008). Seasonal variation in cytokines of cord blood has been considered a possible result from maternal immune response to viral or bacterial pathogens that occur in the autumn and winter (Sullivan Dillie et al. 2008). On the other hand, the risk for allergies, also for FAs, has been previously found to be higher in the firstborn than other children (Karmaus & Botezan 2002), even though the latter are probably more exposed to viral infections at home during their prenatal and neonatal period.

2.6 Need for epidemiological knowledge on food allergies

In the recent decades, the occurrences of allergic diseases have increased and both FAs and self-reported FHSs have been understood to be a public health problem (Valovirta 2009). Population-based knowledge on the occurrences of food-associated symptoms and physician-diagnosed FAs are needed for planning and organising optimal diagnostic procedures and treatments for the population. The knowledge of their risk factors is also a basis for new ideas for preventive measures in unselected populations.

A questionnaire study is a useful method for estimating the occurrence of FAs in the general population, albeit the information it provides is limited to symptoms and/or diagnoses reported by the respondents. Participation rates in epidemiological studies are known to have been generally declined since 1970s, and nearly 70% of such studies fail to report the rate (Morton et al. 2006). The prevalence of the subjects with the outcome in question may be either under- or overrepresented among the participants (Kotaniemi et al. 2001, Rönmark et al. 1999), and thus selective participation is likely to introduce bias and loss in generalizability (Sandler 2002). Comprehensive information on effective methods or combination of various methods to improve the participation rate is therefore useful not only to readers who wish to compare different studies, but also to other researchers planning to conduct similar studies elsewhere.

Several attempts have been made to determine the occurrence of FAs in different populations. Currently, the available methods for confirming the diagnosis of FA are unfeasible in epidemiological studies (Bindslev-Jensen et al. 2004, Caffarelli & Petroccione 2001, Chafen et al. 2010, Reibel et al. 2000,
Sicherer 1999). Published estimates on the prevalence of FAs and FHSs range between 2% and 35%. This variation can be accounted for by variable criteria and methods of diagnosing allergies, the age range of the population studied, and by the spectrum of food items examined (Table 1–4). The target populations have often been incompletely described, and a quite large proportion of the parents have declined their consent to time-consuming tests (Dalal et al. 2002, Eggesbø et al. 2001a, 2001b, Kajosaari 1982, Kristjansson et al. 1999, Saarinen et al. 1999, Venter et al. 2008). Comparisons between various studies are further complicated by whether a point or lifetime prevalence is reported, and in the latter case, by the length of the follow-up period.
3 Aims of the study

The general aim of the South Karelian Allergy Research Project was to quantify the various aspects of the phenomenon of food allergies and food hypersensitivities in a general child population. The specific aims of the study were to quantify:

1. the occurrence and determinants of parent-reported food allergies and food hypersensitivity symptoms associated with different food items
2. the occurrence and determinants of food allergy testing and positive test results
3. the association between the incidences of positive food allergy tests in children and the allergic phenotypes of their biological parents
4. the association of the season of birth and season of gestational phase with the incidences of positive food allergy tests
4 Material and methods

4.1 Conceptual and methodological framework

Medical and popular terminology for food allergies

*Food allergy* (FA) as a medical term is often strictly limited to mean a medical diagnosis verified by DBPCFC or by OFC in infants (subsection 2.3). However, these methods are unsuitable for population studies, and no simple method is available to screen FA (Björkstén 2001). IgE-mediated sensitisation for a food item can be indicated only by SPT or sIgE test for a food item, being solely a medical term, but the real meaning of this condition is unknown without information on FA symptoms. In Finland, food allergy (*ruoka-allergia* in Finnish) is a widely used popular word signifying any food-associated symptoms.

The popular terminology must be used when the focus of the study is to estimate the occurrence of FA symptoms in a population by means of a self-administered questionnaire. However, we can attempt to minimise the misclassification of FA symptoms by describing the typical allergic symptoms in detail in the questionnaire. If the parents report a physician-diagnosed FA for the food item in question, these symptoms can be considered *FA symptoms*. If the food-associated symptoms are reportedly only observed by the parents, they can be considered *FHS symptoms perceived by the parents only*. The quite indefinite term *food-associated symptoms* can be used for all parent-reported food-associated symptoms including FA symptoms and FHS symptoms.

The occurrence of FA diagnosis in a general population cannot be based solely on the results of FA tests in patient registers, because all children with a physician-diagnosed FA have not necessarily been FA tested. However, the collection of FA test results from patient records, combined with the questionnaire survey, offers an adequate framework for describing the phenomenon of physician-diagnosed FAs and FHSs perceived only by the parents in a general population (Figure 1).

Theoretical flow from the symptoms to food allergy diagnosis

In real life, a child has or does not have FA or FHS symptoms associated with eating a food item. If the child has the symptoms associated with food, the parents
either 1) observe these symptoms and their association with a food item or 2) observe the symptoms but ignore the association with a food item, or 3) ignore both the symptoms and their association with any food item (Figure 1). The parents are more likely to contact a physician if they have observed the association of symptoms with an essential rather than a non-essential food item. Similarly, they are more likely to contact a physician more likely in case of persistent or serious symptoms or symptoms caused by several food items than otherwise. These are also indications for further allergological investigations given in the clinical guidelines established by the Pediatric Society of Finland (Pediatric Society of Finland 2004).

Based on a clinical history, the association between the FA or FHS symptoms and the food item may be clear enough that an FA diagnosis may be set without performing any FA tests (basing on a ‘good clinical history’ (Venter et al. 2006, 2008)), or a physician may advise the parents to challenge the suspected food item at home. This is possible for children older than 2 years of age, in case of mild and delayed symptoms and more probably regarding non-essential food items rather than essential ones. Children who are suspected to have FA for essential food items, e.g. for milk or food items that have an important role in cooking, are more likely to be tested than others, as another product must be substituted for the eliminated food item. The use of milk substitutes in particular causes extra expenses for families and for society, since these products are more expensive than milk, and in Finland their costs are partly reimbursed by the Social Insurance Institution of Finland (Kela) to the parents of the milk-allergic child. In order to receive the compensation from Kela, the diagnosis must be set adequately.

In the SKARP study, the phases from the first symptoms to FA diagnosis were quantified by the data from the questionnaire survey and FA tests (Figure 1). The parents’ reports on the age of the child when they perceived the first FA or FHS symptoms in their child describe the first, FA testing (test data) the second, the results of FA tests the third, and parental reports on physician-diagnosed FA the final phase of the FA diagnostic process in the study population.
Fig. 1. Theoretical flow diagram from the first allergy-like symptoms to FA diagnosis and the methods of the SKARP study (questionnaire and collection of FA tests) by which the information on these phases were collected.
4.2 Study area and population

The study was carried out in 2005–2006 in South Karelia, a province in the south-eastern part of Finland (Figure 2) with 135 604 inhabitants, 4851 of whom were 1 to 4 years old (Statistics Finland 2008). The province has an area of 7236 km² (with a land area of 5625 km², the rest being lakes and rivers), and an average population density of 24 per km². The province is divided into 12 local government districts, called communes (kunta in Finnish), three of which are towns (with 59 000, 30 000 and 11 000 inhabitants, respectively) and 9 rural communes (800 to 6200 inhabitants).

![Fig. 2. Location of the study area, South Karelia, a province in the south-eastern part of Finland. The province is divided into 12 communes, the centres of which are indicated by points on the left map.](image)

Ten of the twelve communes form the hospital district of South Karelia, but two of them, Suomenniemi and Parikkala, belong to the neighbouring hospital districts of South Savo and East Savo, respectively. The central hospital of the
hospital district of South Karelia is situated in the town of Lappeenranta, from where the distance to the most remote communal health care centre in the region is 97 km. In 2001–2006, an average of eight paediatricians were working in the public health care sector in the study area (one per about 2500 children and adolescents aged less than 16 years). Two of them, having more advanced training and expertise on allergic diseases than the rest, were mainly responsible for the medical care of these conditions. Due to the relative scarcity of paediatricians, greater responsibility of diagnosing and treating childhood allergic diseases was imposed on general practitioners (GP) and dermatologists than elsewhere in the country.

The eligible subjects comprised children born between 1 April 2001 and 31 March 2006 and scheduled to visit a child health clinic from 1 April 2005 to about 31 May 2006.

4.3 Data collection

4.3.1 Local child health clinics

Finland has a nationwide network of child health clinics, maintained by local health centres. The system is funded by taxes and is therefore free of charge. Practically all the children are followed up at regular intervals and vaccinated at the clinics according to the nationwide vaccination programme (National Public Health Institute 2008b). The child first visits the local clinic with his/her parent(s) a couple of weeks after the delivery, and thereafter several times during the first year of life, for a total of at least 16 times before the age of 7 years (Hermanson & Pelkonen 2004, Ministry of Social Affairs and Health 2006). The present study was carried out in close co-operation with the local child health clinics and 52 public health nurses working at them. The nurses were specifically instructed to ask the parents questions on food-associated symptoms.

Co-operation with the child health clinics was expected to be useful in order to 1) reach the majority of the intended study population, 2) enable interviews with the parents about symptoms perceived in the child, 3) distribute the questionnaires to the parents of the newborn, along with complementary questionnaires on diets, 4) maximize the participation rate, and 5) improve the reliability of the questionnaire study by having the clinic nurse check the returned questionnaires. Apart from checking the self-administered questionnaire, the
nurses were asked, with the parents’ permission, to complete the information on birth weight, birth length, prematurity and other relevant items not answered in the questionnaire but available in the clinic’s records.

The nurses were trained and supplied with written instructions to ask questions on food-related symptoms. Throughout the study they also received guidance by phone, email and at six to seven meetings with the principal investigator (KP). When an appointment was made by phone for a regular visit to the clinic, the nurse reminded the parents about the questionnaire, asking them to fill it in. Additionally, to ensure a high participation rate, the target population was informed about the study and its objectives by a letter accompanying the questionnaire, by regional newspapers, and by television news.

4.3.2 Population data

The addresses of the 1-to 4-year-old subjects were obtained from the Finnish Population Register Centre (Population Register Centre 2006). This register maintains records on every Finnish citizen, which include the personal identity code (PIC), name, gender, the PICs of siblings younger than 18 years who live in the same household, the name of the mother, and the home address. Every Finnish citizen is assigned a PIC at birth, and immigrants who stay in Finland for at least one year receive a PIC as well. Addresses and other personal information were obtained on altogether 4779 children aged 1 to 4 years. The public health nurses identified an additional 19 (<1%) eligible children who resided in the area, but they were not included because their register data were not available.

As some time will elapse after the birth before a newborn is recorded in the population register, data on the newborn would not have been available in the scheduled time. Therefore the questionnaires were given to their parents during the first visit to the child health clinic.

The register data of 1194 newborn infants (names of the child and his/her mother, PIC, gender, mother tongue, address, siblings) were also obtained from the population register at the end of the questionnaire survey. A newborn was defined as eligible to the study population if he or she officially resided in the study area before the age of one month, and was therefore invited to participate during the visit to the clinic. Those who were born in the study area (1189 children) or moved into the area at less than one month of age (5 children) were included. When the participants of the questionnaire study were compared to the register data, the public health nurses had identified an additional 9 newborn
infants (<1%) who would have been eligible based on their age and residence, but they were excluded because their register data were not available. Four newborn who initially participated were excluded because they had moved to the study area after the age of one month. In summary, the eligible study population consists of 1194 newborn and 4779 older children, for a total of 5973 children (Figure 3).

Fig. 3. Forming the five birth cohorts of the SKARP study were based on the Finnish Population Register.

4.3.3 Questionnaires and interviews

Figure 3 shows in detail how the data were collected. The questionnaires were developed specifically for the present study utilizing and modifying previously used questionnaires; the international ISAAC-questionnaire (ISAAC Steering Committee 2008), the Finnish Tuohilampi questionnaire (Susitaival et al. 1996), the FinRisk 2002 questionnaire (National Public Health Institute 2008a), and
several questionnaires from the northern Finland birth cohort 1985/86 study (NFBC study).

The language of the questionnaires was Finnish, which effectively limited participation to children with a parent able to understand Finnish. The nurses were not requested to translate the questionnaires. After the questionnaire survey was completed, English versions of the questionnaires were made available at internet for documentation and publication purposes (EKAT [SKARP study] 2007).

The baseline questionnaire for the parents of the 1- to 4-year-olds was a structured form of 12 pages. The completed baseline questionnaire was checked by the nurse when it was returned. If any symptoms of FA had been perceived within the last 12 months, a detailed interview was conducted by the nurse according to a structured interview questionnaire, specifically developed for this purpose and tested in the pilot study. The baseline questionnaire for the parents of the newborn infants was a modification of the baseline questionnaire described above, with the difference that questions on the mother’s elimination diets during pregnancy were included.

The questions of the interview questionnaire focused on the type of perceived symptoms and the time elapsed between eating a food item and the appearance of the symptoms. The structured interview questionnaire included the questions on FAs (identical with those in the baseline questionnaire), which were asked only the parents who had forgotten to return the baseline questionnaire.

The nurse gave another questionnaire (a structured form of 8 pages) on diets to the parents of all the 1-to 4-year-old children, and it was filled in by the parents at home to be returned by post (Figure 4). This questionnaire asked about the food items that the child was able to eat without symptoms of allergy, and possible diets adhered to by the child during the last three months or by the mother during her pregnancy or the breastfeeding period. If the mother had adhered to some elimination diet because of her own allergies, these were asked to be ticked in each class of food items.

Administration of the questionnaires

Starting in March 2005, on the 10th day of each successive month a batch of questionnaires was posted from the research institute, targeting children who had birthdays during the following calendar month. The birthdays determine the expected time of the annual visit to the clinic. Thus the parents received the baseline questionnaire 2 to 6 weeks before the expected date of the annual visit.
They were asked to fill in the questionnaire at home and to return it to the clinic when visiting, where it was to be checked by a nurse (Figure 4). The first wave participation rate refers to respondents who filled in the questionnaire before the month when the reminder questionnaire was sent, and whose child was not recruited by public health nurse in the clinic.

Fig. 4. Data collection by the questionnaires, interviews and patient registers.
If the parents did not return the questionnaire they were still able to participate by answering the questions during the visit to the child health clinic. The participation rate after these interviews is called the second wave participation rate. A reminder questionnaire was sent to those who did not return the questionnaire within 4 to 5 months. These questionnaires were requested to be returned in prepaid envelopes to the research institute or to the child health clinics. The last batch of reminder questionnaires was mailed on 11 August 2006. The participation rate associated with returning the reminder questionnaire is called the third wave participation rate. The participants of the third wave returned the baseline questionnaire in the same month as or later than they had received the reminder questionnaire, and they had not been recruited into the study by public health nurses (no interviews performed).

Some parents expressed unwillingness to participate in the study. In these cases, the nurses discreetly inquired reasons for refusing, which were classified by the nurses into five categories (interview questionnaire, Figure 4). No names or identification numbers were collected from those who refused, and therefore some of these parents may yet have returned the reminder questionnaire.

The birthday, PIC and name were asked in all questionnaires, and the PIC and the name of the subject were also obtained from the Finnish Population Register (Population Register Centre 2006). All the questionnaires were assigned a study ID number, enabling the investigator to link and arrange the different questionnaires, but no linkage with the patient record data was done in cases where the use of the PIC had been prohibited. The ID number also allowed the investigator to ascertain that the information given in the questionnaires pertained to the particular child, not to any other child in the family. All the questionnaires which were returned to the research institute can be seen in the photo of Figure 5.

Pilot study

The purpose of the pilot study was to perform final tests for the planned study protocol and the questionnaires. The pilot study (from November 2004 to February 2005) comprised 200 children at the child health clinics of Kangasala. Kangasala is a commune outside the study region. In the pilot study, the birthdays of the target population were between 15 November and 15 January. No data from patient records were collected, and therefore no identification data were collected either. The mean time for filling the baseline questionnaire was 22 minutes and 9
minutes for the structured questionnaire on elimination diets. The mean time for an interview was 9 minutes.

The nurses involved in the pilot study attended a lecture, in which the principal investigator introduced the study protocol and their tasks in performing the study. They also received written instructions. No information on this pilot study was given to local mass media, neither were reminder questionnaires posted. The participation rate in the pilot study was 53%. During evaluation, the nurses wished closer co-operation with the principal investigator and more guidance on the study protocol. These suggestions were taken into consideration and applied in the actual study as described above.

4.3.4 Patient records

The results of allergologic tests were collected from existing patient records of the whole study population, both respondents and non-respondents. The results for tests done between 1 April 2001 and 30 September 2006 concerning food, inhalation, contact or drug allergens were collected independently from the
questionnaire study. All the tests had been performed on clinicians’ orders, for clinical reasons, and the results were collected retrospectively from all hospitals, health centres and private clinics in the study area (Figure 4).

All test results included the name of the performing unit or laboratory, the name of the test, the result and the date of performed tests, and the PIC and/or name and the birthday of the child for purposes of data linkage. Some tests had been performed in laboratories outside the study area. These results were also included in the data if the following data were available: results of positive and negative controls of SPTs, specified test results, both negative and positive, and the date of the test. Results of tests performed elsewhere as reported and/or recalled by parents and then transcribed in the medical record were excluded.

**Skin prick tests**

The results of skin prick tests (SPT) for food allergens, respiratory allergens, contact allergens (e.g. latex), and medicines or vaccines including positive and negative controls, were collected from 9 laboratories in the study region (Figure 4): the central hospitals in South Karelia, East Savo and South Savo, two paediatric clinics, one health care centre and three private laboratories.

The mean of two orthogonal diameters of the urticarial weal equal to or above 3 mm, with positive and negative controls, was considered the cut point for a positive result of SPTs. Eight children were included in subsequent analyses even though their positive control was below the cut point. The negative control was positive in one child, who was excluded from the number of positive test results. In addition, the tests of two children (altogether 13 results) were excluded, because the recorded dates of these SPTs were earlier than the pertinent birthday.

**Total immunoglobulin E and specific immunoglobulin E**

The results of both total immunoglobulin E (IgE) and specific immunoglobulin E antibodies (sIgEs) to food and inhalation allergens were collected. IgE antibodies had been analysed in three private laboratories and the laboratories of central hospitals (Figure 4). Almost all results were collected by a computerised system from laboratory records covering the South Karelia hospital district, but some had to be collected manually. The IgE measurements using recommended and routine methods (RAST-CAP FEIA, Magic Lite or Phadiatop Combi) were included. The IgE results measured by the CLA method were not obtained by a laboratory.
The cut point for sIgEs was equal to or above 0.35kU/L (for RAST-CAP FEIA or Phadiatop Combi) in 98% of the tested subjects and in 99% of all positive tests, and 1.43SU/ml (for Magic Lite) among the rest (Kjaer et al. 2009, Kleine-Tebbe et al. 1992). The maximum value of immunoglobulin E was 100kU/L in 5 children and 13 test results. The results below the cut point had been marked as ‘<0.35’ for RAST-CAP FEIA and Phadiatop Combi or ‘<1.43’ for Magic Lite, and the results above the maximum value had been marked as ‘>100’. These recordings were replaced by values 0.34 and 101 in the data-analysis, respectively. In addition, 2 results had been marked as ‘NEG’ and 1 result as ‘POSIT’, and these were also replaced by values 0.34 and 0.35, respectively. Some FA tests (Phadiatop comp or comparable, including food group) are aimed at testing levels of sIgE for certain food items or groups of food items. If all of these sIgE subgroups yielded negative results (114 tests), these had been marked only once as ‘<0.35’, but in the data analysis every single sIgEs included in these combined tests were taken into account as a negative result.

**Open food challenge**

The double-blind placebo-controlled food challenge (Bindslev-Jensen et al. 2004, Sicherer 1999), the ‘gold standard’, is not routinely used in clinical practice in Finland (Kaila et al. 2000) and was not used in the paediatric clinics in the study area either. Instead the ‘open food challenge’ (OFC), controlled by a physician or a nurse, was used in the central hospitals, the paediatric clinics of the health centres and in two child health clinics. The results of the OFCs were collected (Figure 4) by systematically reading altogether 1761 patient records of those who had visited the above-mentioned clinics. Otherwise data on visits had to be obtained among all the patient records in a health care centre. The rest of the OFC results were collected from 230 patient records identified on the basis of international classification of diseases (ICD-10) codes; L20.0, L27.2 and K52.2.

A structured form was used to collect the following data: the specific food item, the maximum portion of the test item eaten, the date of testing, and the result as categorized by the attending paediatrician. The results of OFCs were transcribed from the patient records and notes made by a nurse concerning (i) the status of the skin before the test, (ii) the description of the reaction caused by the challenge food item, (iii) medication, if any, needed to treat the reactions, and (iv) the test result as judged by the physician. If the result of the OFC was negative,
then the principal investigator examined the records further and collected any
notes on delayed symptoms perceived by the parents at home.
The results of OFCs were transcribed as they were in the patient record, i.e. as
negative, positive or not known.

4.3.5 Environmental data

As part of the Finnish pollen information network (Aerobiology Unit, University
of Turku, Finland 2005), daily regional pollen counts were measured throughout
the pollen season, from 1st March to the end of August in 2002–2005, with a
Burkard seven-day volumetric sampler (Hirst 1952) located 119 metres above sea
level on the roof of a 19-metre high building in the town of Joutseno (61° 18’N,
28° 41’E) in the middle of the area concerned (V). Since the location of the
Sampler was moved from a higher to a lower roof after the pollen season in 2001,
the pollen concentrations from the period before 2002 were not comparable to
those during the years 2002 to 2005. The sampling, slide preparation and data
interpretation took place according to the standard methodology adopted by the
Finnish pollen information network and following the principles of the European
Aeroallergen Network (www.polleninfo.org/). The pollen concentrations were
expressed as daily mean counts of pollen grains per cubic metre of air.

The mean monthly temperature in Jyväskylä, as well as the length of the day
(hours) and monthly averages of sunshine hours per day in Helsinki were
measured by the Finnish Meteorological Institute over the years 1973–2000
(www.fmi.fi).

4.4 Specification of variables

Outcomes

The baseline questionnaire (http://kelo.oulu.fi/tutkimus/EKAT/) included
questions about the child’s FAs or FHSs. Before the questions on the specified
food items in the 20 categories, the parents were informed about the allergic
symptoms (II). The outcomes basing on parental reports were defined as follows:
- Physician-diagnosed FA/ FHS perceived by the parents only/ never tasted a food item; for 20 categories of food items (II)
- Age of the first FA symptoms, later diagnosed by a physician (II)
- Age of the first food-associated FHS symptoms, perceived by the parents only (II)
- Age of the first food-associated symptoms (III)

The outcomes of FA testing and those of positive results in these tests were reported according to individual test methods (III-V, respectively). A positive result in either an SPT or an sIgE test (sIgE/SPT), equal or above the cut point, indicates IgE-mediated sensitisation to the pertinent food item (V), but it does not indicate clinical FA (Bischoff & Sellge 2003, Sicherer 2003). A positive result found in OFCs can be interpreted as a physician-diagnosed FA; given that the child took an OFC in a hospital situated in the study area, a physician recorded the result in the patient register and the result was collected successfully. Positive results in either sIgEs/SPTs or OFCs can be considered objective evidence for FA, the former indicating a weaker evidence for FA than the latter.

Explanatory variables

The data on age at the time of invitation, gender and mother tongue (primarily the mother’s native language) were obtained directly from the population register. The birth order variable was created by comparing the child’s birthday with those of any siblings, and was classified into ‘firstborn’ (including both of firstborn twins), and ‘not firstborn’. Place of residence was classified as follows; the ‘provincial capital’ (Lappeenranta), ‘other towns’ (Imatra and Joutseno) and ‘rural areas’ (the remaining communes).

The ages of the biological parents when the child was born were calculated from their ages at the time of the survey as indicated in the questionnaire (http://kelo.oulu.fi/tutkimus/EKAT/). The parents’ educational levels were categorised according to the educational system in Finland as follows: ‘basic’, ‘upper secondary’ and ‘higher education’ (Ministry of Education). If more than one alternative had been ticked, the highest level was used. Parental occupations were classified hierarchically as follows. A ‘health care occupation’ was coded primarily if reported. Secondarily, if farming was reported but no health care occupation, the occupation was categorised as ‘farming’. Finally, those who reported any other occupation were categorised as having ‘other occupations’.

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The month of birth is indicated in the PIC. Parents were advised to mark the duration of the pregnancy found on the maternity card in the questionnaire. In Finland, in over 90% of pregnancies gestational age is ascertained with an ultrasound scan during the 11th to 22nd gestational weeks (Kokkonen 2008). The scan is considered accurate within a frame of 7 days. The calendar month of the 11th week was taken as another explanatory variable, since it was considered critical for the developing immune system (Hertz-Picciotto et al. 2008).

Gender, birth order, the year of the 11th gestational week, any history of hay fever or pollen allergy in the biological mother, and maternal smoking during pregnancy were included in some analyses as covariates (V). The year of the 11th gestational week was used as a crude indicator for annual pollen exposure, the categorisation of which was based on the comparability of the pollen measurements across the years (see above) and on the measured annual cumulative pollen counts from 2002 to 2005. Pollen allergy in the biological mother was classified as follows: ‘No pollen allergy’ and ‘Yes, either self-perceived or physician-diagnosed pollen allergy’. The mother’s smoking during pregnancy was categorised as ‘No’, ‘Yes, occasionally’, and ‘Yes, regularly’.

The parents were asked in the questionnaire whether the child’s biological mother, biological father or both had ever been found to have asthma or any allergic or hypersensitive disease (atopic rash, animal dust allergy, hay fever/pollen allergy, asthma or food allergy). The alternative responses were ‘no’, ‘yes, self-perceived’, ‘yes, physician-diagnosed’ and ‘not known’. These allowed the following categories to be formed: 1) physician-diagnosed allergic disorder (‘yes, physician-diagnosed’), 2) self-perceived allergic disorder (‘yes, self-perceived’ but not ‘yes, physician-diagnosed’), 3) no allergic disorder ever perceived (‘no’) and 4) unknown (‘not known’, or none of the other alternatives). The parent was classified as having ‘allergic asthma’ if he or she had physician-diagnosed asthma and a physician-diagnosed inhalant allergy (animal dust allergy or hay fever/pollen allergy). Based on the above, the following phenotypes were defined for the parents:

a) FA symptoms (self-perceived or physician-diagnosed FA)

b) Physician-diagnosed allergic manifestations other than FA (atopic rash, animal allergy, hay fever/pollen allergy or allergic asthma)

c) Any allergy (any of the above conditions)

Atopic rash and other allergic manifestations were solely based on the parents’ own reports of a diagnosis made by a physician, and no additional documentation
of IgE-mediated sensitisation was available. The children were classified according to the parents’ phenotype: 1) neither, 2) only mother, 3) only father, 4) both parents and 5) missing (complete data on both parents were required for phenotypes A and B). Any allergy (C) was classified according to phenotypes A and B if at least one manifestation of these allergies in either parent was mentioned. A variable was also created expressing the ‘number of allergic manifestations’ in both parents, given that complete data were available on both parents. This variable representing the severity of the parents’ allergic disease was based on the consideration that an allergic predisposition may manifest itself in different organs with a multitude of symptoms and that more severe the predisposition is, the broader the spectrum of manifestations will be.

4.5 Statistical analysis

The lifetime prevalences of FA and FHS up to the time of the survey were estimated according to the parents’ answers to the pertinent questions on food-associated symptoms with classified food items, and on whether a physician had diagnosed FA or FA symptoms had been perceived by parents only (II). The prevalence ratios with approximate 95% confidence intervals (based on the Wald statistic for the logarithm of the risk ratio) were computed by function `twoby2` of the Epi package (Carstensen et al. 2010) of the R environment (releases 2.5.1 to 2.9.2) (R Development Core Team 2010). The filling dates of the questionnaires were presented in a Lexis diagram (I), which was created by the Epi package of R (Carstensen et al. 2010).

The cumulative incidences of the outcomes were estimated by the Kaplan-Meier method for survival analysis using the survfit function of the survival package of R (Therneau & Lumley 2009), based on parental recollections of the age when food-associated symptoms had first been observed. The cumulative incidences of FA testing and those of a positive test result by age were also estimated by the Kaplan-Meier method (Clayton & Hills 1993)(III-V).

The outcome event in these analyses was taken to be either the first parent-reported food-associated symptoms or subsequent physician-diagnosed FA (II-III), the first FA test performed (III, V) or the first positive result observed (III-V), respectively, and the event age was the child’s age on the date of that event. The risk time began at birth and ended at the event age if an event occurred. Among children in whom that event was not observed, the risk time ended with censoring on the closing date of data collection (30 September 2006). In comparison of the
parents’ reports and test results, the risk time ended with censoring on the date when the parents filled the questionnaire (III). In the separate Kaplan-Meier analyses of the incidences of the different test methods were assumed independent censoring method. The cumulative incidences of each outcome in groups defined by categories of various determinants (II-V) were estimated by the Kaplan-Meier method using function `survfit` available in `survival` package of the R software release 2.9.2 (Clayton & Hills 1993, R Development Core Team 2010).

The incidence of first test and that of the first positive result were regressed on the relevant demographic factors using a Cox model (Aitkin et al. 2009, Clayton & Hills 1993, Greenland 1998) with the help of the `coxph` function in the R `survival` package (Therneau & Lumley 2009), in which the assumption of proportional hazards was also assessed by inspecting the cumulative hazard plots obtained from the Kaplan-Meier analyses (III-V).

A method of competing risks was applied in the analysis of the cumulative incidences of the first test method used (sIgE, SPT or OFC) and the method yielding the first positive test result (III); the risk time ended with censoring on the date when the first one of these tests occurred (Clayton & Hills 1993, Greenland 1998).

In the Kaplan-Meier analysis, in which the incidences of positive FA tests were presented according to the season of the 11th gestation week (V), the missing values on the duration of pregnancy were imputed employing the mean duration in the answers given in the questionnaire survey, i.e. 278 days.

Before the simulations for the seasonal models and estimating their amplitudes (see below), the missing data of duration of gestation were imputed by multiple imputation (Aitkin et al. 2009, Thomas 2009). Computations in the analysis of imputed data were performed using the `mitools` package in the R environment (Lumley 2009, 2010). The results concerning both the entire study population and the subpopulation of the complete cases were reported. The script for this purpose was developed by Professor Esa Läärä, and the method is described by him in detail in the statistical appendix of Publication V.

**Seasonal modelling**

Seasonal variations in the incidences of the first positive tests both by the month of birth and by that of the 11th gestational week were further analysed with the Cox proportional hazards model, including two periodic terms with the length of one year and half a year, respectively, with gender and birth order as covariates.
(V). This second-order harmonic model was fitted using function `coxph` in the `survival` package of R (Therneau & Lumley 2009). The predicted daily incidence rates were calculated from the fitted models and the ratio between the highest and the lowest predicted rate was taken as the estimated relative amplitude of the seasonal variation. The 95% confidence intervals for the amplitudes were approximated using a simulation of 10 000 samples from an assumed multivariate Gaussian distribution for the parameter estimates of the harmonic model (Vaiserman et al. 2007). Circular correlation coefficients (Jammalamadaka & Sengupta 2001) were computed by using function `circ.cor` in the `CircStats` package of R to describe the seasonal associations between the time of the first FA test with the time of the 11th gestational week and the date of birth.

**Cohen’s kappa**

Cohen’s kappa coefficient was used to describe the agreement between two categorical variables (Fleiss et al. 2003); parents’ report on FA testing and the tests, which had been collected in the area (I). Landis and Koch (1977) have interpreted values of Cohen’s kappa greater than 0.75 as excellent agreement beyond chance (Fleiss et al. 2003).

### 4.6 Ethical aspects, permissions, and data protection

Despite that the data collection was solely based on the questionnaire survey and retrospectively collected test data from patient records, several ethical aspects had to be considered before and during the survey (Leufkens & van Delen 2005). The voluntary participation of the families, as well as their right to withdraw from the study at any time, was mentioned in a consent form accompanying the questionnaires sent to the target population. In the consent form, the parents were also informed that their decision to withdraw did not have any influence on their treatment or the treatment of any of their family members now or in the future. The letter accompanying the questionnaire included the following information to the parents: the aims of the study, the expected number of children in the target population, a brief description of the study, the source of the addresses of the study population, the voluntary participation, the names of the researchers involved in the study project, and at the end of the letter the name of the contact person (KP) and her phone number for additional information. The nurses were
advised to encourage or motivate the parents to participate and would remind them if needed, but were instructed not to press them in any way. The nurses were frequently reminded about this principle by the principal investigator during her regular visits in the child health clinics.

The study subjects were not exposed to any diagnostic procedures or other medical interventions because of the study. Therefore, the study was not supposed to cause any harm to the subjects, but rather was considered beneficial to the study population. None of the authors in the SKARP study group were involved in the medical care of the child population in the study area.

The patient record data were collected with the permission of the Ministry of Social Affairs and Health in Finland, which is the usual routine in studies of this type. The study protocol, questionnaires and information letter were reviewed by the Ethical Committee of The Northern Ostrobothnia Hospital District. The test results were linked to the questionnaire data using the PIC only if the parents had not refused data linkage. The parents were informed of the study design and possible follow-up phases 5 and 10 years later, and their permission was requested for any future record linkage. In accordance with the Data Protection Act, a notification of collecting data from the patient records was sent to the Data Protection Ombudsman beforehand. Permissions for co-operation were obtained from all eleven health care centres in the study area. A notification of the study was given to the ethical committees of the three Hospital Districts involved before the study began.

Data protection and data security are currently an important field of ethics in the register and questionnaire surveys which include identification data. In the SKARP study, these were carefully planned and these rules are carefully followed e.g. the data analyses were performed on a computer that was never connected to the internet. All datasets including identification items were encrypted, and in accordance with the permission given by the Ministry of Social Affairs and Health, only the research team and two computer specialists were allowed to see the data with PICs and other identification data. The datasets, PICs or any other data enabling identification were or will never be sent by e-mail. The questionnaires are stored and the data protection of them is guaranteed by the Institute of Health Sciences, University of Oulu.

The record linkages follow the study plan and have been performed for the purposes described in the permissions (see above), and the information of the study focus given to the target population. The data from each returned questionnaire were compared to the population register data to ensure that it
concerned the intended child of the parents to whom the questionnaire had been sent. The questionnaire datasets and those of the allergy tests were prepared for the analyses by adding a study ID to each of them and removing any personal identification data. The variables of the questionnaire survey and the results of the allergy tests were merged using the study IDs. The children whose parents had prohibited this linkage (see above) were excluded from any linked analyses.
5 Results

The chapter on the results begins with the comprehensive presentation of the estimates on the coverage of data collection and participation rates of the SKARP study (I), followed by the occurrence estimates of food-associated symptoms, FA testing and FAs (II-III) and further followed by two basic risk factors, inheritance (IV) and seasonality (V). The publications are quoted as Roman numerals (I-V) followed by the number of the table or figure referring to the paper in question.

As a result of the age range and the focus of each publication, the number of subjects (N) had some variation in the denominator (Table 6). The number of tested subjects (n) and those with positive results (n) also varied according to the relevant end date of the follow-up time.

Table 6. Variability in the number of subjects in the published papers of the SKARP study depending on availability of data sources, required parental consent to data linkage, ranges in follow-up times and ages of subjects.

| Focus of the paper (I-V) | Age (years) | Register data N | Questionnaire data (participants) Not refused data linkage Complete cases | Test data on FA tests¹ Not refused data linkage All By the date of participation |
|--------------------------|-------------|-----------------|-----------------------------|---------------------------------|---------------------------------|
| I Methods and participation | 0–4         | 5973            | 3952                        |                                 |                                 |
|                          | 1–4         | 4779            | 3308                        | 3262                            | 4733                            | 750                             |
| II Occurrence of FA and FHS | 1–4         | 4779            | 3308                        |                                 |                                 |
| III Occurrence of FA testing | 0–4        | 5973            | 3899                        | 3899                            | 669                             |                                 |
|                          | 1–4         | 4779            | 3262                        | 3172                            | 3262                            | 523                             |
| IV Inheritance | 0–4        | 5973            | 3800                        | 3800                            | 651                             |                                 |
| V Seasonality | 0–4        | 5973            | 3254                        | 3920                            | 961                             |                                 |

¹ Test data comprised only the children, whose parents had not refused the data linkage between the test data and the questionnaire data.
² The subjects on whom all necessary data were available
5.1 Coverage of data collection and participation rates (I)

Coverage of data collection

The study population comprised the 5973 children on whom data were obtained from the Population Register (Table 6, Figures 3 and 4). The population register data covered 4779 children, aged 1 to 4 years. According to official population statistics, this figure is 99% of the children of the corresponding ages living in the study area at the end of 2005 (Statistics Finland 2008). Due to migration and slight difference in age ranges, these child populations are not exactly the same, but the small difference between these numbers indicates an almost complete coverage of the intended study population. Only 0.9% of the baseline questionnaires were returned from a town or a commune other than the addresses obtained from the Finnish Population Register: 5 outside the study area and 24 from another town or commune inside the study area. Almost all (1167/1189) newborn infants who were born in the area were still resident in the study area in August 2006; 46 had moved inside the study area, whereas 22 newborn infants moved out of the study area and 5 moved into the study area after and before one month of age, respectively.

Data linkage was performed for altogether 5920 (99%) children of the SKARP population (Table 6), thus excluding those 53 whose parents refused to allow their PICs to be used for the linkage. Altogether 10 009 records of allergy tests performed on 1252 children were found (Figure 4). Out of the latter, 941 (including 6 neonates) had been tested first before replying to the questionnaire, or before they should have replied in case of non-respondence. A comparison of the parents’ answers in the questionnaire with the test data showed that the collected test results comprised an estimated 89% (N=553) of the children in the area who, according to their parents’ report, had undergone at least one allergy test (N=623) by the time of responding to the questionnaire. The parents of 86 children for whom a record of an allergy test was actually found (13% of the children tested) failed to report this. For 3188 children, no record of any performed test was found in the area, nor did the parents report any. Cohen’s kappa coefficient (0.85) showed reasonably good agreement between parental reporting of allergy tests and the finding of a record of an allergy test having been performed. According to the parents, only <1% of the participants had been tested solely outside of the geographical area concerned.
Participation rates during the survey

During the whole survey, the participation rates in the first, second and third waves stayed at quite consistent levels, except for slightly lower rates among children born in December and March (I: Figure 3). The spread in the dates of filling and returning the questionnaire among the 1- to 4-year-olds by age and calendar time is illustrated in a Lexis diagram (I: Figure 2). Clusters distinguishable in the diagram and the two peaks in the distribution of the children’s age difference between the filling date and the target age (Figure 6) reflect the dates of posting the questionnaires from the research institute. Most of the children visited the child health clinic close to their anniversary, but the exact timing of the visit and returning the questionnaire varied. Clusters in the Lexis diagram located at 4 to 5 months later on (I: Figure 2), and the second peak in the histogram of the age differences (Figure 6), are associated with the timing of responses to the reminder questionnaires. The parents of newborn infants received the questionnaire from the child health clinics, and no reminder questionnaires were sent, hence no secondary clusters are seen for them. In all age groups, the dates of interviews were close to the birthdays and the annual visit to a child health clinic. The finding was similar regarding the dates of the questionnaires on elimination diets.

The overall response rate in the questionnaire survey was 66%; 54% among the newborn infants and 69% among the 1- to 4-year-old children. The participation rates were two percentage points higher among children whose mothers’ native language was Finnish than among the entire population.

The nurses interviewed the parents of altogether 651 children, 4 of whom were parents of newborn infants. The parents of 382 children had forgotten to return the baseline questionnaire during the follow-up visit, but were willing to participate and be interviewed at the clinic (Figure 4, I: Table 1). These interviews improved the overall response rate from 51% to 59%, from the first to second wave among the 1- to 4-year-olds. Most of the interviewed parents (81%) had also returned the baseline questionnaire. The reminder questionnaires improved the participation rates by an additional 10 percentage points from the second to the third wave, from 59% to 69%.
Interviews and the diet questionnaire

The parents of altogether 442 children were interviewed about the type of their child's hypersensitivity symptoms perceived within the last 12 months and assumed to be associated with a food item (I: Figure 1). These interviews were conducted with 71% of those who had reported food-associated symptoms in their children within the last 12 months.

The diet questionnaires were returned by 68% (2257/3308) of the participating children aged 1 to 4 years (Figure 4). The response rate of the diet questionnaire was lower than the first wave participation rate to the baseline questionnaire, even though the diet questionnaire was shorter and quicker to fill in.

![Fig. 6. The distribution of the difference (in months) between the child's age at the date when the parents filled in the baseline questionnaire, and the target age, i.e. the child's anniversary which determines the expected date of the annual visit to the child health clinic (among children aged 1 to 4 years) is shown in the figure.](image)

Participation according to a history of allergy testing

Children on whom some allergy tests were performed either for food or other allergies, had a clearly lower response rate in the first wave of returning the questionnaire (I: Table 2). However, in the second wave, the participation was clearly improved among children with a history of FA tests. Thus the final participation rate of children tested for FA was similar to that of children without
any allergy tests. Even after the third wave, the participation remained lower among children with a history of allergy tests for other than FAs. In these groups, participation rates showed a similar decrease with an increase in age, the number of siblings, and the child’s birth order (data not shown).

5.2 Occurrences of food hypersensitivities and food allergies (II)

Prevalences of food allergies and food hypersensitivities

Based on parents’ reports, the overall lifetime prevalence of physician-diagnosed FA was 9% and an additional 21% of children had FHS perceived by their parents only (Table 7). The prevalence of physician-diagnosed FA was higher in boys than in girls (RR 1.37; 95% CI 1.11 to 1.71), and appeared lower among the one-year-olds than among older children. Likewise the FHS perceived by the parents only was least common among the one-year-olds, but this proportion seemed less dependent on gender and the number of siblings (II: Table 1, II: Figure 1).

Milk and egg were the most commonly reported essential food items causing symptoms, for 13% and 6% of participants, respectively (Table 7). The most commonly reported non-essential food items causing food-associated symptoms were strawberry, chocolate and tomato (12% for these items pooled into one group), fruit (7%), and citrus fruit (6%). Symptoms associated with non-essential food items, in contrast with essential food items, were far more often observed by parents only than diagnosed by a physician. Nut was the most often eliminated food item from the diet, although perceived symptoms associated with nut were reported in <1% of the children.

The most common single essential food item causing symptoms was milk; in 4% of participating children as diagnosed by a physician and in 5% as observed by the parents only (II: Table 3). Milk in combination with other essential foods was responsible for FA in 3% of the subjects. Egg alone had caused FA in <1% of the subjects and FHS in 2% and in combination with cereals 1% and <1%, respectively. Symptoms associated with non-essential food items alone (13%) were almost entirely observed by parents alone.

Two thirds of all physician-diagnosed FAs and one third of all FHSs perceived by the parents only were for milk. One fourth of all FAs were for wheat and another essential food item, but wheat alone comprised only 3% of all FAs.
Table 7. Prevalence (%) and number (n) of subjects with symptoms associated with essential and selected non-essential food items among children aged 1 to 4 years. The total number of children providing adequate data was 3308.

<table>
<thead>
<tr>
<th>Food items</th>
<th>Physician-diagnosed</th>
<th>Parent-perceived</th>
<th>Never tasted a food</th>
<th>Never perceived</th>
<th>Illogical answers(^1)</th>
<th>Missing data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>Essential food items</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk or milk products</td>
<td>6.4 (213)</td>
<td>6.4 (212)</td>
<td>0.8 (27)</td>
<td>85 (2798)</td>
<td>0.1 (2)</td>
<td>1.7 (56)</td>
</tr>
<tr>
<td>Egg</td>
<td>2.8 (94)</td>
<td>3.4 (113)</td>
<td>5.0 (164)</td>
<td>86 (2843)</td>
<td>0.3 (11)</td>
<td>2.5 (83)</td>
</tr>
<tr>
<td>Wheat</td>
<td>2.6 (86)</td>
<td>1.5 (51)</td>
<td>0.3 (10)</td>
<td>93 (3077)</td>
<td>0.2 (5)</td>
<td>2.4 (79)</td>
</tr>
<tr>
<td>Barley, Rye</td>
<td>1.9 (64)</td>
<td>1.6 (53)</td>
<td>0.8 (26)</td>
<td>93 (3083)</td>
<td>0.1 (2)</td>
<td>2.4 (80)</td>
</tr>
<tr>
<td>Other cereals; Oat, maize, rice, millet, buckwheat</td>
<td>1.4 (46)</td>
<td>1.8 (58)</td>
<td>0.2 (8)</td>
<td>94 (3110)</td>
<td>0.1 (4)</td>
<td>2.5 (82)</td>
</tr>
<tr>
<td>Total</td>
<td>8.4 (279)</td>
<td>9.3 (307)</td>
<td>4.8 (158)</td>
<td>76 (2513)</td>
<td>0.1 (4)</td>
<td>1.4 (47)</td>
</tr>
<tr>
<td>Non-essential food items</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nut</td>
<td>0.2 (7)</td>
<td>1.5 (49)</td>
<td>25.5 (845)</td>
<td>70 (2322)</td>
<td>0.4 (13)</td>
<td>2.2 (72)</td>
</tr>
<tr>
<td>Legumes; Peanut, peas, bean, soy, lentil</td>
<td>1.1 (36)</td>
<td>2.6 (87)</td>
<td>4.5 (149)</td>
<td>89 (2949)</td>
<td>0.5 (18)</td>
<td>2.1 (69)</td>
</tr>
<tr>
<td>Fish</td>
<td>0.6 (20)</td>
<td>4.0 (132)</td>
<td>3.2 (105)</td>
<td>90 (2982)</td>
<td>0.1 (4)</td>
<td>2.0 (65)</td>
</tr>
<tr>
<td>Strawberry/Chocolate/Tomato</td>
<td>0.8 (28)</td>
<td>11.6 (383)</td>
<td>4.1 (134)</td>
<td>81 (2677)</td>
<td>0.6 (21)</td>
<td>2.0 (65)</td>
</tr>
<tr>
<td>Citrus fruit</td>
<td>0.5 (15)</td>
<td>5.6 (184)</td>
<td>8.8 (291)</td>
<td>83 (2753)</td>
<td>0.1 (2)</td>
<td>1.9 (63)</td>
</tr>
<tr>
<td>Fruit; apple, pear, cherry, peach, banana</td>
<td>0.7 (22)</td>
<td>6.5 (215)</td>
<td>0.1 (3)</td>
<td>91 (2998)</td>
<td>0.2 (6)</td>
<td>1.9 (64)</td>
</tr>
<tr>
<td>Total(^2)</td>
<td>9.3 (308)</td>
<td>20.9 (693)</td>
<td>19.0 (630)</td>
<td>50 (1638)</td>
<td>0.1 (4)</td>
<td>1.1 (35)</td>
</tr>
</tbody>
</table>

\(^1\) A child must have eaten or tasted a given food item to be eligible as having food allergy or hypersensitivity to that particular item.

\(^2\) The total includes the items listed in this table but also all the other food items explicitly inquired in the baseline questionnaire (e.g. root crops, spices, additives, berries, meat and poultry).
Elimination diets

Restrictions on non-essential food items without any indication of FA or FHS were more prevalent than on essential food items (II: Table 3). The latter were typical among the one-year-old children, most commonly applying to egg or milk (18% and 3% of all one-year-olds, respectively). At least one essential food item had been eliminated from the child’s diet without any indication of symptoms in 4% of participants, and 15% of the children adhered to an elimination diet with regard to certain non-essential items, most commonly nuts.

The prevalences of the children with primarily followed elimination diets (never tasted a food item without having been observed any hypersensitivity symptoms associated with the food item in question) among all the participants declined from 72% to 8% in the age groups of 1- to 4-year-old children, respectively. Children with a physician-diagnosed FA had restrictions in diets more commonly than those with only parent-perceived FHS (41% vs. 26%).

Cumulative incidences of food allergy by age, gender and number of siblings

The cumulative incidence curves by age for physician-diagnosed FA, estimated by the Kaplan-Meier method, increased steeply during the first year of life but nearly stabilized by the age of 1.5 years (II: Figure 1). The curves were at an equal level across the different age groups at survey, but reached a higher level among boys than girls and also among firstborn children than the others. The age of the child when food-associated symptoms were first perceived was missing or illogical for 7% out of all reported cases of FAs. As this proportion had only negligible variation by the age of the child at the time of the survey, no essential bias was induced to the relative comparisons of the curves between the groups of interest, although the absolute levels of cumulative incidences were slightly underestimated. In contrast, the age at the first occurrence of symptoms was missing for 25% of the children reported to have parent-perceived FHSs only. As this proportion additionally had an increasing trend from 19% of the one-year-olds to 29% of the four-year-olds at the time of the survey, the analogous Kaplan-Meier curves for FHS, like those for FA, would be severely biased and are thus not presented.
5.3 Food allergy testing (III)

Altogether 961 children from 887 families (19% of all families) had undergone at least one FA test in the final study population. In all, 5849 FA tests had been performed (mean 6.1, range 1 to 37 tests per child) on 1989 testing occasions (mean 2.1, range 1 to 13 occasions per child) (Table 8). The number of FA tested subjects and that of individual FA tests were highest for sIgE and lowest for OFC, while the proportion of positives out of the individual tests and the tested subjects were lowest for sIgE and highest for OFC. In 80% of the OFC-tested children, the OFC had been preceded by sIgE/SPT. The OFC was the first positive test in 28% of the positive tests. Up to the age of 4 years, the incidences of any test, sIgE, SPT, and OFC for essential food items were 17%, 12%, 7% and 4%, and for other food items 9%, 7%, 3% and 1%, respectively.

Table 8. Number of food allergy tests and positive results with proportion of positives out of tested subjects (PPT) and out of the test results (PPTR) among the study population (N=5920) living in South Karelia.

<table>
<thead>
<tr>
<th>Test method</th>
<th>Subjects</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tested n</td>
<td>Positives n</td>
</tr>
<tr>
<td>Specific immunoglobulin E</td>
<td>812</td>
<td>204</td>
</tr>
<tr>
<td>Skin prick test</td>
<td>420</td>
<td>138</td>
</tr>
<tr>
<td>Open food challenge</td>
<td>251</td>
<td>181</td>
</tr>
<tr>
<td>Any test</td>
<td>961</td>
<td>390</td>
</tr>
</tbody>
</table>

Among children aged 1 and 2 years, the cumulative incidences of food-associated symptoms exceeded 25% by the age of 1.5 years (III: Figure 1). Since these curves in older age groups were severely affected by probable recall bias, they were not presented. All the incidence curves of FA testing by the age groups rose steeply during the first year of life and levelled off thereafter, reaching 18% by the age of 4 years. The incidence of FA testing was slightly higher among the participants than among non-participants (19% vs. 17%).

Overall, boys had a 30% higher risk to be FA tested than girls (III: Figure 1), the direction of the difference persisting for all test methods. Similar incidence figures were seen according to FA tests for any essential food items and separately for milk, too. The cumulative incidence curves of FA testing were at a slightly higher level in the firstborn child than the others (19% vs. 18%).
The incidence of sIgE/SPT testing of the children was more than twofold higher if both biological parents and almost twofold higher if either biological parent had been reported any allergic manifestation than in the children of non-allergic parents (III: Table 1). By the age of 2 years, the relative rates of the food-associated symptoms showed similar figures in children according to their parents’ allergic phenotype. The incidence of OFC testing was fourfold higher in the children of two allergic parents and twofold higher if either parent had reported an allergic manifestation than in the children of non-allergic parents. Similar incidence figures according to different FA test methods and parental allergies were observed for milk or any essential food items, too. The relative rates of the symptoms and FA testing according to different test methods were also multiplicatively associated with the number of allergic manifestations in parents (Figure 7).

FA testing was slightly more common in children whose parents had a healthcare occupation than other occupations (21% vs. 19%) (III: Table 1). A weak positive association was also seen between FA testing and the educational level of the parents. The total risk of FA testing was less dependent on the place of residence, however, although sIgE tests had been performed more often than SPTs outside the provincial capital.

The incidence of any FA test or a primary test (sIgE/SPT) for milk or essential food items was 90% in children reportedly having a physician-diagnosed FA for these food items (III: Table 2). In children with a physician-diagnosed milk allergy, the incidence of an OFC (in hospital) for milk was 47% and that of a positive OFC was 40%. The majority of the parents of these children with a positive OFC for milk (77/84) or for any food item (92/100) also reported a physician-diagnosed FA. Almost all (133/138) OFC-tested children had been reported either having a physician-diagnosed FA or FHS perceived by the parents only. Among the children with a physician-diagnosed FA, the incidence of a positive FA test for non-essential food items was 37%, and only for milk and an essential food item did it exceed 65%.

By the age of 4 years, the incidences of a positive sIgE/SPT and OFC were 7% and 4% (Table 9), respectively. The incidences of a positive OFC for essential and non-essential food items were 3% and 1%, respectively. Although the lifetime prevalence of children with symptoms related with non-essential food items was 20% and another 21% had never tasted some of these food items, the cumulative incidence of a positive sIgE/SPT for these food items was only 2%. The incidence of a positive FA test was 44% higher for boys than for girls, and slightly higher
for the firstborn than for the others and for the participants than for the non-
participants (III: Figure 1).
Table 9. Summary table presenting the number of subjects (n) and the mean lifetime prevalences of parentally reported food allergies (FA) and food hypersensitivity symptoms perceived by parents only (FHS) (N=3308; II:Table 2) and the incidences of FA testing and positive FA tests for different food items among participating children aged 1 to 4 years up to the age of filling in the questionnaire (N=3262; III:Table 2) and among the entire population up to the age of 4 years (N=5920).

<table>
<thead>
<tr>
<th>Food item(s) and population</th>
<th>Parental reports</th>
<th>FA tests</th>
<th>Any test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never tasted</td>
<td>FHS</td>
<td>FA</td>
</tr>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>Milk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>1 (27)</td>
<td>6 (212)</td>
<td>6 (213)</td>
</tr>
<tr>
<td>Entire population</td>
<td>16 (848)</td>
<td>3 (156)</td>
<td>4 (209)</td>
</tr>
<tr>
<td>Egg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>5 (164)</td>
<td>3 (113)</td>
<td>3 (94)</td>
</tr>
<tr>
<td>Entire population</td>
<td>8 (426)</td>
<td>3 (154)</td>
<td>0.2 (7)</td>
</tr>
<tr>
<td>Essential food items</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>5 (158)</td>
<td>9 (307)</td>
<td>8 (279)</td>
</tr>
<tr>
<td>Entire population</td>
<td>15 (878)</td>
<td>5 (271)</td>
<td>4 (235)</td>
</tr>
<tr>
<td>Non-essential food items</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>21 (679)</td>
<td>20 (671)</td>
<td>3 (101)</td>
</tr>
<tr>
<td>Entire population</td>
<td>9 (443)</td>
<td>2 (82)</td>
<td>1 (57)</td>
</tr>
<tr>
<td>Any food item</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>19 (630)</td>
<td>21 (693)</td>
<td>9 (308)</td>
</tr>
<tr>
<td>Entire population</td>
<td>18 (948)</td>
<td>6 (289)</td>
<td>5 (251)</td>
</tr>
</tbody>
</table>
Fig. 7. Relative rates (RR) of the child’s first food-associated hypersensitivity symptoms (A; III:Figure 2A), the first food allergy (FA) test (A-B; III:Figure 2), the first positive FA test for any food item (C; IV:Figure 2A) and for milk (D; IV:Figure 2B) are presented according to the number of allergic manifestations in both biological parents. OFC, open food challenges; sIgE, specific immunoglobulin E antibodies; SPT; skin prick tests for a food item and 95% confidence intervals of relative rates are shown by vertical lines.

5.4 Inheritance of food allergies (IV)

The questionnaires of altogether 3800 (97%) participating children contained some information on the allergic conditions of the child’s biological parents (Table 6). 73% of these children belonged to families from which a single child was recruited to the survey, and 80% of the participants were the only participants
from their families. In 49 families, multiple participants had been FA tested, and in 11 of these families, multiple participants had a positive FA test result. The prevalence of maternal asthma with inhalation allergy was 6.5% and that of paternal asthma with inhalation allergy 4.6%.

The cumulative incidence of any positive FA test in the children by 4 years of age was threefold higher if both biologic parents and twofold higher if either parent were reported any allergies than if neither parents were reported allergies (Table 10). The incidences of a positive sIgE/SPT for any food item and separate incidences regarding essential food items, milk and egg followed the same pattern. Associations of a similar kind were repeated for each individual manifestation of allergy in the biological parents and FA test results in their children (IV: Table 1). The incidence of positive OFCs was higher in the case of each separate manifestation of maternal than that of paternal allergy alone, the finding being largely similar regarding essential food items, and milk in particular.

Table 10. Numbers (N) of children participating in the questionnaire survey, the cumulative incidences (%) up to 4 years of age and gender and birth order adjusted relative rates (RR) of a positive result in food allergy (FA) tests (during the follow-up) in relation to any allergy in the biological parents. Numbers of cases (n) and 95% confidence intervals are shown in parentheses.

<table>
<thead>
<tr>
<th>Parental allergy</th>
<th>N</th>
<th>First positive FA test for any food item</th>
<th>Any FA test</th>
<th>sIgE or SPT</th>
<th>OFC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% (n)</td>
<td>RR (95%CI)</td>
<td>% (n)</td>
</tr>
<tr>
<td>None</td>
<td>1502</td>
<td>4.0 (57)</td>
<td>1</td>
<td>3.0 (42)</td>
<td>1</td>
</tr>
<tr>
<td>Mother only</td>
<td>1093</td>
<td>9.1 (93)</td>
<td>2.3 (1.6, 3.3)</td>
<td>2.3 (1.6, 3.2)</td>
<td>4.9 (49)</td>
</tr>
<tr>
<td>Father only</td>
<td>693</td>
<td>9.1 (58)</td>
<td>2.3 (1.6, 3.3)</td>
<td>2.4 (1.6, 3.7)</td>
<td>3.1 (20)</td>
</tr>
<tr>
<td>Both</td>
<td>512</td>
<td>14.5 (65)</td>
<td>3.5 (2.4, 5.0)</td>
<td>3.2 (1.8, 5.6)</td>
<td>6.2 (29)</td>
</tr>
<tr>
<td>Total</td>
<td>3800</td>
<td>7.9 (273)</td>
<td>6.2 (209)</td>
<td>3.6 (126)</td>
<td></td>
</tr>
</tbody>
</table>

* Including specific immunoglobulin E antibodies (sIgE) for any food item, skin prick tests (SPT) for a food item or open food challenges (OFC).

**Number of allergies in parents and positive FA tests in their offspring**

The incidence of positive FA tests increased with the number of allergic manifestations among the parents (Figure 7). The Cox analysis showed that the incidence of any positive FA test for any food item and separately for milk and egg (IV: Table 2), too, increased by a factor of 1.3 for each additional allergic
manifestation in the biological parents. The incidence of both a positive sIgE/SPT to a food item and a positive OFC was associated with the number of allergic manifestations in the parents. The incidence of a positive OFC and separately that of a positive sIgE/SPT for milk increased also by 1.3 for each additional parental allergy.

**Positive predictive values of food allergy tests**

The positive predictive values of FA tests (PPV) were 45% if the mother alone and 43% if the father alone, and 48% if both parents had an allergic manifestation, and 33% if neither parents had an allergic manifestation. A 50% higher risk for a positive result in any FA test was found in the children of one or two allergic parents than in the children of non-allergic parents. The PPVs were also higher for sIgE, sIgE/SPT and any test in the biological children of allergic than non-allergic parents (IV: Table 3). The PPVs for SPTs and OFCs were higher for the children of non-allergic than allergic parents, but due to low numbers, this finding remained equivocal.

5.5 **Seasonal risk factors for food allergies (V)**

By the age of 4 years, the cumulative incidence of a positive result in any FA test reached 11% among the children who had experienced the 11th gestational week in April-May, while the incidence remained lower (6–8%) among all other children. These patterns were largely similar for the sIgEs and OFCs separately, too. The smoothed incidence from the fitted harmonic model for any positive FA test, and for a positive sIgE test alone, was highest in the children whose 11th gestational week was in April-May and lowest in those for whom it was in October-December.

The amplitude of seasonal variation in any positive FA test, estimated as the relative ratio between the peak and trough of the smoothed incidence curve over the year, was 2.03 (95%CI 1.52 to 2.76). A largely similar seasonal pattern was also observed in a positive sIgE for any food item (RR amplitudes being 2.47; 95%CI 1.68 to 3.71), these amplitudes being especially pronounced for milk (3.07; 95%CI 1.81 to 5.50) and egg (3.03; 95%CI 1.86 to 5.18). Similar curves and amplitudes were observed according to the month of birth, as were the amplitudes according to the month of the 11th gestational week, but the peaks were in November-December and the troughs in May-June (V: Table 2).
The RRs of FA testing by any test or sIgE showed a more modest seasonal variation according to the season of birth and that of the 11th gestational week than the RRs of the positive tests (Figure 8,V: Table 1). Only a weak association was found between the test date and the season of birth or that of the 11th gestational week (circular correlations 0.18 and 0.17, respectively).

A pronounced seasonal variation of environmental pollen concentrations and sunlight exists in Finland (Figure 8). The seasonal peaks in mean temperature, day length and sunshine hours occur between in May to July, and the concentrations of alder and birch pollen are highest in April and May and are followed by smaller increases in grass and mugwort pollen 2–3 months later. In the years 2002–2005, during which the measurements of pollen counts were comparable, the annual cumulative sums of pollen grains (including birch, alder, mugwort and grass) per m³ were 61 000, 30 000, 29 000 and 27 000, respectively. When the year of the 11th gestational week was added to the harmonic model, the estimated RRs of a positive FA test and separately that of a positive sIgE test were higher for children whose 11th gestational week was in 2002 than for those for whom it was in 2003 to 2005 (RR 1.16; 95%CI 0.90 to 1.49 and RR 1.69; 95%CI 1.19 to 2.40, respectively).
Fig. 8. Incidence of any positive food allergy (FA) test, FA testing, a positive test result in specific immunoglobulin E tests (sIgE) and sIgE testing by the month in which the 11th gestational week occurred (A), mean weekly concentrations of environmental pollen (averaged over the years 2002–5) (B) and the climatic pattern (C). The points in panel A indicate monthly estimates of relative rates (from the Cox model, adjusted for gender, birth order and year of 11th gestational week) and the continuous lines values smoothed with a 2nd order harmonic model (V: Figure 3).
6 Discussion

Population-based knowledge on the occurrences and risk factors of FAs has been scarce, although FA is often the first manifestation of allergic diseases in early childhood (Björkstén 2005, Cochrane et al. 2009, Rona et al. 2007, Sicherer 2002). The SKARP study quantified the occurrences of food-associated hypersensitivity symptoms, FA testing, positive test results and physician-diagnosed FAs in a general child population. The symptoms of FAs and FHSs were demonstrated to be common in the first few years of life. Although the heredity of other allergic manifestations had largely been recognised, the positive association between parental allergies and FAs in their offspring were quantified for the first time in a general population. Additionally, the spring season in the end of the first gestational trimester was found to predict sensitisation to food items in a general child population.

6.1 Methodological issues and solutions

Participation rates and selective participation

Low participation rates have been found to be a problem in observational epidemiological studies (Morton et al. 2006, Sandler 2002). A possible overrepresentation of FA or FHS among the participants has been thought to cause a bias for the occurrence estimates (Osterballe 2009, Rona et al. 2007). Stringent eligibility criteria and a large proportion of parents who had denied their consent to clinical investigations may have impacted the participation rates and the occurrences of confirmed FAs as well, thus the occurrence estimates should be interpreted and generalized with caution. The SKARP study population can be considered fairly representative for a general child population, because the inclusion criteria of the study were only the date of birth and residence in a given geographical area, based on the Population Register (Figure 3 and Appendix 3).

A recent meta-analysis discussed the methodological problems in the prevalence studies on FA and an obvious selection bias (Rona et al. 2007), but the self-selection bias has not previously been estimated. A possible selection bias was taken into consideration in the study plan and during the SKARP study. Both the parents of allergic and non-allergic children were equally encouraged to participate by a letter accompanying the questionnaire, by the regional
newspapers and by the regional television news. The baseline questionnaire of the present study was more difficult and demanding to fill for the parents of allergic than non-allergic children, which probably caused the lower first wave participation rate among the allergy-tested children. Without any co-operation with the child health clinics, the questionnaire study would probably have introduced some under-representation of the FA tested children and selection bias among the participants. The nurses presumably motivated similarly the parents of both allergic and non-allergic children to participate as they were advised to, but the parents whose child had a diagnosed or suspected allergic condition probably had a somewhat higher motivation to participate than the others. The reminder questionnaires (the third wave) improved the participation rates among both tested and untested children. In the end, only a slight overrepresentation of allergy tested children could be found among the participants (I, III). This points to a very minor selective effect, which is probably attributable to the equally distributed information given to the population before and during the survey.

Children’s allergies are probably not considered a highly sensitive subject either, and intrusive questions were avoided in the questionnaires. Furthermore, children in the present study were very young and were not expected to have a long history of very sensitive data in their patient records. Therefore, requesting a written consent for data linkage was not expected to have a great impact on the parents’ decision to participate, which had previously been suspected to be a reason for non-participation (Daniels et al. 2006, Edwars et al. 2002, Korkeila et al. 2001).

**Combining questionnaire survey with register data**

The questionnaire survey and register data together enabled the quantification of the phenomenon of FAs from two different perspectives. The questionnaire data represents parental comprehensions and perceptions of FAs in a general child population. The tests reflect attempts on the part of the parents (a perspective of population) and the physician (a perspective of diagnostic practices) to find out or confirm connections between eating a food item and symptoms.

Conducting all FA tests for all participants would have been unfeasible for several reasons, and most likely would have substantially declined the participation rate (Daniels et al. 2006, Johnke et al. 2006, Osterballe et al. 2005, Osterballe 2009, Roehr et al. 2004, Rona et al. 2007, Venter et al. 2008). Performing a large number of FA tests purely on scientific grounds on children
who had no indication of food-associated symptoms and some of whom had previously had a severe reaction to food items would be unethical, since neither SPTs nor sIgEs are painless tests and both SPTs and food challenges may cause systemic reactions (Bindslev-Jensen et al. 2004, Reibel et al. 2000, Valyasevi et al. 1999). The test data, albeit retrospectively collected, also enabled the description of the real life process of FA testing in the population.

The true coverage of test data collection in a population cannot be evaluated by any objective method. The allergy test data were compared with parents’ reports on skin tests, blood tests and food challenges. However, the coverage estimates must be interpreted with caution, as the parents cannot be expected to remember all the tests performed on their children or to recall the names of the tests correctly. The main purpose of the questions on allergy testing was to find out failures in the collecting process in any health care units, but no such a unit was found. The proportion of the failed reports increased according to the child’s age at the time of invitation, but the proportions of collected, reported and missing test data showed no systematic variations according to the other demographic background factors.

The combination of a questionnaire survey and register data offers a more versatile view of the outcome than each method alone. A questionnaire study is still the only feasible method of obtaining information on all perceived allergy symptoms and relevant exposure factors in a general population. However, since no objective method is available by which the prevalence of very mild symptoms of allergy could be estimated, the allergy symptoms perceived only by parents remain a subjective issue or opinion. On the other hand, only the IgE-mediated sensitisation to food items and the symptoms which repeatedly appear after eating a certain food item can be verified by the FA tests, as has been done in the previous studies (Tables 2–4, Appendix 3).

**Definition and misclassification of food allergies**

In the SKARP study, the phenomenon of FAs was quantified by different occurrence estimates based on the test data available in patient registers and the information given by the parents in the questionnaire survey. The physician-diagnosed FA is not always based on any objective tests at all (Figure 1), but a physician compares the results of the FA tests with a clinical history of symptoms associated with the food item in question. The physician-diagnosed FA is dependent on the test methods available and the food items used to be FA tested,
which emphasises FAs for essential rather than for non-essential food items (III). In the children of the same population, the occurrence of symptoms associated with non-essential food items was more frequently reported than the symptoms for essential food items (II). Therefore, the FAs for non-essential food items were probably underestimated among physician-diagnosed FAs due to testing practices.

Performing the FA tests in several laboratories with varying practices and procedures as well as different cut points might have caused some non-differential misclassification of the outcome. However, the heterogeneity of the test data in this regard should be quite independent of the exposure factors, e.g. parental allergies or gestational season (IV-V), and thus it most likely attenuated the estimates of the relative rates towards unity. Therefore, non-differential misclassification is at least partly counteracted by the possible biasing effect of any differential misclassification caused by a recall bias.

Co-operation with the child health clinics may have decreased the misclassification of the outcomes in a general child population. The public health nurses frequently observe and examine each child living in the geographically defined area. Thus the nurses have a special experience of FAs in the child population for which they are responsible. Moreover, the nurses are able to consult a physician in cases of suspected FA in a child, and they may advise the parents to contact a physician. The close co-operation with the child health clinics may have improved the quality of the data as well, because the public health nurses checked the questionnaires, completed missing items and interviewed the parents about their perceptions of food-associated symptoms.

The researchers attempted to reduce misclassification of outcomes by careful development of the questionnaires and the study design. In the questionnaire, all parents were given equal information on the organs where the symptoms might possibly emerge (II, IV). Recall bias, to which especially the mild symptoms were expected to be sensitive, was controlled by the study design; the survey was performed at the age when the occurrence of food-associated symptoms was expected to be highest. Yet, the question on the age when food-associated symptoms appeared at the first time was found to be affected by the obvious recall bias in two of the oldest age groups, concerning especially FHSs perceived by the parents only (II-III). The trend of declining participation rates depending on the age of the child may also reflect fading recollections, which were taken into account in analyses and must be taken into account in further study plans as well.
The lifetime prevalences of parental allergies, particularly parental FAs, may be affected by recall bias or a generation effect. However, the lifetime prevalences of allergic and non-allergic asthma in both parents were surprisingly well in line with a previous Finnish population survey (IV) (Pallasaho et al. 2005).

6.2 Occurrences of food-associated symptoms and food allergies

Comparison with occurrence estimates elsewhere

The main focus of the literature search was on the population-based studies on the occurrences of any FA and their risk factors. Before the occurrence estimates of the SKARP study and the previous studies can be compared, the following criteria modified in a spirit of the strengthening the reporting of observational studies in epidemiology (STROBE) guideline (Vandenbroucke et al. 2007) should be considered and fulfilled:

1. the study population is a representative part of general population, not chosen from hospital populations including patients with increased risk or selected according to some clinical characteristics
2. the occurrence estimates can be considered credible and comparable, because of sufficient participation rate; the outcome in question is not over- or underrepresented among participants, and this can be estimated by means of e.g. registers or given reasons for non-participation.
3. any primary selection or eligibility criterion has not biased the results and the study had originally been planned to address the occurrence of the outcome in question,
4. the study designs can be expected to produce comparable results of the outcomes, e.g. the birth seasons of the study population are not restricted to few months of the year, thereby all seasons of birth should be represented,
5. the age ranges of participants/subjects in the studies are sufficiently similar,
6. the outcomes include a similar variety of food items; not e.g. peanuts or milk only except when the aim is to compare FAs for these food items only,
7. FAs (or other outcomes) are defined and tested similarly, and
8. the statistical measures describing the occurrence estimates must be comparable; either point prevalences, lifetime prevalences or cumulative incidences at certain similar age point or by the same age.
The definition of outcomes has varied between different studies, and different test methods have been used to provide objective evidence of the outcomes (Tables 1–4). Some of the previous studies have also limited their focus to certain food items or reported FAs for selected food items only (Tables 2–4). The cumulative incidences or lifetime prevalences of self-reported food-associated symptoms were higher than the point prevalence of the same outcome (Tables 1–2). Likewise, the cumulative incidence of FA and sensitisation to food items in real life can be expected to be higher than the point prevalence of the same outcomes based on the clinical investigations performed according to a preconcerted schedule at certain age points.

According to the previous survey from the Isle of Wight and the SKARP study, elimination diets are quite frequently seen in early childhood (Tables 5, 7 and 9). A common reason for primarily followed elimination diets is probably part of the normal process of increasing the variety of food items stepwise. The prevalence of these diets was also higher in children who had a physician-diagnosed FA.

The cumulative incidence of FA testing reflects parental perceptions or physician-suspected FAs (Figure 1), which are relatively common in the area. However, the occurrence estimates of FA testing in real life are incomparable, since no previous information regarding this has been published thus far. According to both parental reports and FA test data, the symptoms associated with essential food items were more often diagnosed by a physician and FA tests more frequently performed for these food items than for non-essential food items. Essential food items (milk, cereals and egg) have an important role in cooking, in Finland, and are thus not easily avoided. The association between daily eaten essential food items and food-associated symptoms is not as easily perceived as an association between the symptoms and more rarely eaten non-essential food items (e.g. fish, fruits, berries or chocolate). In case it is necessary to eliminate all milk protein from the diet before the age of 2 years, cow milk must be substituted by a surrogate product. The costs of the surrogates are partly reimbursed by Kela, the Social Insurance Institution of Finland, to the parents of the milk-allergic child (subsection 4.1). Therefore both Kela and parents should have a motivation and a common financial interest to reach and confirm the diagnosis of milk allergy appropriately.

The prevalences of food-associated symptoms as estimated in the SKARP study are quite well in line with previous studies (Table 11). Although great variations were seen in the study designs (Appendix 3), the lifetime prevalences
of food-associated symptoms to any food item are quite consistent in Oslo, in the Isle of Wight and in South Karelia (the SKARP) by the age of 3 years, but slightly higher for the specified food items in South Karelia than elsewhere.

Table 11. Lifetime prevalences of food-associated symptoms according to the age of the child in previous studies and in South Karelia.

<table>
<thead>
<tr>
<th>Age and study area</th>
<th>Year of birth</th>
<th>N</th>
<th>Milk</th>
<th>Egg</th>
<th>Fish</th>
<th>Any food item</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oslo¹</td>
<td>1992-3</td>
<td>2803</td>
<td>7.5 (211)</td>
<td>1.5 (41)</td>
<td>1.2 (35)</td>
<td>19 (533)</td>
</tr>
<tr>
<td>The Isle of Wight²</td>
<td>2001-2</td>
<td>969</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Karelia</td>
<td>2004-5</td>
<td>853</td>
<td>11.0 (94)</td>
<td>4.6 (39)</td>
<td>3.8 (32)</td>
<td>23.2 (198)</td>
</tr>
<tr>
<td>2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oslo¹</td>
<td>1992-3</td>
<td>2803</td>
<td>11.6 (326)</td>
<td>4.4 (123)</td>
<td>3.1 (86)</td>
<td>35.4</td>
</tr>
<tr>
<td>South Karelia</td>
<td>2003-4</td>
<td>852</td>
<td>13.5 (115)</td>
<td>6.2 (53)</td>
<td>5.0 (43)</td>
<td>34.4 (293)</td>
</tr>
<tr>
<td>3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odense³</td>
<td>1999-2002</td>
<td>486</td>
<td></td>
<td></td>
<td></td>
<td>15 (74)</td>
</tr>
<tr>
<td>The Isle of Wight²</td>
<td>2001-2</td>
<td>807</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Karelia</td>
<td>2002-3</td>
<td>784</td>
<td>13.4 (105)</td>
<td>7.0 (55)</td>
<td>4.5 (35)</td>
<td>32.3 (253)</td>
</tr>
</tbody>
</table>

¹Eggesbø et al. 1999, ²Venter et al. 2006, 2008, ³Osterballe et al. 2005
Table 12. Lifetime prevalences of sensitisation to food items according to the age of the child in the previous studies and in South Karelia.

<table>
<thead>
<tr>
<th>Age and study area</th>
<th>Year of birth</th>
<th>N</th>
<th>Milk % (n)</th>
<th>Egg % (n)</th>
<th>Any food item % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Isle of Wight</td>
<td>2001-2</td>
<td>763</td>
<td>&lt;1.0 (2)</td>
<td>1.8 (14)</td>
<td>2.2 (17)</td>
</tr>
<tr>
<td></td>
<td>2004-5</td>
<td>842</td>
<td>2.1 (18)</td>
<td>1.8 (15)</td>
<td>3.8 (32)</td>
</tr>
<tr>
<td>South Karelia</td>
<td>2004-5</td>
<td>842</td>
<td>3.7 (31)</td>
<td>1.8 (15)</td>
<td>5.1 (43)</td>
</tr>
<tr>
<td>2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Isle of Wight</td>
<td>2001-2</td>
<td>658</td>
<td>&lt;1.0 (3)</td>
<td>2.1 (14)</td>
<td>3.8 (25)</td>
</tr>
<tr>
<td>Helsinki</td>
<td>1994-5</td>
<td>6209</td>
<td>1.6 (101)</td>
<td>2.3 (144)</td>
<td></td>
</tr>
<tr>
<td>South Karelia</td>
<td>2003-4</td>
<td>839</td>
<td>3.0 (25)</td>
<td>2.3 (19)</td>
<td>4.8 (40)</td>
</tr>
<tr>
<td></td>
<td>2002-3</td>
<td>779</td>
<td>4.8 (40)</td>
<td>2.3 (19)</td>
<td>6.7 (56)</td>
</tr>
<tr>
<td>3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Isle of Wight</td>
<td>2001-2</td>
<td>642</td>
<td>&lt;1.0 (3)</td>
<td>1.4 (9)</td>
<td>5.3 (29+7)</td>
</tr>
<tr>
<td>South Karelia</td>
<td>2002-3</td>
<td>779</td>
<td>3.2 (25)</td>
<td>3.5 (27)</td>
<td>6.7 (52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.9 (38)</td>
<td>3.5 (27)</td>
<td>8.1 (63)</td>
</tr>
</tbody>
</table>

1 Venter et al. 2008, 2 Saarinen et al. 2001, * Point prevalence, ** Any positive FA test including positive OFC, ^ Sensitisation was based on a positive result in a skin prick test, † Sensitisation was based on a test indicating specific Immunoglobulin E antibodies for a food item

In the SKARP study, the lifetime prevalence of sensitisation to any food item seemed to be higher than the prevalence of sensitisation to food items on the Isle of Wight (Table 12), which can be explained by different statistical measures (the cumulative incidences being higher than the point prevalences) and the methods used to indicate the sensitisation to the food items. In the Isle of Wight study, only SPT was included in the study design, when in the SKARP either SPT or sIgE or both were available. However, the occurrence of sensitisation to egg among one-year-olds seemed to be similar both on the Isle of Wight and in South Karelia.
Table 13. Lifetime prevalences of OFC-confirmed food allergies according to the age of the child in previous studies and in the SKARP.

<table>
<thead>
<tr>
<th>Age and study area</th>
<th>Year of birth</th>
<th>N</th>
<th>Milk % (n)</th>
<th>Any food item % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helsinki1</td>
<td>1979</td>
<td>261</td>
<td>2 (5)</td>
<td>19 (50)</td>
</tr>
<tr>
<td>The Isle of Wight2</td>
<td>2001-2</td>
<td>969</td>
<td>3.6 (35), 4.0 (39)</td>
<td></td>
</tr>
<tr>
<td>South Karelia</td>
<td>2004-5</td>
<td>842</td>
<td>2.6 (22)</td>
<td>4.2 (35)</td>
</tr>
<tr>
<td>2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helsinki1</td>
<td>1978</td>
<td>202</td>
<td>5 (10)</td>
<td>22 (44)</td>
</tr>
<tr>
<td>Helsinki2</td>
<td>1994-5</td>
<td>6209</td>
<td>1.9 (118)</td>
<td></td>
</tr>
<tr>
<td>The Isle of Wight2</td>
<td>2001-2</td>
<td>858</td>
<td>&lt;1.0 (5)</td>
<td>2.5 (21)</td>
</tr>
<tr>
<td>South Karelia</td>
<td>2003-4</td>
<td>839</td>
<td>2.4 (20)</td>
<td>3.3 (28)</td>
</tr>
<tr>
<td>3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helsinki1</td>
<td>1977</td>
<td>200</td>
<td>2 (4)</td>
<td>27 (54)</td>
</tr>
<tr>
<td>The Isle of Wight2</td>
<td>2001-2</td>
<td>807</td>
<td>&lt;1.0 (7)</td>
<td>6.0 (58)</td>
</tr>
<tr>
<td>South Karelia</td>
<td>2002-3</td>
<td>779</td>
<td>2.8 (22)</td>
<td>3.3 (23)</td>
</tr>
</tbody>
</table>

1 Kajosaari 1982, 2 Saarinen & Savilahti 2000, 3 Venter et al. 2006, 2008

* The number of tested subjects were calculated from the prevalence estimates

b Based on using OFC and a clear convincing clinical history as the endpoint

c Point prevalence

FAs for milk or any food item confirmed by an OFC were relatively well in line with the previous studies from the Isle of Wight (Venter et al. 2006, 2008) and Finland (Saarinen & Savilahti 2000, Saarinen et al. 2001)(Table 13). A Finnish study conducted 30 years ago (Kajosaari 1982) reported relatively high prevalences of FAs for specified food items, which might partly be explained by the food challenges performed at home (Table 13). However, in the latter study, the prevalences of FAs were based on relatively small numbers of cases, and a lack of information on participation rates made these prevalence estimates difficult to interpret.

In the SKARP, the incidences of food-associated symptoms showed little variation between genders. However, the incidences for FA testing, sensitisation and physician-diagnosed FAs were higher in boys than in girls (II-III) which is in line with the Isle of Wight study (Arshad et al. 2001, 2005, Tariq et al. 1998). These findings together raise but cannot answer the following questions: do the parents or health care personnel have different attitudes to food-associated symptoms depending on the gender of the child that are more likely to lead to contacting a physician and FA testing for boys than for girls or do severe or
several symptoms and/or IgE-mediated immunological mechanism actually occur more frequently among boys than girls?

The cumulative incidence of the first food-associated symptoms reported by parents was clearly higher than that of positive FA tests. 70% of physician-diagnosed FAs were based on a positive result in FA tests (III), the data of which were available in the study area. Some FA diagnoses are known to have been based on OFCs performed at home, and some diagnoses may have been based on a history of food-associated symptoms reported by parents only (Figure 1). Most children who were reported as having a physician-diagnosed milk allergy had also been undergone at least one FA test for milk (III: Table 2). Therefore, it can be assumed that most of these children underwent examination for milk allergy also by a physician.

The costs of FA testing could possibly be estimated according to the occurrence of FA testing in real life (III). These results might also be compared to the forthcoming results of multinational EuroPrevall survey (Keil et al. 2010, Kummeling et al. 2009, Miles et al. 2005, Mills et al. 2007), provided that the effects of the different study designs are taken into consideration. The occurrence of FA testing in real life is a ground for the development of testing practices in the population.

6.3 Inheritance of food allergies

The inherited nature of other allergic manifestations is well established (Cochrane et al. 2009, Thomsen et al. 2008, von Mutius 2004). Although FAs are known to be the first manifestation of allergic diseases (Kjaer et al. 2009, Sicherer 2002), information on their risk factors is scarce, including the inheritance of FAs (Cochrane et al. 2009).

The SKARP quantified the inheritance of food-associated symptoms, sensitisation to food items and physician-diagnosed FAs in a general child population (IV). Parental allergies, FA symptoms and the number of allergic manifestations were positively associated with IgE-mediated sensitisation to food items and positive OFCs in their biological children. The incidence of food-associated symptoms, FA testing and their positive results increased multiplicatively according to the number of atopic manifestations in the parents. A similar finding has previously been reported regarding other atopic manifestations (Kjellman 1977).
A higher frequency of parental reports on food-associated symptoms and FA testing were seen in the children of allergic than non-allergic parents (IV). Allergic parents may recognise and report the food-associated symptoms more sensitively than others (III), but the strong association between parental allergies and positive FA tests in their biological children cannot be explained by this alone, however, because also the PPVs of FA tests seemed to be higher for the children of allergic than non-allergic parents (IV). Although the PPVs for sIgEs, sIgE/SPT and any FA test were higher for the children of allergic than non-allergic parents, the causal role of genetic and social risk factors cannot be ascertained without genetic and immunological tests for both biological parents and their offspring in general population. Some previous genetic studies have found higher frequencies of particular HLA types and polymorphism among nut allergic patients than among others (Amoli et al. 2002, Hand et al. 2004). A higher frequency of a certain polymorphism has also been found among FA patients than others (Cambos Alberto et al. 2008). These previous genetic findings together with the population-based findings of the SKARP study conform to the hypothesis of the genetic inheritance of FAs.

6.4 Seasonality as a risk factor for sensitisation to food items

Seasonal environmental changes, such as seasons of high and low exposure of pollen grains especially in the Nordic countries, provide a natural experiment for uncovering some etiologic factors for diseases (Barnett & Dobson 2010). The data of the SKARP study included the dates of birth in the entire study population and the duration of pregnancy for the participants. The missing data on the duration of pregnancy were complemented by multiple imputations, thus the season of the gestational phases could be estimated for the entire population. The end of the first trimester of pregnancy has been considered a critical period for the development of the IgE antibodies (Hertz-Picciotto et al. 2008), therefore the month of the 11th gestational week was inspected as an explanatory factor for the incidence of positive FA tests. After the data imputation, the associations between the season in the end of the first trimester of pregnancy and FA testing and their positive results could be examined in the entire population. The incidences of FA testing showed rather weak seasonal variation according to the month of the 11th gestational week. A relatively strong association was seen between the timing of the end of the first trimester of pregnancy in spring and the incidence of a positive FA test (V). Similar findings were seen separately for sensitisation to milk and
egg. However, the incidence of a positive sIgE indicating IgE-mediated sensitisation to food items was positively associated with the 11th gestational week occurring in the spring months. These results (V) are in accordance with the previous findings on the association between the birth season being in autumn or in winter and a higher prevalence of some FAs (Aalberse et al. 1992, Kuzume & Kusu 2007, Nilsson et al. 1997, Vassallo et al. 2010).

A possible reason for the present observations about the seasonality of sensitisation to food items might be the pollen exposure and/or the scarcity of vitamin D production or other seasonal factors in nutrition. However, the incidences of positive results in FA tests, particularly in the tests indicating IgE-mediated sensitisation, seemed to be higher in children whose 11th gestational week was in the year with exceptionally high concentrations of pollen grains (V). These findings conform to the theory according to which immunological development of atopy begins during the gestational period (Hertz-Picciotto et al. 2008, Jones et al. 2000).
7 Conclusions and implications

The population register data and the retrospectively collected data on FA tests enabled an estimation of the participation rates in the entire geographically restricted population and were an aid in assessing the selection bias associated with non-response. Working closely together with the child health clinics and sending reminder questionnaires improved the participation rates by 8 and 10 percentage points, respectively, but only a slight overrepresentation of FA tested children was observed among the participants. The final participation rate (67%) was relatively high, but varied from 54% to 77% according to the child’s age and the mother’s native language. The highest participation rate was found among the mothers whose native language was Finnish and whose child was one year of age. A higher participation rate would have probably been reached if shorter questionnaires had been used and the reminder letters had been sent for the parents of newborn infants as well.

The occurrences of physician-diagnosed FAs based on parental reports were in accordance with the occurrences of positive FA tests collected concurrently with but independently from the questionnaire survey. The occurrence estimates for FAs, FHSs and FA testing showed that food-associated symptoms constitute a major public health problem in early childhood. In a general child population, the occurrence of physician-diagnosed FAs could artificially be declined by decreasing FA testing or tightening the criteria of the FAs, but the occurrence of food-associated symptoms which the children experience and their parents observe remains the same. Physician-diagnosed FAs for essential food items were more often based on FA tests than the FAs for non-essential food items. Despite that the essential food items have central role in nutrition and in cooking in Finnish culture, some non-essential food items (fruit, vegetable, peanut and treenut) are known to have potential cross-reactivity among patients with pollen allergy. Therefore, the symptoms associated with these food items might precede pollen allergy, being the first and important signs of pollen allergy. Thus further evidence and population-based knowledge are needed from longitudinal cohort studies on the natural history of FAs and FHSs, also comprising parental observations of symptoms associated with non-essential food items, which are less frequently FA tested and diagnosed by a physician.

In a general population, a great number of children had never tasted one or several food items in their first years of life, even though they had never had any symptoms associated with any food items. The proportion of these diets declined
according to age, which probably indicates a stepwise diversification of nutrition
in a child population. The prevalence of these diets has an effect on the
occurrences of FAs in the general population, and therefore it should be taken into
account either as missing observations or reported separately.

The incidence figures of food-associated symptoms were quite similar for
boys and girls. However, the incidences of FA testing, positive test results and
physician-diagnosed FAs rose to a higher level for boys than girls. Severe or
several symptoms and/or IgE-mediated immunological mechanisms may actually
occur more frequently among boys than girls, or the gender of the child may
otherwise have an effect on parents contacting a physician or on physicians
performing FA tests.

The SKARP has quantified the inheritance of FAs for the first time in a
general population. The incidence of food-associated symptoms, FA testing and
positive FA tests were twofold higher in the offspring of either and threefold
higher in the offspring of both allergic than in offspring of both non-allergic
parents. Allergic parents were also found to observe and report food-associated
symptoms more frequently in their offspring than non-allergic parents. However,
higher PPVs of FA tests among offspring of allergic parents can be considered
evidence for the inheritance of FAs. A lack of biological samples for genetic or
immunological investigations on both participants and their first degree relatives
restricts further studies of genetic epidemiology in the SKARP at its present stage.
However, the SKARP is planned as a longitudinal study and at the follow-up
phase of the cohort, a collection of genetic samples for a case-control study is
possible. The population-based evidence on the inheritance of FAs should
motivate comparable population-based surveys in other populations, too.

The highest incidence of positive FA tests, particularly IgE-mediated
sensitisation, was observed in the children whose 11th gestational week had
occurred in the spring season. However, further experimental investigations are
needed to confirm the mechanisms regarding the seasonal exposure factors and
their effects on the development of IgE-mediated immunological response. The
age range of the study population was from newborn infants up to the age of 4
years, but these children should be followed-up further and similar analyses
should be performed for inhalation allergens (the test data of the SKARP study
include allergy tests on animal and pollen allergens, as well).
References


Appendices
Appendix 1. Cut points, sensitivities, specificities, positive and negative predictive values (PPV and NPV, respectively) of specific immunoglobulin E antibodies compared with food challenges and the number of subjects and selection criteria of these previous studies.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Food item</th>
<th>Cut point (kU/L)</th>
<th>Sensitivity % (95%CI)</th>
<th>Specificity % (95%CI)</th>
<th>PPV % (95%CI)</th>
<th>NPV % (95%CI)</th>
<th>No. of subjects</th>
<th>Selection criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hill et al. 2004</td>
<td>Milk</td>
<td>≥32</td>
<td>≥95</td>
<td>≥95</td>
<td>820</td>
<td></td>
<td></td>
<td>median 13.1 months, suspected allergy for milk and/or egg</td>
</tr>
<tr>
<td></td>
<td>Egg</td>
<td>≥6</td>
<td>≥95</td>
<td>≥95</td>
<td></td>
<td></td>
<td></td>
<td>(mean 2.1 years)</td>
</tr>
<tr>
<td></td>
<td>Peanut</td>
<td>≥15</td>
<td>≥95</td>
<td>≥95</td>
<td></td>
<td></td>
<td></td>
<td>Suspected FA</td>
</tr>
<tr>
<td>Niggemann et al. 2000</td>
<td>Immediate reaction (milk, egg, wheat, soy)</td>
<td>≥0.35</td>
<td>95</td>
<td>29</td>
<td>62</td>
<td>59</td>
<td>39</td>
<td>&lt; 2 years</td>
</tr>
<tr>
<td></td>
<td>Immediate or delayed reactions (milk, egg, wheat, soy)</td>
<td>≥0.35</td>
<td>86</td>
<td>29</td>
<td>62</td>
<td>59</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delayed reactions</td>
<td>≥0.35</td>
<td>71</td>
<td>29</td>
<td>37</td>
<td>72</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Majamaa et al. 1999a</td>
<td>Milk</td>
<td>NA</td>
<td>26 (16-38)</td>
<td>94 (85-98)</td>
<td>82 (60-95)</td>
<td>54 (44-63)</td>
<td>143</td>
<td>&lt; 2 years</td>
</tr>
<tr>
<td>Majamaa et al. 1999b</td>
<td>Wheat</td>
<td>≥0.7</td>
<td>20 (7-44)</td>
<td>93 (66-100)</td>
<td>80 (28-99)</td>
<td>45 (26-64)</td>
<td>39</td>
<td>Suspected wheat allergy</td>
</tr>
<tr>
<td>Vanto et al. 1999</td>
<td>Milk</td>
<td>≥0.7</td>
<td>58 (88)</td>
<td>70 (81)</td>
<td>81 (81)</td>
<td>301</td>
<td>&lt; 1 yr (7.1±1.8 months)</td>
<td></td>
</tr>
<tr>
<td>Boyano-Martinez et al. 2001</td>
<td>Egg white</td>
<td>≥0.35</td>
<td>91 (84-98)</td>
<td>77 (57-97)</td>
<td>94 (88-100)</td>
<td>68 (47-89)</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Egg yolk</td>
<td>≥0.35</td>
<td>63 (51-75)</td>
<td>93 (80-100)</td>
<td>98 (94-100)</td>
<td>37 (22-52)</td>
<td></td>
<td>Suspected egg allergy (Immediate reaction)</td>
</tr>
<tr>
<td>Niggemann et al. 1999</td>
<td>Egg</td>
<td>≥0.35</td>
<td>95</td>
<td>38</td>
<td>79</td>
<td>75</td>
<td>107</td>
<td>5 months - 12 years</td>
</tr>
<tr>
<td></td>
<td>Milk</td>
<td>≥0.35</td>
<td>85</td>
<td>38</td>
<td>61</td>
<td>71</td>
<td></td>
<td>&lt; 2 years (89/107)</td>
</tr>
<tr>
<td></td>
<td>Wheat</td>
<td>≥0.35</td>
<td>80</td>
<td>6</td>
<td>43</td>
<td>25</td>
<td></td>
<td>Atopic eczema</td>
</tr>
<tr>
<td></td>
<td>Soy</td>
<td>≥0.35</td>
<td>100</td>
<td>26</td>
<td>23</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sampson 2001</td>
<td>Egg</td>
<td>≥6</td>
<td>64</td>
<td>90</td>
<td>96</td>
<td>39</td>
<td>100</td>
<td>Suspected FA (62 boys: 38 girls), 61% atopic eczema, 50% asthma, 90% atopic family background</td>
</tr>
<tr>
<td></td>
<td>Milk</td>
<td>≥32</td>
<td>34</td>
<td>100</td>
<td>100</td>
<td>44</td>
<td></td>
<td>3 months - 14 years (mean 3.8 years)</td>
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<tr>
<td></td>
<td>Peanut</td>
<td>≥15</td>
<td>57</td>
<td>100</td>
<td>100</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fish</td>
<td>≥20</td>
<td>25</td>
<td>100</td>
<td>100</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soy</td>
<td>≥65</td>
<td>24</td>
<td>99</td>
<td>86</td>
<td>78</td>
<td></td>
<td></td>
</tr>
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<td>100</td>
<td>100</td>
<td>76</td>
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</tr>
<tr>
<td>Roehr et al. 2001</td>
<td>Milk</td>
<td>≥0.35</td>
<td>84</td>
<td>38</td>
<td>70</td>
<td>59</td>
<td>71</td>
<td>2 months - 11.2 years (mean 13 months)</td>
</tr>
<tr>
<td></td>
<td>Egg</td>
<td>≥0.35</td>
<td>96</td>
<td>36</td>
<td>75</td>
<td>83</td>
<td>42</td>
<td>Atopic eczema</td>
</tr>
<tr>
<td></td>
<td>Wheat</td>
<td>≥0.35</td>
<td>67</td>
<td>47</td>
<td>57</td>
<td>57</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soy</td>
<td>≥0.35</td>
<td>75</td>
<td>52</td>
<td>23</td>
<td>92</td>
<td>25</td>
<td></td>
</tr>
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</table>
Appendix 2. Cut points, sensitivities, specificities, positive and negative predictive values (PPV and NPV, respectively) of skin prick tests compared with food challenges and the number of subjects and selection criteria of these previous studies.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Food item</th>
<th>Cut point (mm)</th>
<th>Sensitivity (% (95% CI))</th>
<th>Specificity (% (95% CI))</th>
<th>PPV (% (95% CI))</th>
<th>NPV (% (95% CI))</th>
<th>No of subjects</th>
<th>Selection criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verstege et al. 2005</td>
<td>Milk</td>
<td>≥17</td>
<td>99</td>
<td>99</td>
<td>385</td>
<td>median 22 months, patients suspected symptoms to milk, egg, wheat and/or soy</td>
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<tr>
<td></td>
<td>Egg</td>
<td>≥18</td>
<td>99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hill et al. 2004</td>
<td>Milk</td>
<td>≥6</td>
<td>20</td>
<td>100</td>
<td>100</td>
<td>88</td>
<td>467</td>
<td>&lt;2 years, high-risk population for the investigation of FA</td>
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<tr>
<td></td>
<td>Egg</td>
<td>≥5</td>
<td>62</td>
<td>100</td>
<td>100</td>
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<tr>
<td></td>
<td>Peanut</td>
<td>≥4</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>58</td>
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</tr>
<tr>
<td></td>
<td>Milk</td>
<td>≥8</td>
<td>30</td>
<td>100</td>
<td>100</td>
<td>58</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Egg</td>
<td>≥7</td>
<td>52</td>
<td>100</td>
<td>100</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peanut</td>
<td>≥8</td>
<td>51</td>
<td>100</td>
<td>100</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strömberg 2002</td>
<td>Milk</td>
<td>≥5</td>
<td>41</td>
<td>99</td>
<td>96</td>
<td>68</td>
<td>141</td>
<td>&lt;2 years, mean 16 months Atopic eczema</td>
</tr>
<tr>
<td></td>
<td>Egg</td>
<td>≥5</td>
<td>60</td>
<td>97</td>
<td>96</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Wheat</td>
<td>≥5</td>
<td>13</td>
<td>98</td>
<td>80</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roehr et al. 2001</td>
<td>Milk</td>
<td>≥3</td>
<td>78</td>
<td>69</td>
<td>81</td>
<td>64</td>
<td>71</td>
<td>2 months to 11.2 years (mean 13 months) Atopic eczema</td>
</tr>
<tr>
<td></td>
<td>Egg</td>
<td>≥3</td>
<td>89</td>
<td>57</td>
<td>81</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wheat</td>
<td>≥3</td>
<td>67</td>
<td>53</td>
<td>60</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niggemann et al. 2000</td>
<td>Immediate reactions (milk, egg, wheat, soy)</td>
<td>≥3</td>
<td>95</td>
<td>70</td>
<td>69</td>
<td>95</td>
<td>39</td>
<td>mean 2.1 years Suspected FA Atopic eczema 69/75</td>
</tr>
<tr>
<td></td>
<td>Immediate and/or delayed reactions (milk, egg, wheat, soy)</td>
<td>≥3</td>
<td>83</td>
<td>70</td>
<td>79</td>
<td>75</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>Majamaa et al. 1999a</td>
<td>Delayed reactions Milk</td>
<td>≥3</td>
<td>58</td>
<td>70</td>
<td>41</td>
<td>81</td>
<td>21</td>
<td>&lt;2 years, Suspected milk allergy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7-25)</td>
<td>(92-100)</td>
<td>(59-100)</td>
<td>(42-60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Majamaa et al. 1999b</td>
<td>Wheat</td>
<td>≥3</td>
<td>23</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>39</td>
<td>&lt;2 years, Suspected wheat allergy</td>
</tr>
<tr>
<td>Vanto et al. 1999</td>
<td>Milk</td>
<td>≥3</td>
<td>69</td>
<td>91</td>
<td>79</td>
<td>85</td>
<td>301</td>
<td>&lt;1 year (7.1 ± 1.8 month, 2-11 months), Suspected milk allergy</td>
</tr>
<tr>
<td>Boyano-Martinez et al. 2001</td>
<td>Egg white</td>
<td>≥3</td>
<td>97</td>
<td>71</td>
<td>93</td>
<td>86</td>
<td>81</td>
<td>&lt;2 years, Suspected egg allergy (immediate reaction)</td>
</tr>
<tr>
<td></td>
<td>Egg yolk</td>
<td>≥3</td>
<td>78</td>
<td>88</td>
<td>96</td>
<td>52</td>
<td>81</td>
<td>(34-70)</td>
</tr>
</tbody>
</table>
Appendix 3. Flow diagrams of study designs and occurrences of food allergies and food hypersensitivities in populations. (C M = Cow milk, NA=Missing information)

Oslo

- Source population N=6400
- Language N=1045
- Drug abuse N=16
- Severe illness N=26
- Not Oslo residents N=195

- 78% Eligible N=4873

- N=1219
  - 59% Birth cohort N=3754

- N=131
  - 57% Cohort N=3623
  - 54% 2 year follow up N=3486

- 44% complete information N=2803

- 35% Any FHS

  - 12% CM n=325
  - 4% Egg n=122
  - 3% Fish n=88

the Isle of Wight

- All pregnant woman at antenatal clinic delivery (estim)
- Sept 2001 to Aug 2002
- N=1063

- 91% participated N=969

- 87%, 86%, 85%, 85% questionnaire (by phone) at age of
  - 3, 6, 9, 12 months
  - N=927, 912, 900, 900

- Two members of the team screened the information and adverse reactions were contacted n=132, 83, 49, 65

- Any FHS
  - 26% by 1year n=250
  - 34% by 3years n=272

- SPT
  - 72% at 1year n=763
  - 60% at 3years n=642

- OFC
  - 2%, 5% SPT+ n=17, 29

- DBPCFC
  - n=15/15+9
  - n=0/1

- 35% Any FHS

Odense

- Target population N=1095
- Serious illness
  - Language
  - Plan to move
- N=98

- Declined N=435

- 51% Newborn infants, born within the 1st 14days of each month N=962

- Cohort and their relatives were examined when the child was 3 year old, N=486

- 54% SPT&IgE n=306

- 50% IgE+
  - 6% SPT+

- 15% Self-reported FHS
  - n=74
  - 58+30=88!

- Contact urticaria n=58 -- not OFC

- 6% OFC n=30

- 2% OFC+ n=11

- 2% Egg+ n=8

- 0.6% CM+ n=3

1Eggesbø et al. 1999, 2Venter et al. 2006, 2008, 3Osterballe et al. 2005
Appendix 3 continued.

---

*Saarinen & Savilahti 2000, Saarinen et al. 1999, 2001*

*Kull et al. 2006, Wickman et al. 2002*
Original publications


Reprinted with permission from the SAGE publications Ltd (I), John Wiley & Sons Ltd (II, III, IV) and BMJ Publishing Group Ltd (V).

Original publications are not included in the electronic version of the dissertation.
1075. Kinnunen, Urpo (2010) Blood culture findings during neutropenia in adult patients with acute myeloid leukaemia: the influence of the phase of the disease, chemotherapy and the blood culture systems


1077. Reponen, Jarmo (2010) Teleradiology—changing radiological service processes from local to regional, international and mobile environment


1081. Alahuhta, Maija (2010) Tyypin 2 diabeteksen riskiryhmään kuuluvien työikäisten henkilöiden painohallinnan ja elin State’s general and regional and mobile health care services

1082. Hurskainen, Merja (2010) The roles of collagens XV and XVIII in vessel formation, the function of recombinant human full-length type XV collagen and the roles of collagen XV and laminin α4 in peripheral nerve development and function

1083. Rasi, Karolina (2010) Collagen XV as a matrix organizer: its function in the heart and its role together with laminin α4 in peripheral nerves


1085. Mäkelä, Kari Antero (2010) The roles of orexins on sleep/wakefulness, energy homeostasis and intestinal secretion


1089. Miettinen, Johanna (2011) Studies on bone marrow-derived stem cells in patients with acute myocardial infarction
Kaisa Pyrhönen

FOOD ALLERGIES AND HYPERSENSITIVITIES AMONG CHILDREN IN SOUTH KARELIA

OCCURRENCE, INHERITANCE AND SEASONALITY