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Kaisa Pyrhönen, Esa Läära, Minna Kaila, Liisa Hiltunen and Simo Näyha

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STUDY DESIGN ARTICLE

SKARP – A population-based cohort study of childhood food-associated symptoms perceived by parents and food allergies diagnosed by physicians: Design, methods and participation

KAISA PYRHÖNEN^{1,2}, ESA LÄÄRÄ³, MINNA KAILA⁴, LIISA HILTUNEN^{2,5}
& SIMO NÄYHÄ^{6,7}

¹South Karelia District of Social and Health Services, Lappeenranta, Finland, ²Unit of General Practice, Oulu University Hospital, Oulu, Finland, ³Department of Mathematical Sciences, University of Oulu, Oulu, Finland ⁴Paediatric Research Centre, Tampere University Hospital and University of Tampere, Tampere, Finland, ⁵Health Centre of Oulu, Oulu, Finland ⁶Institute of Health Sciences, University of Oulu, Finland and ⁷Finnish Institution of Occupational Health, Oulu, Finland

Abstract

Background: Few epidemiological studies exist on food-associated symptoms and allergies in large unselected child populations. **Aims:** To describe the design, methods and participation rate of the South Karelian Allergy Research Project (SKARP), a population-based epidemiological study on food-associated symptoms and physician-diagnosed food allergies. **Methods:** The study population of 5,973 children born between 2001 and 2006 and resident in the province of South Karelia, Finland, was identified from the nationwide population register. The parents received a questionnaire to be returned at their child's annual visit to the child health clinic, where supplementary interviews were performed. Results of allergy tests (skin prick tests, immunoglobulin E antibodies and open food challenges) performed on participants and non-participants were collected from the relevant health care units in the area. **Results:** Participation rates in the questionnaire study were 54% (644/1,194) among the parents of neonates and 69% (3308/4,779) among those of the children aged 1 to 4 years. Cooperation with the child health clinics and mailing of a reminder questionnaire improved participation by 8 and 10 percentage points, respectively. The final participation rate seemed to be unaffected by whether the child had or had not been tested for suspected allergy. **Conclusions:** A reasonably good participation rate and almost complete coverage of allergy tests were achieved thanks to successful cooperation with the child health clinics and test laboratories. This baseline study forms a representative database to estimate the occurrence of food-associated symptoms, physician-diagnosed food allergies and allergy testing in the general population.

Key Words: Child, food allergy, food hypersensitivity, participation rate, population, test

Background

Allergic and hypersensitivity diseases, especially food allergies (FA) and food hypersensitivities (FHS), are believed to be common in the general population and constitute a notable public health problem because they increase the financial burden imposed on society and the healthcare system [1,2]. FAs are often the first manifestations of allergic diseases in early childhood [3]. Published estimates of the prevalence of FAs and FHSs range between 2% and 35% – a

variation that can be accounted for by differences in the criteria and methods used for diagnosing allergies, the selection of the study subjects and their age range, and the spectrum of food items examined [2,4,5]. Only a few epidemiological studies on the occurrence of food-associated symptoms, FAs and FHSs in unselected child populations have been published, however [5,6].

Food allergy tests are performed in diagnosis of FA. The atopy patch tests indicate delayed mechanisms (late phase clinical reactions) of sensitization,

Correspondence: Kaisa Pyrhönen, Institute of Health Sciences, University of Oulu, PO Box 5000, FI-90014 University of Oulu, Finland.
E-mail: kaisa.pyrhonen@oulu.fi

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and blood tests for immunoglobulin E antibodies, and skin prick tests IgE-mediated sensitization (immediate-type reactions). The “double-blind, placebo-controlled, food challenge” is regarded as the gold standard for FA diagnosis [6,7], but it is not feasible for use in epidemiological studies because of the potential health risk, the time required to perform the tests, and the overall costs [8–10]. The lack of information on diagnostic cut points employed in other allergy tests such as immunoglobulin E antibodies and skin tests, especially in infants, raises problems with respect to the interpretation and comparison of the results of epidemiological studies [6,7,11]. One problem inherent in population surveys based on self-reported symptoms and diagnoses is the possibility of bias introduced by selective participation [4–6]. Information on the occurrence of food associated symptoms and FAs with their associated factors in the general population is nevertheless a prerequisite for the rational planning of diagnostic protocols, treatments, and appropriately focused preventive measures, and also for making comparisons between population groups.

Aims

The South Karelian Allergy Research Project (SKARP) was planned to provide information on the occurrence of food-associated symptoms and physician-diagnosed FAs and their risk factors in an unselected child population, as well as to characterize their natural history. An ancillary objective was to assess the frequency and determinants of FA testing by various test methods in such a population. The rationale of the study, not previously deployed in allergy research, was to link all tests performed for suspected allergy with an independent questionnaire survey conducted in the same geographically defined target population.

The present paper: (1) describes the overall design of the study, (2) reports on the data collection process, complying with the STROBE guidelines [12], and (3) examines the dependence of participation rate on demographic factors, allergy testing and practical arrangements.

Material and methods

Geographical area

The province of South Karelia in the south-east of Finland covers an area of 7,236 km² and is divided into 12 local government districts, called communes (*kunta* in Finnish and *kommun* in Swedish), three of

which are towns (with 59,000, 30,000 and 11,000 inhabitants, respectively) and nine rural communes (800 to 6,200 inhabitants). The population density in the province averaged 24 inhabitants per km² and the total population in 2005 was 135,000, of which 6,000 were under 5 years of age [13].

Study population and recruitment

Potential participants were identified from the Finnish Population Register [14]. Eligible for the study were the children who were resident in the province one month prior to their scheduled visit to the child health clinic (close to their birthday) and born between April 2001 and March 2006 (aged under 5 years in 2005–6, when the work was carried out) (Figure 1). The address and unique personal identity code (PIC), name, gender, PICs of siblings younger than 18 years who lived in the same household, mother's name, mother's native language and the home address of the mother of each of the 1 to 4 year-old participants were obtained from this register [14]. As some time elapses before information on a newborn child is available in the population register, the parents of newborn infants were recruited directly at their first visit to the child health clinic (Figure 2), and their records were obtained from the population register at the end of the questionnaire survey. All newborn infants who were officially resident in the area during their first month of life were included.

Questionnaires and interviews

The questionnaires were developed specifically for the present purpose, partly by modifying previously used questionnaires [15–17]. Initially they were in Finnish only, but were afterwards translated into English [18]. The protocol and the questionnaires were tested in a pilot study comprising 200 children in a municipality outside the region in question and were slightly modified as a result. The participants in the pilot survey were not included in the SKARP population.

The *baseline questionnaire* contained questions about the child's neonatal characteristics; early nutrition; history of allergic diseases and symptoms, especially FAs diagnosed by a physician and/or food-associated symptoms perceived by the parents; the clinics where allergy tests had been performed, if any; treatments; background of the family; and items on the living environment. The newborn questionnaire contained additional questions on the mother's diet during pregnancy.

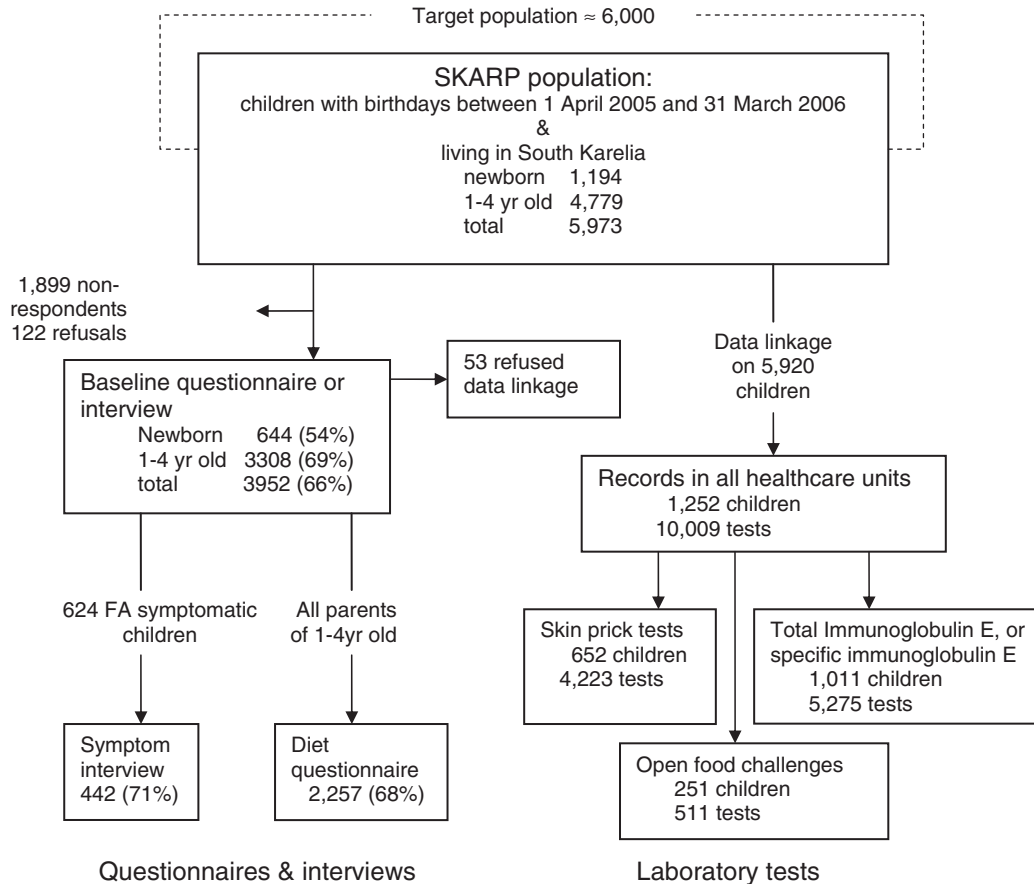


Figure 1. The study design of the South Karelian Allergy Research Project (SKARP).

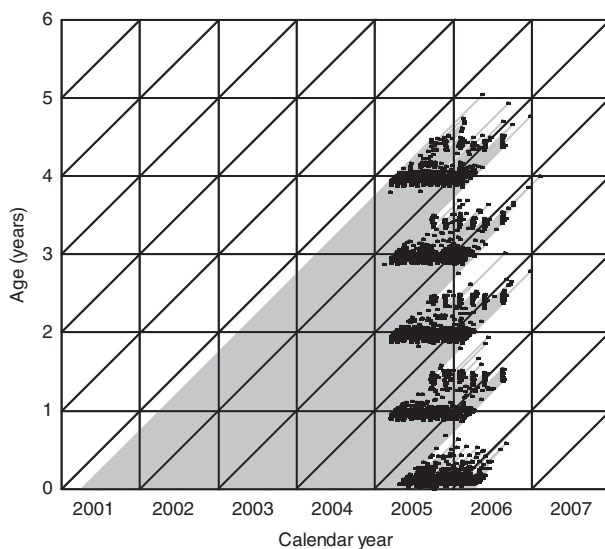


Figure 2. Lexis diagram depicting the course of the baseline study. The dates of returning the questionnaires are indicated by black circles.

The completed baseline questionnaire was checked by a nurse when it was returned. If any symptoms of FA had been perceived within the last 12 months, a structured *symptom interview* was conducted by the nurse. The interview form designed by the research team focused on the types of perceived symptoms and the time elapsing between eating a food item and the appearance of the symptoms.

On returning the baseline questionnaire to the child health clinic, the parents of all the 1 to 4 year-old children received a *diet questionnaire* asking about the food items the child was able to eat without symptoms of allergy and any diets adhered to by the child during the last three months or by the mother during her pregnancy or the breastfeeding period. Mothers who had pursued an elimination diet because of their own allergies were asked to indicate this.

Administration of the baseline questionnaires

The baseline questionnaires were posted in batches, two weeks before the month of the child's birthday,

i.e. the month of each child's scheduled annual visit to the child health clinic. The parents were requested to return the questionnaire during this visit; termed here the "first wave" of returning the questionnaire. Those failing to return it were given a reminder questionnaire by a public health nurse and were asked to post this to the research institute in a prepaid envelope provided (the "second wave"). If the parents were unwilling to participate, they were discreetly, and without any information on identification, asked by the nurse for their reasons for declining. A second reminder questionnaire was mailed to those who did not return the previous one within four to five months (the "third wave").

Collection of allergy test results

Our aim was to collect the results of all allergological tests performed among the subjects between 1 April 2001 and 30 September 2006 from all relevant hospitals, health centres and private clinics in the area independently of the questionnaire survey (Figure 1). This information was collected for both respondents and non-respondents to the questionnaire. Some children had been tested in laboratories outside the area, and their data were included if the following information was available: positive and negative controls of skin prick tests, specified name of the test, the test results, and the date of the test.

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 nine laboratories in the region: those of the central hospitals of South Karelia, East Savo and South Savo, two paediatric clinics at local health centres (in Imatra and Lappeenranta), one health centre (at Parikkala) and three private laboratories.

The results of specific immunoglobulin E antibodies (sIgE) to food and inhalation allergens and total immunoglobulin E antibodies (IgE) were collected. IgE tests had been analyzed in the three private laboratories and the laboratories of the central hospitals. Almost all the results were retrieved from a computerized laboratory system covering the South Karelia hospital district, but some of them had to be collected manually. All IgE measurements that followed recommended and routine methods were included.

To obtain data on open food challenges (OFC), the laboratory records at all the health centres and clinics where these tests had been performed were manually screened for children born from 1 April 2001 to 31 March 2006, limiting the search to specified allergy diagnoses where necessary. Altogether, 1,991 patient

records for these children were read and information on their OFCs, as entered by the physician, was collected on structured forms.

Statistical analysis

The R environment (release 2.9.2) was used for checking and correcting the data and transforming the variables, and also for performing and documenting the analyses [19]. The dates of filling in the questionnaires were plotted on a Lexis diagram created using the Epi-package of the R environment [20].

Ethics, permissions and record linkage

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 kind. The protocol was reviewed by the Ethical Committee of the Northern Ostrobothnia Hospital District. The parents were informed of the design and subsequent follow-ups, and their permission was requested for future record linkages, too. The data were analyzed without any identification. The authors did not provide any medical care for the study population.

Results

Participation in the questionnaire survey

A total of 5,973 children were identified from the population register (Figure 1). The overall participation rate in the questionnaire survey was 66% ($n = 3,952$), being 54% among the newborn infants and 69% among the 1 to 4-year-old children, and higher in cases where the mother's native language was Finnish (56%, 77%, 73%, 69% and 66% among the newborn and 1, 2, 3 and 4-year-old children, respectively).

Most of the parents filled in and returned the questionnaire close to the child's birthday, but the Lexis diagram (Figure 2) also shows clusters four to five months after each birthday, indicating the returning of reminder questionnaires. The parents of newborn infants received the questionnaire from the child health clinics and no reminders were sent out, hence no secondary clusters are seen in these cases. The participation rate in the first wave was 51%. This figure improved by 8 and 10 percentage points after the visit to the clinic and the reminder questionnaire, respectively (Table I, Figure 3).

The parents of 122 children (Figure 1) declined to participate, for reasons that included language difficulties (nine parents), drug, alcohol or mental health

Table I. Numbers of subjects (*n*) and participation rates (%) at different phases of data collection among the 1 to 4 year-olds, classified by selected background factors.

	Whole population <i>n</i>	Baseline questionnaire returned			Total of baseline questionnaire or interview % (<i>n</i>)	Diet questionnaire % (<i>n</i>)
		1st wave: At visit % (<i>n</i>)	2nd wave: After interview ^a % (<i>n</i>)	3rd wave: After reminder % (<i>n</i>)		
Target age (years)						
1	1,163	56 (648)	8 (93)	11 (131)	75 (872)	50 (582)
2	1,189	52 (620)	9 (103)	11 (128)	72 (851)	49 (580)
3	1,170	50 (583)	8 (92)	9 (111)	67 (786)	46 (542)
4	1,257	48 (600)	7 (94)	8 (105)	64 (799)	44 (553)
Gender						
Boys	2,441	51 (1,252)	8 (204)	9 (228)	69 (1,684)	46 (1,135)
Girls	2,338	51 (1,199)	8 (178)	11 (247)	69 (1,624)	48 (1,122)
No. of siblings						
None	1,498	53 (797)	9 (133)	11 (167)	73 (1,097)	48 (726)
One	2,075	53 (1,092)	8 (173)	9 (185)	70 (1,450)	49 (1,021)
Two or more	1,206	47 (562)	6 (76)	10 (123)	63 (761)	42 (510)
Order of birth						
Firstborn ^b	2,137	54 (1,162)	9 (183)	10 (209)	73 (1,554)	50 (1,070)
Not firstborn	2,642	49 (1,289)	8 (199)	10 (266)	66 (1,754)	45 (1,187)
Place of residence						
Provincial capital	2,250	52 (1,166)	7 (148)	10 (218)	68 (1,532)	46 (1,026)
Other urban	1,392	50 (698)	9 (125)	10 (139)	69 (962)	47 (654)
Rural area	1,136	52 (587)	10 (109)	10 (118)	72 (814)	51 (577)
Mother tongue						
Finnish	4,479	53 (2,381)	8 (365)	10 (433)	71 (3,179)	49 (2,204)
Russian	208	25 (53)	6 (12)	14 (29)	45 (94)	19 (39)
Other	92	18 (17)	5 (5)	14 (13)	38 (35)	15 (14)
Total	4,779	51 (2,451)	8 (382)	10 (475)	69 (3,308)	47 (2,257)

^aIncluding the parents of 71 children, who were interviewed only on food allergies (identical questions to those in the baseline questionnaire) at the child health clinics, but who did not otherwise return the completed baseline questionnaire after the interview.

^bIncluding twins without older siblings.

problems, sickness, or a difficult situation in life (six), no interest in studies of this kind (21), some other reason (61) and no particular reason (25).

Altogether, the parents of 624 children reported food-associated symptoms in their children over the past 12 months, and 71% of these parents underwent a detailed interview on the symptoms. A dietary questionnaire was returned by the parents of 68% of the children (Figure 1), i.e. 47% of the total number of 1 to 4-year-olds.

Coverage of test data collection

Data linkage could be performed for 5,920 (99%) children of the SKARP population (Figure 1), excluding 53 whose parents refused to allow their PICs to be used for the data linkage. Altogether, we found 10,009 records of allergy tests performed on 1,252 of the children (Figure 1), of whom 941 children (including six neonates) had been tested first before replying to the questionnaire, or before

they should have replied in case of non-respondents. In addition, two children had the date of the SPT (13 results) before their birthday; these tests were therefore omitted. A comparison of the parents' answers in the questionnaire with the test data showed that we had collected test results for 89% (*n* = 553) of the children in the area who according to their parents' report had undergone at least some allergy test (*n* = 623) by the time the parents responded 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 the fact. For 3,188 children no record of any 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, 22 participants (<1%) had been tested only outside the province. The proportion of missing tests was unrelated to gender, place of residence, mother's native language,

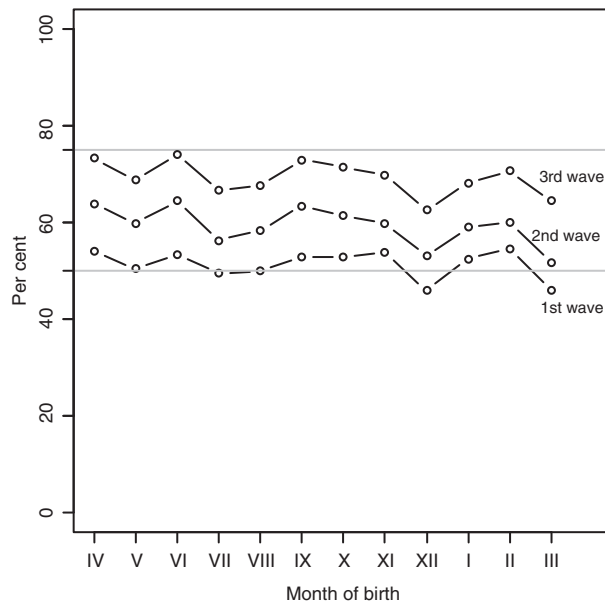


Figure 3. Rates of participation in the SKARP study among the 1 to 4 year-olds by the child's month of birth. The participants in the 1st wave returned the baseline postal questionnaire during the child's annual follow-up visit to a child health clinic, those in the 2nd wave responded after having been motivated and recruited by public health nurses, and those in the 3rd wave returned the reminder questionnaire. Participation rates from the 1st wave to the 3rd wave were between 50% and 75% (grey lines) throughout the survey, except for lower participation rates in the 1st wave among children born in December or March.

birth order or month of birth, but the proportion of missing reports of tested children increased with age of the child (9%, 12%, 12% and 18% for ages 1 to 4 years, respectively).

Effect of allergy testing on participation

The children on whom at least one FA test had been performed showed lower participation rates than the others in the first wave of returning the baseline questionnaire (Table II), but their participation improved greatly in the second and third waves, so that the final rates were at least as good as those for the non-tested children. Participation rates remained relatively low among children tested for allergies other than FAs at the age of 3 or 4 years, however (Table II).

Discussion

The SKARP study was launched to assess the occurrence of food-associated symptoms reported by the parents and physician-diagnosed FAs reported

by the parents and recorded by a physician and their determinants in the general child population. The possibility for record linkage on an individual basis throughout the study provides an opportunity to examine variations in participation rate, and to assess the biases associated with selective participation. Close co-operation with the local child health clinics, which are free of charge and attended by almost all children according to a pre-scheduled scheme, encouraged the parents to participate. Our study could be repeated in any country that has comparable child health clinics, population and patient registers, and facilities for linking the data.

Participation rates compared with previous studies of food allergy

Low participation rates or missing information on participation can often be a problem in epidemiological studies. Participation or complete information rates in FA studies range from 31% to 89% [4–6,21,22], but some authors fail to report the participation rate at all [23–25]. Also, other pre-defined eligibility criteria are sometimes set out, such as birth weight or participants not planning to move away from the area, or in some cases only healthy and/or full-term neonates or only families who volunteer to participate are included [24–26]. These criteria may have led to higher participation rates, but they will also have given biased estimates of the occurrence of FAs and FHSs in the total population. The participation rate achieved in our study can be regarded as very good for one based on the general population.

Coverage of test data collection

Our body of test data is the first ever to be collected in a large unselected population and forms a unique database for studying the real-life epidemiology of allergy testing and test results. There is no objective method for evaluating the true coverage of test data collection in a population, and our coverage estimates for a collection routine based on parents' reports on "skin tests", "blood tests" and "food challenges" probably underestimate the true coverage, because questions on allergy tests cannot be formulated well enough in a questionnaire. The parents cannot be expected to remember all the tests performed on their children, or to remember the names of the tests correctly. 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

Table II. Number of subjects (*n*) and participation rates (%) at different phases of data collection among the 1 to 4 year-olds, classified by target age and food allergy or other allergy test performed.

	Whole population <i>n</i>	Baseline questionnaire returned			Total of baseline questionnaire or interview % (<i>n</i>)
		1st wave: At visit % (<i>n</i>)	2nd wave: After interview ^a % (<i>n</i>)	3rd wave: After reminder % (<i>n</i>)	
Target age (years)					
-Allergy test					
1					
No allergy test	1,007	58 (584)	6 (65)	10 (96)	74 (745)
Food allergy test	127	38 (48)	20 (26)	21 (27)	80 (101)
Other allergy test only	17	53 (9)	6 (1)	24 (4)	82 (14)
2					
No allergy test	953	53 (507)	7 (70)	10 (99)	71 (676)
Food allergy test	187	46 (86)	17 (31)	9 (17)	72 (134)
Other allergy test only	36	67 (24)	0 (–)	11 (4)	78 (28)
3					
No allergy test	900	52 (469)	6 (53)	10 (89)	68 (611)
Food allergy test	212	44 (93)	17 (37)	7 (14)	68 (144)
Other allergy test only	53	34 (18)	4 (2)	11 (6)	49 (26)
4					
No allergy test	938	49 (464)	6 (59)	8 (75)	64 (598)
Food allergy test	224	45 (101)	12 (26)	8 (17)	64 (144)
Other allergy test only	79	37 (29)	9 (7)	6 (5)	52 (41)
Total of allergy tests					
No allergy test	3,798	53 (2,024)	7 (247)	9 (359)	69 (2,630)
Food allergy test	750	44 (328)	16 (120)	10 (75)	70 (523)
Other allergy test only	185	43 (80)	5 (10)	10 (19)	59 (109)
Total	4,733	51 (2,432)	8 (377)	10 (453)	69 (3,262)

^aIncluding the parents of 71 children who were interviewed only on food allergies (identical questions to those in the baseline questionnaire) at the child health clinics, but who did not otherwise return the completed baseline questionnaire after the interview.

systematic variations according to the other demographic background factors.

Self-selection and information bias

In a recent meta-analysis of studies on the prevalence of FA, low participation rates were thought to cause bias as the non-participants probably had a lower prevalence of FA and a different socioeconomic profile [6]. A higher prevalence of physician-diagnosed asthma and respiratory syndromes was found among participants than non-participants in one Finnish study, whereas the finding was the opposite in Sweden [27,28].

Close cooperation with the child health clinics apparently improved the quality of the data in the present SKARP study, because the nurses checked the questionnaires, completed missing items and interviewed the parents about perceived food-associated symptoms or symptoms of FA, and they were also able to motivate the parents of both allergic and non-allergic children to participate. The “first wave” participation was actually lower among the

children with a suspected allergy, but this was offset by higher rates in the subsequent waves, so that by the end comparable participation rates were achieved among the tested and non-tested children. The awareness among parents that their child either has or may have FA is therefore unlikely to be a significant source of bias.

The sensitivity of the items asked about in the questionnaire and the permission with regard to record linkages may also have caused bias [29], but the effect of these factors is difficult to estimate. Children’s allergies, especially FAs, are not usually regarded as sensitive issues, however, and the subjects’ history of sensitive life events is obviously short, which would also reduce the likelihood of any selection bias.

We cannot rule out the possibility of a recall bias in the case of mild symptoms, and especially regarding the question of the age at which the food-associated symptoms first appeared [30], and with regard to allergy tests in the oldest age class. The decline in participation with age, which itself could indicate a selection bias, may reflect parents’ fading

recollections of the symptoms and other items asked about in the questionnaire.

Limitations and benefits of combining questionnaire survey with register data

A questionnaire study is still the only feasible method of obtaining information on all perceived allergy symptoms and relevant exposure factors in an unselected population. Only the symptoms that appear persistently after a particular food item can be confirmed by the food challenges. Conducting all FA tests for all participants would have been unfeasible both financially and logistically, and most likely would have decreased the participation rate. Performing a large number of FA tests purely on scientific grounds on children who had no indication of FA symptoms and some of whom had previously suffered a severe reaction to food items would be unethical as well, because neither SPTs nor sIgEs are painless tests and both SPTs and food challenges may cause systemic reactions [9,10,31]. Our test data, albeit retrospectively collected, also enabled the estimation of the real-life process of FA testing in the 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.

Conclusions

The SKARP study provides a useful database for assessing the occurrence of food-associated symptoms perceived and reported by the parents; FA testing; and physician-diagnosed FAs reported by the parents and/or recorded by a physician in the general child population. Given the almost complete registration of the population and the existing techniques for performing practically error-free data linkages on an individual basis, the population studied can be considered to cover the theoretical target population in the best conceivable way. The SKARP database is also the first one in this field to enable a long-term follow-up with linkages made to other healthcare registers. This design therefore offers a possibility to obtain a longitudinal picture of the natural history of diagnoses of sensitization, especially to food items, in an unselected population. The present approach will provide a means for assessing the sensitivity, specificity and predictive values of parents' reports, which is important information also from a public health perspective. The study design also presents a model for how information on food-associated symptoms

and physician-diagnosed FAs gathered by different methods can be deployed in countries having a comparable healthcare system.

Competing interests

None declared.

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References

- [1] Valovirta E. Allergy: a burden for the patient and for the society. In: Pawankar R, Holgate ST, Rosenwasser LJ, editors. *Allergy frontiers: epigenetics, allergens and risk factors*. New York: Springer; 2009. p. 40.
- [2] Haahtela T, von Herzen L, Mäkelä M, Hannuksela M, the Allergy Programme Working Group. Finnish Allergy Programme 2008–2018 – time to act and change the course. *Allergy* 2008;63:634–45.
- [3] Sicherer SH. Food allergy. Review. *Lancet* 2002;360:701–10.
- [4] Mills ENC, Mackie AR, Burney P, Beyer K, Frewer L, Madsen C, et al. The prevalence, costs and basis of food allergy across Europe [review article]. *Allergy* 2007;62:717–22.
- [5] Osterballe M. Epidemiology and food hypersensitivity. In: Pawankar R, Holgate ST, Rosenwasser LJ, editors. *Allergy frontiers: epigenetics, allergens and risk factors*. New York: Springer; 2009. pp. 145–59.

- [6] Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120:638–46.
- [7] Eigenmann PA, Beyer K, Burks AW, Lack G, Liacouras CA, Hourihane JO'B, et al. New visions for food allergy: an iPAC summary and future trends. *Pediatr Allergy Immunol* 2008;19(Suppl 19):26–39.
- [8] Sicherer SH. Food allergy: when and how to perform oral food challenges. *Pediatr Allergy Immunol* 1999;10:226–34.
- [9] Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, et al. Standardization of food challenges in patients with immediate reactions to foods – position paper from the European Academy of Allergy and Clinical Immunology. *Allergy* 2004;59:690–7.
- [10] Reibel S, Röhr C, Ziegert M, Sommerfeld C, Wahn U, Niggemann B. What safety measures need to be taken in oral food challenges in children? *Allergy* 2000;55:940–4.
- [11] Niggemann B, Beyer K. Diagnostic pitfalls in food allergy in children. *Allergy* 2005;60:104–7.
- [12] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Epidemiology* 2007;18:800–4.
- [13] Statistics Finland. Population according to age (1-year) and gender by area 1980–2009. Available from: http://pxweb2.stat.fi/database/StatFin/vrm/vaerak/vaerak_en.asp. Online statistics (accessed 8 December 2010).
- [14] Population Register Centre. Personal identity code. Available from: <http://www.vaestorekisterikeskus.fi/vrk/home.nsf/pages/951E0BDFF6E9FCA7C2257244003FBBE1?opendocument> (accessed 8 December 2010).
- [15] ISAAC, the International Study of Asthma and Allergies in childhood. Available from: <http://isaac.auckland.ac.nz/> (accessed 8 December 2010).
- [16] Susitaival P, Husman T, the Tuohilampi-group. Tuohilampi – a set of questionnaires for population studies of allergic diseases of the respiratory tract, skin and eyes. Helsinki: Hakapaino Oy; 1996.
- [17] Description of the NFBC 1986 – study. Available from: <http://kelo.oulu.fi/NFBC/koho1986/nfbc1986description.htm> (accessed 8 December 2010).
- [18] South Karelian Allergy Study. Questionnaires. Available from: <http://kelo.oulu.fi/tutkimus/EKAT> (accessed 8 December 2010).
- [19] R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria; R Foundation for Statistical Computing; 2010. ISBN 3-900051-07-0. Available from: <http://www.r-project.org/> (accessed 8 December 2010).
- [20] Carstensen B, Plummer M, Lääre E, Hills M. Epi: A package for statistical analysis in epidemiology. R package version 1.1.17. Available from: <http://CRAN.R-project.org/package=Epi/> (accessed 8 December 2010).
- [21] Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Higgins B, et al. Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life. *Allergy* 2008;63:354–9.
- [22] Roehr CC, Edenharter G, Reimann S, Ehlers I, Worm M, Zuberbier T, et al. Food allergy and non-allergic food hypersensitivity in children and adolescents. *Clin Exp Allergy* 2004;34:1534–41.
- [23] Kajosaari M. Food allergy in Finnish children aged 1 to 6 years. *Acta Paediatr Scand* 1982;71:815–9.
- [24] Saarinen KM, Juntunen-Backman K, Järvenpää A-L, Klemetti P, Kuitunen P, Lope L, et al. Breast-feeding and the development of cows' milk protein allergy. *Adv Exp Med Biol* 2000;478:121–30.
- [25] Saarinen KM, Savilahti E. Infant feeding patterns affect the subsequent immunological features in cow's milk allergy. *Clin Exp Allergy* 2000;30:400–6.
- [26] Eggesbø M, Halvorsen R, Tambs K, Botten G. Prevalence of parentally perceived adverse reactions to food in young children. *Pediatr Allergy Immunol* 1999;10:122–32.
- [27] Kotaniemi J-T, Hassi J, Kataja M, Jönsson E, Laitinen LA, Sovijärvi ARA, et al. Does non-responder bias have a significant effect on the results in a postal questionnaire study? *Eur J Epidemiol* 2001;17:809–17.
- [28] Rönmark E, Lundqvist A, Lundbäck B, Nyström L. Non-responders to a postal questionnaire on respiratory symptoms and diseases. *Eur J Epidemiol* 1999;15:293–9.
- [29] Korkeila K, Suominen S, Ahvenainen J, Ojanlatva A, Rautava P, Helenius H, et al. Non-response and related factors in a nation-wide health survey. *Eur J Epidemiol* 2001;17:991–9.
- [30] Pyrhönen K, Näyhä S, Kaila M, Hiltunen L, Lääre E. Occurrence of parent-reported food hypersensitivities and food allergies among children aged 1–4 yr. *Pediatr Allergy Immunol* 2009;20:328–38.
- [31] Valyasevi MA, Maddox DE, Li JTC. Systemic reactions to allergy skin tests. *Ann Allergy Asthma Immunol* 1999;83:132–6.