

REGULAR ARTICLE

Caesarean section and allergic manifestations: insufficient evidence of association found in population-based study of children aged 1 to 4 years

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ABSTRACT

Aim: To provide evidence on the association between caesarean section and allergic manifestations in an unselected child population.

Methods: Research focused on all children aged from one to 4 years ($N = 4779$), born between April 2001 and March 2005 and living in the province of South Karelia, Finland. They were identified from the nationwide population register. Questionnaire data on 3181 participants were individually merged with allergy test results (skin prick tests, IgE antibodies and open food challenges) from all patient records.

Results: Compared with vaginal delivery, the adjusted relative incidence of positive allergy tests (with 95% confidence intervals, CI) in children born by caesarean section was 1.14 (0.79, 1.65) for food, 1.16 (0.66, 2.05) for animals, 0.94 (0.46, 1.92) for pollen and 1.19 (0.87, 1.63) for any allergens. The corresponding adjusted prevalence odds ratios (with 95% CI) of physician-diagnosed allergic manifestations were 1.15 (0.80, 1.63) for food allergy, 0.90 (0.47, 1.59) for pollen allergy or hay fever, 1.00 (0.75, 1.31) for atopic eczema, 0.96 (0.53, 1.65) for asthma and 1.08 (0.85, 1.38) for any allergic manifestation.

Conclusion: Insufficient evidence was found in our population for any association between birth by caesarean section and allergic manifestations. Further evidence from unselected populations, with longer follow-up periods, is needed.

INTRODUCTION

Allergies have become an epidemic in industrialized countries (1). Food allergies and atopic eczema are often the first manifestations of allergic conditions to appear during the first year of life (2,3), and these constitute risk factors for other allergies and asthma (4). Therefore, we need well-designed longitudinal studies, conducted in unselected populations, to increase our understanding of early-life risk factors for allergic diseases.

Caesarean section has often been suggested as a potential risk factor for allergic manifestations, compared with children born by vaginal delivery, due to delayed microbe colonization (5–18). For example, caesarean section was associated with a moderately increased risk of asthma in two meta-analyses (5,6). However, reports from a large register-based study from Sweden (19) and a population-based cohort study from New Zealand (20) considered lack of exposure to vaginal microflora as an unlikely explanation for the association between caesarean section and asthma. Hospital delivery has also been associated with colonization of *clostridium difficile* (15), stimulating debate about whether this infection is either a marker of reduced colonization of other microbiota or a possible reason for

allergic diseases (21,22). Three studies have found a positive association between caesarean delivery and sensitization or allergy to food items among healthy, full-term newborn infants (8–10,12). Two of them restricted their study population to offspring with a family history of allergy (8,9,12), which begs the question of a possible interaction between family history and mode of delivery. Yet, the association and its causal nature remain unclear (6,11,19–23).

Key notes

- Questionnaire data on 3181 children aged from 1 to 4 years were individually merged with allergy test results.
- The association between the mode of delivery and asthma suggested in earlier meta-analyses could not be replicated in this large unselected child population.
- No sufficient evidence was found for an association between caesarean section and any allergic manifestation or positive test results for food, pollen or animal allergens up to the age of 4 years.

The South Karelian Allergy Research Project (SKARP) is a population-based study comprising all children of a given age range and living in the same province. Data were collected by questionnaire and drawn from existing records on allergy tests that had been performed for diagnostic purposes (24,25). This study addresses the hypothesis that caesarean section is associated with the occurrence of allergy testing, positive test results and physician-diagnosed allergic manifestations up to 4 years of age. It also explores whether the possible effect of caesarean section is modified by parental allergies in a real-life epidemiological setting.

POPULATION AND METHODS

Population

This study comprised all children born between April 2001 and March 2005, who lived in the province of South Karelia, and were 1 to 4-year-olds when their parents were invited to take part in the questionnaire-based survey (N = 4779) (Fig. 1). The study population is a subset of the whole population of the SKARP study (N = 5973),

identified from the Finnish Population Register Centre (24), excluding all children who were newborn at the time of the survey.

Data collection

A questionnaire-based survey was conducted in close cooperation with local child health clinics between March 2005 and September 2006, when the children had their annual check-ups (24). The questionnaires were returned by the parents of 3308 children (69%).

The results of all the allergy tests that had been ordered by a physician for clinical purposes, and performed between April 2001 and September 2006, were collected from all healthcare units in the area. These covered the same population as the survey, but were independent of it, as we wanted to cover the entire population as explained in a previous paper (24).

The child's unique personal identity code (PIC) was used to individually merge the test data with the questionnaire data for 3262 of the children, for further analysis. The parents of 46 children refused permission for this process.

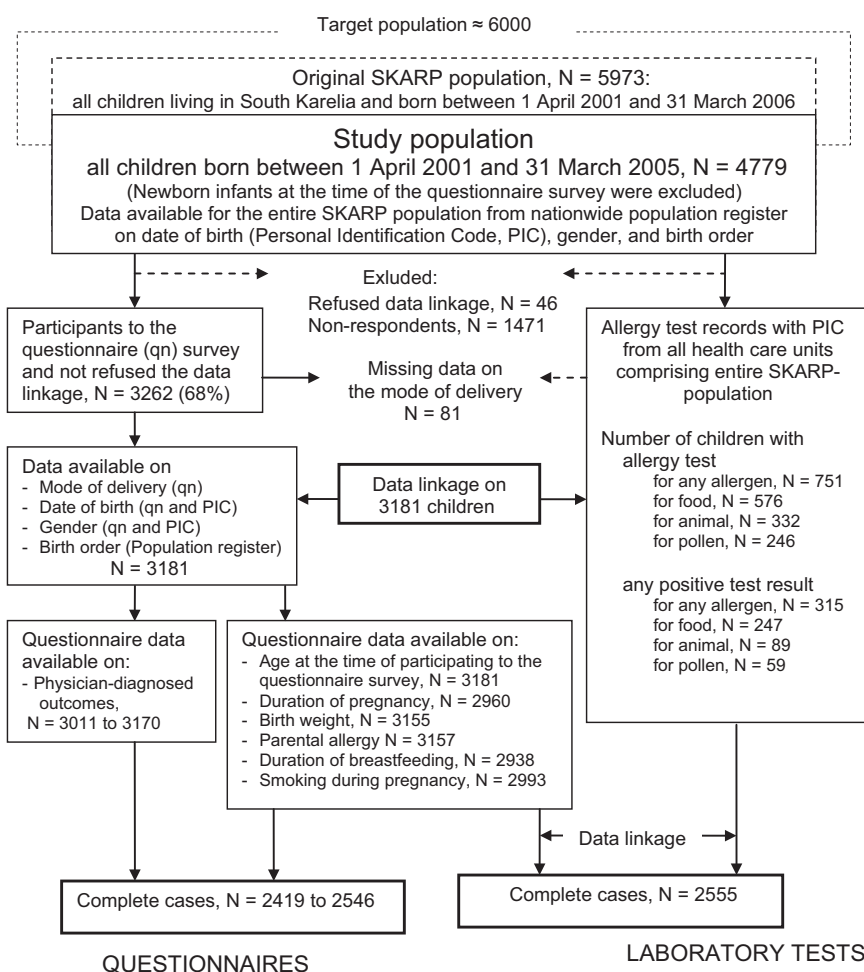


Figure 1 Flow diagram showing the study population and complete cases from the target population and data sources of the South Karelia Allergy Research Project (the SKARP), from which different items of data were available and data linkages were performed.

Details of the study design, participation rates and methods have been previously reported (24,25).

Ethics and permissions

The study subjects were not exposed to any diagnostic procedures or other medical interventions because of the study. The protocol was reviewed by the Ethical Committee of the Northern Ostrobothnia Hospital District. The allergy test data were collected with the permission of the Finnish Ministry of Social Affairs and Health. All eleven health centres in the region consented to cooperate. Parents were asked for their permission for the data linkage in the questionnaire.

Outcomes

We considered the occurrence of the first test and the first positive test result separately for food, animal, pollen and any allergens, respectively, when it came to longitudinal outcomes, based on laboratory records on allergy tests. The cut-off point for a positive result from a specific IgE was 0.35 kU/L with RAST-CAP FEIA or Phadiatop Combi and 1.43 standardized units per ml with Magic Lite. The cut-off point for a positive total IgE result was defined as 20 kU/L for babies under 5 months of age, 70 kU/L for babies aged 5 to 12 months, 110 kU/L for infants aged 1 to 2 years and 130 kU/L for children aged 2–7 years. The cut-off point for skin prick tests was defined as the mean of two orthogonal diameters of the urticarial weal of 3 mm, applied to both positive and negative controls. Test values equal or above the cut-off point were considered as positive. The open food challenge was considered 'positive' when labelled as such in the patient records.

As cross-sectional outcomes, based on parental responses to the questionnaire, we used: the history of physician-diagnosed allergy for animal, food, pollen or physician-diagnosed hay fever, atopic eczema ('atopic rash'), allergic urticaria, allergic conjunctivitis ('allergic inflammation of the eyes'), symptoms of asthma (defined as wheezing or persistent cough without flu) and diagnosis of asthma.

Explanatory variables

The date of birth and gender of the child (both included in the PICs) were obtained from the national population register. The PICs of the siblings living in the same household (including twins and step-siblings) were also obtained from the population register. Based on the PICs of the child and the siblings, the birth order was classified as 'firstborn' and 'not firstborn'. Firstborn twins were both classified as firstborn.

The parents were asked to record the anthropometric details from the maternity card (birth weight, duration of pregnancy) in the questionnaire. In Finland, gestational age is determined by an ultrasound scan during the 11th to 22nd gestational weeks in more than 90% of pregnancies, and the error margin is considered to be <7 days. The duration of pregnancy was classified according to the International Classification of Diseases 10 (ICD-10) (26)

as preterm (<37 weeks), full term (37–42 weeks) and post-term (>42 weeks).

Parent who completed the questionnaire were asked whether the delivery was: (a)'normal birth in a general or maternity hospital', (b)'caesarean operation in a hospital', (c)'normal birth at home or somewhere else than in a general or maternity hospital (e.g. in a taxi or ambulance)' and (d)'not known'. Children whose parents answered 'c' (n = 3) were combined with those answered 'a', and those whose parents answered 'd' were excluded from the further analyses (Fig. 1).

Further questions asked whether the child's biological mother, biological father or both had ever had asthma or any allergic or hypersensitive disorder (atopic rash, animal dust allergy, hay fever or pollen allergy, asthma or food allergy). Based on the answers, the following categories were formed: (i) physician-diagnosed allergic disorder, (ii) self-perceived allergic disorder, (iii) no allergic disorder ever perceived and (iv) unknown. 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 or pollen allergy). The phenotype of parental allergy (any of the conditions below) was based on the parents' own reports of a diagnosis made by a physician (atopic rash, animal allergy, hay fever/pollen allergy or allergic asthma) or on self-perceived or physician-diagnosed food allergy symptoms. Their children were classified according to the parents' allergic phenotype: (i) neither, (ii) only mother, (iii) only father, (iv) both parents and (v) missing.

Parents were asked to note the total duration of breastfeeding in months and weeks. This variable was classified into four categories. If the parents answered that their child was still being breastfed, the duration of breastfeeding was coded as more than 6 months. Mother's smoking during pregnancy was classified as 'No', 'Yes, occasionally (less often than daily)' and 'Yes, regularly (daily)'. The questionnaires are available at <http://kelo.oulu.fi/tutkimus/EKAT/>. Table 1 and Figure 1 show the number of children where data were available for each explanatory variable.

Statistical methods

The cumulative incidence of each outcome event by age was described by the Kaplan–Meier method, using the *survfit* function of the survival package in the R environment release 2.15.2 (www.r-project.org). The outcome event was either the first allergy test performed or the first positive test, as appropriate. The risk time began on the date of birth and ended at the event age (the child's age on the date of that event) if such an event occurred. For children without any pertinent event, the risk time ended on the closing date of data collection (September 30, 2006). The incidence of the first test and first positive test result (our test data include the exact dates for all tests and test results) for each allergy was regressed on the mode of delivery, gender, birth order, weight at birth, duration of pregnancy, parental allergies, total duration of breastfeeding and smoking during pregnancy using the Cox model (the *coxph* function

Table 1 Proportions (%; numbers in brackets) of children born by caesarean section according to selected demographic and clinical factors. Data available for 3181 children

	Group size	Caesarean section
Target age (years)		
1	835	18.2 (152)
2	819	17.1 (140)
3	759	16.2 (123)
4	768	17.7 (136)
Gender		
Girl	1561	16.8 (262)
Boy	1620	17.8 (289)
Birth order		
Firstborn	1495	22.5 (337)
Not firstborn	1686	12.7 (214)
Duration of pregnancy (weeks)		
<37	158	36.1 (57)
37–42	2702	16.1 (434)
>42	100	19.0 (19)
Missing	221	18.6 (41)
Birth weight (g)		
<2500	121	41.3 (50)
2500–3500	1300	18.5 (241)
3500–4200	1472	13.6 (200)
>4200	262	20.2 (53)
Missing	26	26.9 (7)
Parental allergies		
None	1248	16.7 (209)
Mother only	907	18.6 (169)
Father only	564	14.7 (83)
Both	438	19.4 (85)
Missing	24	20.8 (5)
Total duration of breastfeeding (months)		
0	142	33.8 (48)
0–4	666	21.5 (143)
4–6	342	21.3 (73)
>6	1788	13.7 (245)
Missing	243	17.3 (42)
Mother's smoking during pregnancy		
No	2601	17.3 (450)
Occasionally	199	16.1 (32)
Regularly	193	17.1 (33)
Missing	188	19.1 (36)
Total	3181	17.3 (551)

in the R survival package). Adjusted estimates of incidence rate ratios (RR) were obtained from these.

The cross-sectional outcomes referred to their life-time occurrence by the age of the child at the time their parents answered the questionnaire. These were analysed by logistic regression (function glm in R), in which the prevalence odds ratios (OR) were calculated from the fitted model, adjusted for the same variables as in the Cox model above plus the child's age when the parents returned the questionnaire.

The children with missing data on the relevant variables were excluded from the analyses when fitting these models.

RESULTS

Data on the mode of delivery were available for 3181 participating children, covering 98% of all those responding to the questionnaire and 67% of all those (N = 4779) who were initially invited to take part in the study (Fig. 1). Of those 3181 participants, 751 children (24%) had at least one allergy test taken by September 30, 2006. This percentage was similar (24%, N = 370) to the 1552 subjects for whom data on delivery were not available and whose parents had not refused the data linkage.

Overall, 17% of the children were born by caesarean section (Table 1). This proportion was higher for firstborn and preterm infants, those weighing <2500 g at birth and those breastfed for a short duration. It was also higher in the children whose mothers suffered from allergies. Mode of delivery seemed to be essentially independent of the gender of the child and maternal smoking.

The baseline occurrence of the different allergic outcomes by the age of 4 years varied from two to 10%. No clear difference was observed between caesarean section and vaginal delivery for any category of allergy in the cumulative incidence of allergy testing or of positive test results by 4 years of age (Table 2 and Fig. 2). Compared with children born by vaginal delivery, the adjusted relative incidence of positive allergy test (with 95% confidence intervals, CI) in children born by caesarean section was 1.14 (0.79, 1.65) for food, 1.16 (0.66, 2.05) for animal, 0.94 (0.46, 1.92) for pollen and 1.19 (0.87, 1.63) for any allergens. When the estimated rate ratios noted above were adjusted for selected covariates, they were all close to unity. Based on the location of the pertinent confidence limits at both sides of one, these findings do not provide adequate statistical support for the hypothesis that the mode of delivery would be associated with the outcome of interest. However, due to the relatively small numbers of cases included in our study, our results were too imprecise to rule out the possibility of such an association existing.

The adjusted odds ratios (with 95% CI) of the prevalence of physician-diagnosed allergic manifestations were 1.15 (0.80, 1.63) for food allergy, 1.24 (0.59, 2.41) for animal allergy, 0.90 (0.47, 1.59) for pollen allergy or hay fever, 1.00 (0.75, 1.31) for atopic eczema, 0.96 (0.54, 1.61) for allergic urticaria, 1.12 (0.56, 2.10) for allergic conjunctivitis, 0.96 (0.53, 1.65) for asthma, 1.37 (0.98, 1.90) for symptoms of asthma and 1.12 (0.87, 1.42) for any allergic manifestation. No evidence could thus be found for elevated odds of any of these outcomes in children born by caesarean section, when compared with children born by vaginal delivery (Table 2). Yet, the confidence intervals in these comparisons were also relatively wide.

Insufficient evidence was found for a possible modification of parental allergies on the effect of caesarean section (data not shown). However, evaluation of the relevant interaction terms was based on too small numbers in the key subgroups for any adequate statistical precision.

Table 2 Cumulative incidence (%; from Kaplan–Meier analyses) up to 4 years of age of first allergy test and of first positive test result, respectively, for different allergens, and the lifetime prevalence (%) of physician-diagnosed allergies and allergic conditions by mode of delivery. Estimated incidence rate ratios (RR) and prevalence odds ratios (OR) of respective outcomes for children born by caesarean section compared with those born by vaginal delivery (N = group size, n = number of cases, 95% CI = 95% confidence interval)

Allergic manifestation*	Mode of delivery		RR†/OR‡ (95% CI)
	Vaginal N = 2630 % (n)	Caesarean N = 551 % (n)	
Food allergy			
First test	18.7 (470)	19.0 (106)	1.05 (0.83, 1.32)†
First positive test	8.0 (200)	8.0 (47)	1.14 (0.79, 1.65)†
Physician-diagnosed	9.4 (245)	9.9 (54)	1.15 (0.80, 1.63)‡
Animal allergy			
First test	12.1 (271)	13.5 (61)	0.97 (0.72, 1.33)†
First positive test	3.2 (71)	3.6 (18)	1.16 (0.66, 2.05)†
Physician-diagnosed	2.2 (56)	2.1 (11)	1.24 (0.59, 2.41)‡
Pollen allergy (or hay fever)			
First test	9.4 (201)	10.1 (45)	0.90 (0.63, 1.30)†
First positive test	2.4 (47)	2.4 (12)	0.94 (0.46, 1.92)†
Physician-diagnosed	3.2 (83)	3.4 (18)	0.90 (0.47, 1.59)‡
Atopic eczema			
Physician-diagnosed	18.7 (480)	19.3 (104)	1.00 (0.75, 1.31)‡
Allergic urticaria			
Physician-diagnosed	4.6 (116)	4.5 (24)	0.96 (0.54, 1.61)‡
Allergic conjunctivitis			
Physician-diagnosed	2.4 (60)	3.2 (17)	1.12 (0.56, 2.10)‡
Symptoms of asthma			
Physician-diagnosed	9.8 (252)	13.9 (75)	1.37 (0.98, 1.90)‡
Diagnosis of asthma			
Physician-diagnosed	4.1 (106)	4.3 (23)	0.96 (0.53, 1.65)‡
Any allergy			
First test	25.1 (610)	27.0 (141)	1.10 (0.89, 1.35)†
First positive test	10.4 (254)	11.1 (61)	1.19 (0.87, 1.63)†
Physician-diagnosed	26.2 (686)	28.1 (154)	1.08 (0.85, 1.38)‡

*Data on allergy testing and positive test results were available for all 3181 children, but regarding physician-diagnosed allergic manifestations for 3011–3170 children (95% to 100%).

†For the incidence of allergy testing and of positive test results, the rate ratios (RR) were estimated by a Cox proportional hazards model adjusted for gender, birth order, duration of pregnancy, birth weight, parental allergy, duration of breastfeeding and smoking during pregnancy, as estimated from complete cases (N = 2555).

‡For the prevalence of physician-diagnosed allergic manifestations, the odds ratios (OR) were estimated by logistic regression model adjusting for the same variables as in the Cox models above, plus the child's age when the parents filled the questionnaire, as estimated from complete cases (data available for 2419–2546 children depending on the outcome variables).

DISCUSSION

Our results did not provide adequate support for the hypothesis of a positive association between caesarean section and the emergence of allergic manifestations or sensitization during the first 4 years of life. Even though the baseline occurrence of the different allergic conditions varied from 2% to 10%, the relative contrasts between the

caesarean section group and the vaginal delivery group were all very close to one, when adjusted for important potential confounders. However, many of the confidence intervals in our results were relatively wide. Therefore, this overall negative finding cannot rule out the possibility of caesarean section having some effects, albeit not very strong, on the risk of allergies and/or asthma.

The main strength of this study is the population-based longitudinal database (24) comprising both questionnaire and allergy test data. Unlike previous studies, we could describe the associations between the mode of delivery and several allergic outcomes in an unselected population in a real-life setting. This is also one of the largest studies ever conducted on this topic in unselected child populations (4,5). It also appears to represent the general population well. For example, the 17.3% of children born by caesarean section was close to the 16.6% reported for all of Finland in the year 2004 (27). In addition, the proportions of premature infants (5.3%) and of children with birth weights of <2500 g (3.8%) were also close to those in the whole country during 2004 (5.8% and 4.4%, respectively) (27). Another important strength of our data is that it included the exact dates of both allergy testing and positive test results, which enabled us to display the cumulative incidences of outcomes according to the mode of delivery and to apply survival methods in the data analysis.

As to the shortcomings of the study, we would first mention the fact that one-third of the parents invited to take part in the questionnaire survey did not respond. However, based on our findings in previous research (24) and in this study, this nonresponse does not seem to have negatively affected the representativeness of the final study population. Also, we find it reassuring that the overall percentage of the allergy tested children among the nonrespondents was not different from the percentage among the respondents. Selection bias would be an issue, if nonresponse and/or experiencing allergy testing were dependent both on the main risk factor and on the study outcomes. Such a joint dependency cannot be directly examined, though. Nevertheless, we find it unlikely that participation in the survey, and/or exposure to allergy testing, would be at all dependent on the mode of delivery when this dependence is considered as conditional on any indication for such a test being ordered. Indirect support for the latter standpoint is provided by the fact that the 4-year incidence of any allergy testing among the participants was only slightly higher for the caesarean section group than for the vaginal delivery group.

In the final study population, certain covariates were absent, but the percentage of missing values was clearly <10% for all of them. These missing data can hardly be considered to be dependent either on the mode of delivery or on the outcomes to such an extent that the estimates of interesting rate ratios or odds ratios would be seriously affected.

The heterogeneity of the test data obtained from several laboratories might have introduced some misclassification of the outcome, but it is unlikely that this would have

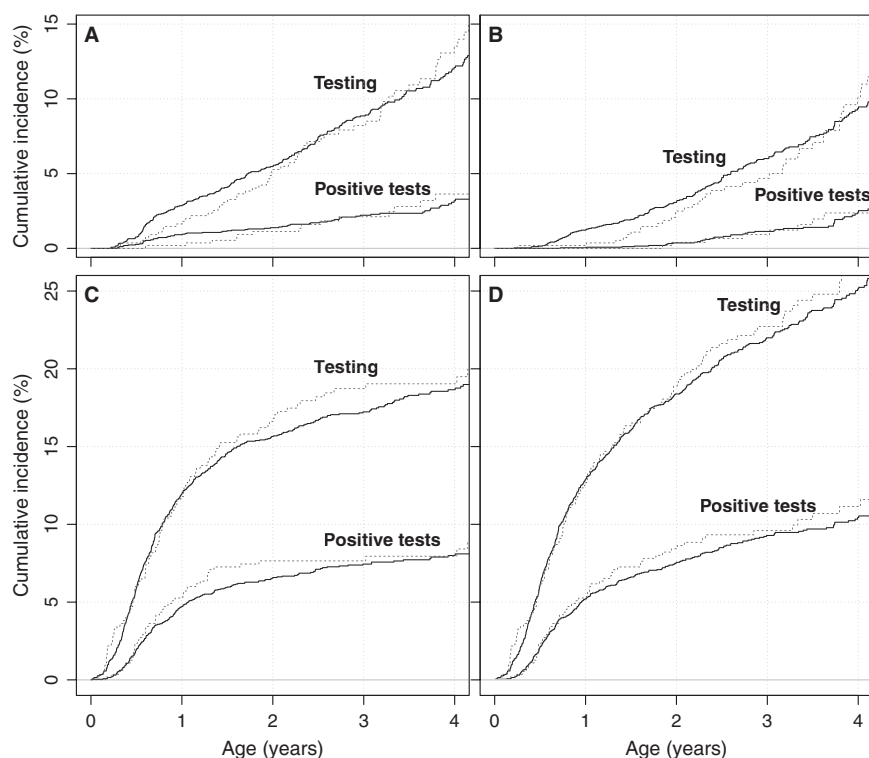


Figure 2 Cumulative incidences of allergy testing and positive test results separately for animal (A), pollen (B), any food (C) and any allergens (D) according to mode of delivery ($N = 3181$). Solid line = vaginal delivery and dashed line = caesarean section.

affected the findings with respect to the mode of delivery and the other covariates considered. The same can be said about the variability in the timing of responding to the questionnaire and of the allergy tests, there apparently being no systematic differences between the caesarean section group and the vaginal delivery group.

The questionnaire method may perhaps be considered as the main weakness of our study. More accurate perinatal data could, in principle, be obtained from the Medical Birth Register of Finland. Unfortunately, we did not have resources for the necessary record linkage. However, parents are likely to recall the mode of delivery, duration of pregnancy and birth weight accurately. Moreover, most questionnaires were returned during a visit to the child health clinic and the public health nurse checked them and completed the relevant missing items from the documents or patient records kept at the clinic (24), thereby further improving the quality of the data. Thus, we have good grounds to believe that our perinatal data were not affected by recall bias. On the other hand, the questionnaire was the only feasible method of obtaining all the relevant information from a sufficiently large population. Many of our outcome variables, as well as the covariates describing parental allergies, mother's smoking and duration of breastfeeding, were only based on the questionnaires and would not be available from any register.

The questionnaire lacked more specific classification for caesarean section (e.g. elective or emergency) or vaginal delivery (e.g. use of forceps or vacuum extraction). During

the years 2004 and 2005 (28), forceps were rarely used in Finland overall (0.1% of all deliveries) and in none of the deliveries in South Karelia. Thus, it is highly likely that forceps were only used for a handful of deliveries, at most, among the SKARP study participants. Moreover, in South Karelia, only 6.5% of singleton deliveries were assisted by vacuum extraction, 8.9% were assisted by elective caesarean sections, and 8.9% were subjected to emergency or urgent sections (28). Any analyses based on this more refined classification of deliveries, even if available, would have resulted in greater imprecision in the estimation and wider confidence intervals of the interesting relative effects in these subgroups in our study.

A further limitation was that the follow-up only lasted up to the age of 4 years, which is apparently too early to be informative for asthma and pollen allergy or hay fever, although quite sufficient for food allergies and atopic eczema. A longer follow-up would obviously have yielded a higher number of cases and narrower confidence intervals for all outcomes. As the age of the child at the end of the follow-up, and at the time of the questionnaire survey, was allowed for in the regression models, heterogeneity of ages of the study population only affected the precision of the results, but hardly caused any major bias.

A positive association between caesarean delivery and allergy or sensitization to food items has been reported in several studies (8–10,12). Our estimates did not disagree with these when taking into account the statistical error margins. However, none of those studies were based on an

unselected population like ours. Moreover, the finding of Eggesbø et al. (8) was confined only to children with an allergic mother, the population studied by Laubreau et al. (12) comprised only offspring with a family history of allergy and Koplin et al. (29) could not confirm the association between caesarean section and egg allergy among children with a maternal history of allergy. In our population, the subgroup of children born by caesarean section and with parental allergies was too small for sufficiently precise evaluation of whether the effect of caesarean section would be different in children with such a family history than in other children. The authors of a meta-analysis (6) expressed concern about the possibility of publication bias explaining the reported positive association between caesarean section and food allergies. Also, the variability in the food allergens and the cut-off points used in different studies make any comparisons across different studies difficult. No association between caesarean section and inhalant atopy or eczema/atopic dermatitis could be found in the same meta-analysis (6) or in a population-based cohort from New Zealand (20), our observations being concordant with both of these reports.

There appears to be a discrepancy between the relative odds estimates for the history of symptoms of asthma and of physician-diagnosed asthma, both based on parental reports. However, when the error margins are taken into account, these do not conflict with each other. They are also statistically consistent with the results of two meta-analyses reporting a moderately increased risk of asthma among children born by caesarean section (5,6) and with the previous Finnish studies on this topic (13,14,17). A register-based Finnish Birth Cohort in 1990 (17) and Northern Finland Birth Cohorts in 1985 and 1966 (NFBC1985 and NFBC1966) (13,14) all reported that caesarean section was associated with the occurrence of diagnostic codes for asthma by the age of 7 years, with history of physician-diagnosed asthma or hospitalization due to asthma (49 cases) by the age of 7 years and with physician-diagnosed asthma (14 cases) in adulthood, respectively. In the study population of the NFBC1966, caesarean section was not found to be associated with atopy, hay fever or atopic eczema (14).

Our results are also well in accordance with the results of two population-based cohorts from Brazil (18) and with large population-based cohorts from Denmark (30) and from New Zealand (20), in which no association could be found between asthma and the mode of delivery. A large register-based Swedish study by Almqvist et al. (19) found that the association between elective caesarean section and use of asthma medication disappeared when they carried out a sibling control analysis. They also concluded that the indications of emergency caesarean section, rather than the mode of delivery or delayed microbial contact, are related to the use of asthma medication among the offspring. In the birth cohort from New Zealand (20), forceps assistance during vaginal delivery was associated with atopy and asthma at the ages of 13 and 32 years, but after adjustments, the positive association disappeared or was greatly weakened. Hancox et al. (20) suggested that some other

background factors associated with the mode of delivery might act as more probable risk factors for atopic outcomes than the lack of microbial contact in conjunction with caesarean section. However, in our cohort, parental factors (allergies), maternal factors (e.g. mother's smoking, duration of breastfeeding) and foetal factors (e.g. measurements at birth) were included as covariates in the models.

In conclusion, our results do not, as such, provide sufficient support for the hypothesis that caesarean section would increase the risk of allergic manifestations or allergic sensitization in early childhood. As these results have a relatively wide margin of error, we cannot rule out the possibility that caesarean section having some effects, albeit not very strong, on the risk of allergies and/or asthma. Replication in other, and hopefully even larger, unselected populations and a longer follow-up period are required for a more reliable evaluation of the hypothesis.

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CONFLICT OF INTERESTS

None declared.

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