

## Original Contribution

# Maternal and Perinatal Characteristics and the Risk of Cow's Milk Allergy in Infants up to 2 Years of Age: A Case-Control Study Nested in the Finnish Population

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Initially submitted December 9, 2009; accepted for publication March 16, 2010.

This study examined whether maternal background and perinatal factors were associated with the risk of cow's milk allergy (CMA) in infants up to 2 years of age in a nested case-control study. All children born in 1996–2004 in Finland and diagnosed with CMA by 2006 were identified ( $n = 16,237$ ). For each case, one matched control was selected. Information on maternal and perinatal factors was derived from the Medical Birth Register. The associations were analyzed by conditional logistic regression. Cesarean section (adjusted odds ratio (OR) = 1.18, 95% confidence interval (CI): 1.10, 1.27) and high maternal age ( $\geq 35$  years; adjusted OR = 1.23, 95% CI: 1.11, 1.36) were associated with increased risk, whereas low maternal socioeconomic status (adjusted OR = 0.65, 95% CI: 0.59, 0.71), smoking (adjusted OR = 0.72, 95% CI: 0.67, 0.79), high number of previous deliveries ( $\geq 5$ ; adjusted OR = 0.71, 95% CI: 0.59, 0.86), and multiple pregnancy (adjusted OR = 0.70, 95% CI: 0.60, 0.82) were associated with decreased risk of CMA. In conclusion, maternal background and perinatal factors may play a role in the development of CMA, but further research is needed to clarify these associations and the underpinning biologic mechanisms.

cesarean section; child; cohort studies; milk hypersensitivity; registries; risk factors; siblings

Abbreviations: CI, confidence interval; CMA, cow's milk allergy; OR, odds ratio.

Cow's milk allergy (CMA) is a common food allergy in infancy, with an incidence rate of 2%–3% in the first year of life (1). Both genetic and environmental factors play a role in the development of allergic diseases including CMA, and the critical period for these factors to come into play seems to be early childhood or even during pregnancy (2). Despite active research, evidence on the association between early life circumstances and allergic diseases such as asthma, hay fever, or atopic dermatitis is not consistent (3). Far fewer studies have used food allergy (4–11) or CMA (6, 11) as the outcome.

Compared with vaginal birth, cesarean section has been associated with parentally reported reactions to foods and immunoglobulin E-mediated CMA (5, 11) but not with other food allergies (6–9). Furthermore, an increased risk of food allergy has been reported among firstborn children and children with mothers older than 30 years of age at delivery (4).

In addition, prematurity and low birth weight have been hypothesized to be associated with increased risk of food allergy via increased food antigen uptake caused by intestinal permeability related to prematurity (12), but recent studies have not found support for this hypothesis (7, 13). The aim of this study was to assess whether maternal background and perinatal factors were associated with the risk of CMA in infants up to 2 years of age in a population-based, nested case-control study including 16,237 case-control pairs.

## MATERIALS AND METHODS

### Data sources

Data were obtained from 4 national registers and were linked by the unique personal identity codes assigned to

all Finnish citizens shortly after birth (14). The Special Reimbursement Register and the Population Register maintained by the Social Insurance Institution were used to select cases and controls, respectively. The Prescription Register of the Social Insurance Institution was used to obtain information on purchases of special infant formula. In Finland, all special infant formulas (soy-based formulas, extensively hydrolyzed formulas, or elemental formulas) are sold in pharmacies. Purchases of those special infant formulas prescribed by pediatricians and reimbursed by the National Sickness Insurance Scheme are registered in the Prescription Register. Information on maternal background and perinatal factors was derived from the Finnish Medical Birth Register, maintained by the National Institute for Health and Welfare.

### Study population

In Finland, infants up to 2 years of age who need special infant formulas for management of diagnosed CMA are entitled to a special reimbursement for the cost of these formulas (15). We identified all infants who were born between January 1, 1996, and April 30, 2004, and had received a special reimbursement based on diagnosed CMA by the end of November 2005 ( $n = 19,111$ ). The Medical Birth Register data were not available for the children not born in Finland ( $n = 310$  subjects, 79 cases and 231 controls), and these children were excluded from the cohort. To avoid false-positive diagnoses of CMA, infants with a special reimbursement of short duration ( $<6$  months,  $n = 257$ ) or none or only occasional purchases (a maximum of 2) of special infant formulas ( $n = 2,536$ ) were excluded from the cohort. For each case, one control, who had no special reimbursement for CMA, was randomly selected and matched on date of birth ( $\pm 28$  days), gender, and the hospital district in which the infant was born. Finally, 16,237 case-control pairs were included in the study.

### CMA diagnosis

To grant the special reimbursement, the Social Insurance Institution requires a specific certificate from a pediatrician stating that CMA was diagnosed according to specified criteria. The criteria included clinical examination with a careful history, symptoms suggestive of CMA, and disappearance of the symptoms when cow's milk was eliminated from the diet. Furthermore, either a positive skin-prick test, elevated serum-specific immunoglobulin E, or an open-challenge test performed in the hospital's inpatient or outpatient unit was required. In most instances, final confirmation of the diagnosis was based on an open-challenge test (16). Finally, all special reimbursement applications and certificates are reviewed by a clinical specialist, in most instances by a pediatrician, at the Social Insurance Institution.

### Exposures

The maternal background variables used in this study were age at delivery ( $<25$ , 25–29, 30–34, and  $\geq 35$  years), smoking during pregnancy (no/yes, including those who

quit during the first trimester), and socioeconomic status. Socioeconomic status was derived from maternal occupation recorded according to the national standards applied by Statistics Finland (17). If information on occupation was not available, the highest educational level was converted into socioeconomic status. Socioeconomic status was further aggregated into 4 groups based on a previously used categorization (18): upper-white-collar workers; lower-white-collar workers; blue-collar workers; and "others" (all parenthetical numbers and percentages that follow refer to women in this "others" group), including students ( $n = 2,374$ , 45.4%), housewives ( $n = 2,037$ , 39.0%), farmers ( $n = 340$ , 6.5%), entrepreneurs ( $n = 326$ , 6.2%), unemployed ( $n = 141$ , 2.7%), and retired ( $n = 9$ , 0.2%). Number of previous maternal deliveries (0, 1, 2, 3, 4, and  $\geq 5$ ) was used to assess the number of older siblings.

The perinatal variables included were multiple pregnancy (twin/triplet pregnancy, no/yes); mode of delivery (normal vaginal delivery, assisted vaginal delivery, and cesarean section including planned and unplanned cesarean sections); complications during pregnancy (none, maternal high blood pressure during pregnancy that had to be treated in hospital, placental complications including placenta previa and placenta avulsion, abnormal presentation including breech and other abnormal presentations, and fetal asphyxia); Apgar score at 1 minute (0–6, 7–8, 9–10); prematurity (i.e., gestational age  $<37$  weeks), low birth weight (i.e., birth weight  $<2,500$  g), and gestational-age-adjusted birth weight, defined according to Finnish sex-specific population-based growth curves (small for gestational age =  $\leq -2$  standard deviations of the mean birth weight for gestational age, appropriate for gestational age = within mean  $\pm 2$  standard deviations, large for gestational age =  $\geq$  mean + 2 standard deviations) (19). In addition, children were stratified according to gestational age, birth weight, birth length, and ponderal index (birth weight/birth length<sup>3</sup>) at birth on the basis of quintiles of the controls. No information on the father was available in the Medical Birth Register. The study was approved by the national data protection authority, the institutions keeping the registers, and the institutional review board of the National Public Health Institute (National Institute for Health and Welfare since 2009).

### Statistical analysis

The associations between maternal background and perinatal factors have been studied and reported previously (20). The associations of maternal background and perinatal factors with the risk of CMA were analyzed by conditional logistic regression, with results displayed as odds ratios and 95% confidence intervals. Firstly, a crude model including only one explanatory variable at a time was fitted. The variables multiple pregnancy, mode of delivery, ponderal index, Apgar score, and complications were, however, adjusted for gestational age. Secondly, a full model including maternal age, socioeconomic status, smoking during pregnancy, and previous deliveries, as well as multiple pregnancy, mode of delivery, gestational age, and the ponderal index of the child, was fitted.

Furthermore, to evaluate the association between birth weight and length and the risk of CMA, both a model

including only gestational age and a full model including the variables described above, except for ponderal index, were fitted. A test for trend was performed by fitting a conditional logistic regression model for the linear effect of birth weight, length, gestational age, or maternal age using a likelihood ratio test. To examine whether associations between maternal background or perinatal factors and the risk of CMA were modified by maternal age, smoking during pregnancy, and socioeconomic status, an interaction term was included in the full model and a likelihood ratio test was used to compare the models with and without an interaction term. Statistical significance was set at the 5% level, and 2-sided *P* values were used. All analyses were performed by using STATA, version 9.1, software (StataCorp LP, College Station, Texas).

## RESULTS

The special reimbursement for CMA was received at a mean age of 6.0 months (standard deviation, 3.7). CMA was more common in boys (59%) than in girls (41%) (*P* < 0.001).

In the crude models, cesarean section and assisted vaginal delivery were associated with an increased risk, whereas high number of previous deliveries, multiple pregnancy, low socioeconomic status, and smoking during pregnancy were associated with a decreased risk of CMA in the offspring (Table 1). Maternal age varied between 14 years and 50 years, and it was directly associated with the risk of CMA (test for trend *P* < 0.001). The associations between planned and unplanned cesarean section separately and the risk of CMA did not differ substantially (adjusted odds ratio (OR) = 1.18, 95% confidence interval (CI): 1.07, 1.30 and adjusted OR = 1.15, 95% CI: 1.05, 1.27, respectively). The associations remained essentially similar in the full model.

A direct association was observed between birth weight and the risk of CMA in the gestational-age-adjusted model (test for trend *P* < 0.001) (Figure 1). Further adjustment for potential confounders attenuated the association, but the trend remained significant (test for trend *P* = 0.011). No such consistent association was observed with birth length (in the gestational-age-adjusted model, test for trend *P* = 0.002; in the full model, test for trend *P* = 0.980). None of the other factors related to fetal growth (prematurity, low birth weight, or gestational-age-adjusted birth weight) were significantly associated with the risk of CMA (data not shown).

A weak association was observed between low Apgar scores and the risk of CMA (OR = 1.11, 95% CI: 1.00, 1.24 for Apgar scores 0–6 and OR = 1.00, 95% CI: 0.95, 1.06 for Apgar scores 7–8 compared with the highest scores: 9–10). Maternal or fetal complications were not significantly associated with CMA (OR = 1.06, 95% CI: 0.99, 1.13 for any complication; OR = 1.03, 95% CI: 0.92, 1.15 for maternal high blood pressure; OR = 1.28, 95% CI: 0.94, 1.76 for placental complications; OR = 1.05, 95% CI: 0.96, 1.15 for fetal abnormal presentation; and OR = 1.05, 95% CI: 0.90, 1.23 for fetal asphyxia). In addition, we did not observe significant effect modification by maternal age, smoking, or socioeconomic status (*P* for all interactions > 0.05).

## DISCUSSION

In this large, population-based study, several maternal background and perinatal factors were associated with CMA. An increased risk of CMA was observed for children whose delivery was assisted or whose birth weight was high. Maternal low socioeconomic status, smoking during pregnancy, and multiple pregnancy were associated with a decreased risk of CMA. In addition, maternal age was directly and number of previous deliveries was inversely associated with the risk of CMA.

The hypotheses of prenatal and postnatal programming have been developed to explain the mechanisms underlying allergic diseases. The postnatal programming hypothesis, based on Strachan's original hygiene hypothesis (21), suggests that delayed establishment of the normal intestinal microflora and impairment of the gut barrier may lead to a higher risk of developing allergic diseases in later life. Thus, issues affecting establishment of intestinal microflora, such as cesarean section (22), may be potential risk factors for food allergies. We observed a weak association between cesarean section and an increased risk of CMA. Previously, one study reported an increased risk of immunoglobulin E-mediated CMA (11) in children born by cesarean section compared with those born vaginally, but, in another study, the increased risk of CMA/cow's milk intolerance was limited to children whose mothers were allergic (6). Furthermore, some evidence exists for an increased risk of sensitization to food allergens in children born by cesarean section (23, 24). We observed an association, although weak and of borderline significance, between assisted vaginal delivery and an increased risk of CMA. To our knowledge, no studies exploring this association have been published previously, but some evidence, although not consistent, on assisted vaginal delivery and an increased risk of other allergic diseases exists (25, 26).

The associations observed for multiple pregnancies and number of maternal previous deliveries support both the prenatal and postnatal hypotheses. It has been suggested that the protective association of multiple pregnancies and older siblings is due to increased exposure to infections in early childhood from close contact with siblings (21, 27). On the other hand, these associations may have their origin in the prenatal period because hormonal and immunologic conditions in the uterus in twin or subsequent pregnancies are different from those in single-fetus or first pregnancies, respectively, and this factor may affect the health outcomes of the children later in life (28). A decreased risk of allergic diseases with increasing number of older siblings has been observed in several studies (28, 29), but the evidence related to food allergies is limited (4, 5).

Evidence on the association between parental socioeconomic status and allergic diseases in children is controversial; both direct (30, 31) and inverse (32) associations have been reported. One can speculate that the direct association can be explained by the fact that mothers of high socioeconomic status consult a physician more often compared with mothers of lower socioeconomic status (33). However, it is worth noting that, in Finland, all mothers and infants, regardless of their socioeconomic status, are entitled to

**Table 1.** Associations of Maternal Background and Perinatal Factors With the Risk of Cow's Milk Allergy in Infants Born in 1996–2004 in Finland and Diagnosed With Cow's Milk Allergy by the End of November 2005

| Factor                                                     | Cases<br>( <i>n</i> = 16,237) |      | Controls<br>( <i>n</i> = 16,237) |      | Crude Model |            |                             | Full Model <sup>a</sup> |            |                             |
|------------------------------------------------------------|-------------------------------|------|----------------------------------|------|-------------|------------|-----------------------------|-------------------------|------------|-----------------------------|
|                                                            | No.                           | %    | No.                              | %    | OR          | 95% CI     | <i>P</i> Value <sup>b</sup> | OR                      | 95% CI     | <i>P</i> Value <sup>b</sup> |
| Maternal age, years                                        |                               |      |                                  |      |             |            | <0.001                      |                         |            | <0.001                      |
| <25                                                        | 2,348                         | 14.5 | 3,200                            | 19.1 | 1.00        |            |                             | 1.00                    |            |                             |
| 25–29                                                      | 5,356                         | 33.0 | 5,289                            | 32.6 | 1.38        | 1.29, 1.47 |                             | 1.21                    | 1.12, 1.32 |                             |
| 30–34                                                      | 5,571                         | 34.3 | 4,289                            | 29.8 | 1.58        | 1.47, 1.68 |                             | 1.34                    | 1.23, 1.46 |                             |
| ≥35                                                        | 2,962                         | 18.2 | 2,910                            | 17.9 | 1.40        | 1.29, 1.50 |                             | 1.23                    | 1.11, 1.36 |                             |
| Maternal socioeconomic status                              |                               |      |                                  |      |             |            | <0.001                      |                         |            | <0.001                      |
| Upper-white-collar worker                                  | 3,290                         | 20.0 | 2,553                            | 15.7 | 1.00        |            |                             | 1.00                    |            |                             |
| Lower-white-collar worker                                  | 6,571                         | 40.5 | 6,039                            | 37.2 | 0.83        | 0.78, 0.89 |                             | 0.89                    | 0.83, 0.95 |                             |
| Blue-collar worker                                         | 1,839                         | 11.3 | 2,466                            | 15.2 | 0.57        | 0.52, 0.62 |                             | 0.65                    | 0.59, 0.71 |                             |
| Others <sup>c</sup>                                        | 2,404                         | 14.8 | 2,823                            | 17.4 | 0.64        | 0.59, 0.69 |                             | 0.75                    | 0.69, 0.82 |                             |
| Missing data                                               | 2,133                         | 13.1 | 2,356                            | 14.5 |             |            |                             |                         |            |                             |
| Maternal smoking during pregnancy                          |                               |      |                                  |      |             |            | <0.001                      |                         |            | <0.001                      |
| No                                                         | 14,287                        | 88.0 | 13,465                           | 82.9 | 1.00        |            |                             | 1.00                    |            |                             |
| Yes <sup>d</sup>                                           | 1,557                         | 9.7  | 2,371                            | 14.6 | 0.62        | 0.58, 0.67 |                             | 0.72                    | 0.67, 0.79 |                             |
| Missing data                                               | 373                           | 2.3  | 401                              | 2.5  |             |            |                             |                         |            |                             |
| Maternal previous deliveries, no.                          |                               |      |                                  |      |             |            | <0.001                      |                         |            | <0.001                      |
| 0                                                          | 6,581                         | 40.5 | 6,741                            | 41.5 | 1.00        |            |                             | 1.00                    |            |                             |
| 1                                                          | 5,765                         | 35.5 | 5,333                            | 32.8 | 1.11        | 1.05, 1.16 |                             | 1.02                    | 0.95, 1.08 |                             |
| 2                                                          | 2,507                         | 15.4 | 2,525                            | 15.7 | 1.02        | 0.95, 1.08 |                             | 0.94                    | 0.87, 1.02 |                             |
| 3                                                          | 823                           | 5.1  | 908                              | 5.6  | 0.93        | 0.84, 1.02 |                             | 0.90                    | 0.79, 1.01 |                             |
| 4                                                          | 245                           | 1.5  | 315                              | 1.9  | 0.79        | 0.67, 0.94 |                             | 0.76                    | 0.62, 0.93 |                             |
| ≥5                                                         | 295                           | 1.8  | 393                              | 2.4  | 0.76        | 0.65, 0.89 |                             | 0.71                    | 0.59, 0.86 |                             |
| Missing data                                               | 21                            | 0.1  | 22                               | 0.1  |             |            |                             |                         |            |                             |
| Multiple pregnancy <sup>e</sup>                            |                               |      |                                  |      |             |            | 0.003                       |                         |            | <0.001                      |
| No                                                         | 15,808                        | 97.4 | 15,700                           | 96.7 | 1.00        |            |                             | 1.00                    |            |                             |
| Yes                                                        | 429                           | 2.6  | 537                              | 3.3  | 0.80        | 0.70, 0.91 |                             | 0.70                    | 0.60, 0.82 |                             |
| Mode of delivery <sup>e</sup>                              |                               |      |                                  |      |             |            | <0.001                      |                         |            | <0.001                      |
| Normal vaginal delivery                                    | 12,119                        | 74.6 | 12,582                           | 77.5 | 1.00        |            |                             | 1.00                    |            |                             |
| Assisted vaginal delivery                                  | 1,094                         | 6.7  | 1,005                            | 6.2  | 1.13        | 1.03, 1.23 |                             | 1.11                    | 0.99, 1.23 |                             |
| Cesarean section <sup>f</sup>                              | 2,996                         | 18.5 | 2,623                            | 16.2 | 1.20        | 1.13, 1.28 |                             | 1.18                    | 1.10, 1.27 |                             |
| Missing data                                               | 28                            | 0.2  | 27                               | 0.2  |             |            |                             |                         |            |                             |
| Gestational age, days (quintiles)                          |                               |      |                                  |      |             |            | 0.314                       |                         |            | 0.373                       |
| <271                                                       | 3,147                         | 19.4 | 3,232                            | 19.9 | 1.00        |            |                             | 1.00                    |            |                             |
| 271–276                                                    | 3,239                         | 20.0 | 3,136                            | 19.3 | 1.06        | 0.99, 1.13 |                             | 0.97                    | 0.90, 1.06 |                             |
| 277–280                                                    | 2,794                         | 17.2 | 2,748                            | 16.9 | 1.04        | 0.97, 1.12 |                             | 0.95                    | 0.87, 1.04 |                             |
| 281–286                                                    | 3,440                         | 21.2 | 3,374                            | 20.8 | 1.05        | 0.98, 1.12 |                             | 0.99                    | 0.91, 1.08 |                             |
| ≥287                                                       | 3,567                         | 22.0 | 3,676                            | 22.6 | 1.00        | 0.93, 1.07 |                             | 0.93                    | 0.86, 1.01 |                             |
| Missing data                                               | 50                            | 0.3  | 71                               | 0.4  |             |            |                             |                         |            |                             |
| Ponderal index, g/cm <sup>3</sup> (quintiles) <sup>e</sup> |                               |      |                                  |      |             |            | 0.080                       |                         |            | 0.450                       |
| <2.58                                                      | 3,125                         | 19.3 | 3,263                            | 20.1 | 1.00        |            |                             | 1.00                    |            |                             |
| 2.58–2.70                                                  | 3,161                         | 19.5 | 3,255                            | 20.1 | 1.01        | 0.94, 1.08 |                             | 1.02                    | 0.94, 1.11 |                             |
| 2.71–2.82                                                  | 3,182                         | 19.6 | 3,203                            | 19.7 | 1.03        | 0.96, 1.11 |                             | 1.00                    | 0.92, 1.09 |                             |
| 2.83–2.97                                                  | 3,330                         | 20.5 | 3,211                            | 19.8 | 1.08        | 1.00, 1.16 |                             | 1.07                    | 0.98, 1.16 |                             |
| ≥2.98                                                      | 3,371                         | 20.8 | 3,216                            | 19.8 | 1.09        | 1.01, 1.17 |                             | 1.06                    | 0.97, 1.15 |                             |
| Missing data                                               | 68                            | 0.4  | 89                               | 0.6  |             |            |                             |                         |            |                             |

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup> The main full model includes all variables listed in the table.<sup>b</sup> *P* values for the whole variable in the crude and adjusted models were obtained by means of likelihood ratio test.<sup>c</sup> Includes students, housewives, farmers, entrepreneurs, unemployed, and retired.<sup>d</sup> Includes those who quit smoking during the first trimester (*n* = 256 for cases, *n* = 331 for controls).<sup>e</sup> Odds ratios are adjusted for gestational age in the crude model.<sup>f</sup> Includes planned cesarean section (*n* = 1,411 for cases, *n* = 1,210 for controls) and unplanned cesarean section (*n* = 1,585 for cases, *n* = 1,413 for controls).

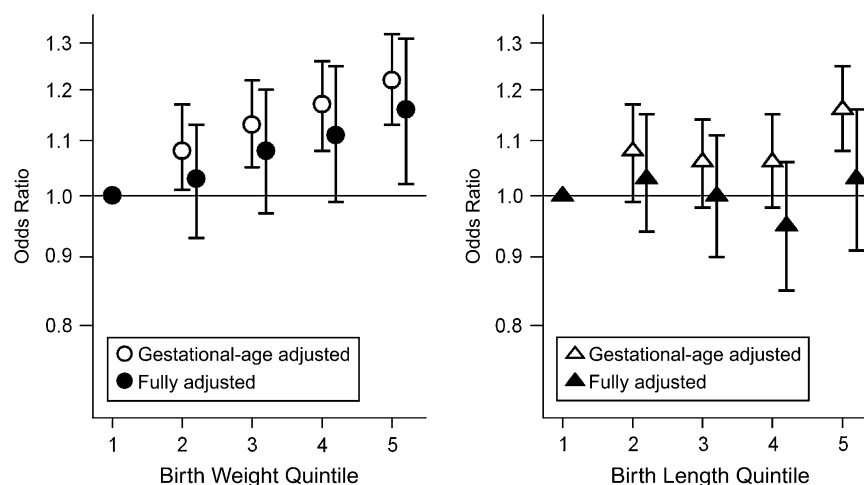


**Figure 1.** Association of birth weight (circles) and birth length (triangles) with the risk of cow's milk allergy in infants born in 1996–2004 in Finland. Data points are gestational-age-adjusted and fully adjusted odds ratios (circles or triangles) with 95% confidence intervals (bars). The fully adjusted model included maternal age, socioeconomic status, smoking during pregnancy, previous maternal deliveries, multiple pregnancy, mode of delivery, gestational age, and birth weight and length (when appropriate). Quintiles of birth weight and length were based on the distribution among the controls—birth weight: 1 =  $\leq 3,129$  g (reference), 2 = 3,130–3,439 g, 3 = 3,440–3,689 g, 4 = 3,690–3,979 g, 5 =  $\geq 3,980$  g; birth length: 1 =  $\leq 48$  cm (reference), 2 = 49 cm, 3 = 50 cm, 4 = 51 cm, 5 =  $\geq 52$  cm.

well-baby clinic services free of charge and to equal access to further medical care (34). Furthermore, it is possible that low socioeconomic status is associated with other factors such as mode of infant feeding (35), which, in turn, have a role in the development of CMA (36).

Our observation that maternal smoking during pregnancy was inversely associated with CMA is in contrast with recent observations of an increased risk of sensitization to foods related to exposure to maternal prenatal and postnatal smoking (37, 38). However, the direct association observed by Keil et al. (37) was present for only those children of parents with allergies, and the evidence related to clinical atopic disease is not consistent (39). We cannot exclude the possibility that the observed association is due to residual confounding; thus, more studies are needed to explore this topic.

We observed a slightly increased risk of CMA for children born at a high birth weight, whereas no associations were found for other variables related to fetal growth. Previous studies on fetal growth and food allergy have mainly focused on prematurity or low birth weight, with both inverse (13) and no (7, 40) associations being reported. Liem et al. (7) also assessed the role of high birth weight in food allergy, but no association was observed. High birth weight has been associated with higher risk of other allergic conditions such as asthma (41–43), atopic dermatitis (44), and sensitization (41, 45, 46), although null associations have also been reported (47–49). This inconsistency in observations between birth anthropometric measures and allergic diseases may in part be due to methodological differences between the studies but also to etiologic differences between allergic diseases. Thus, the role of enhanced fetal growth in the development of CMA or other food allergies should be further clarified.

By using the Finnish unique personal identity codes, we were able to establish a large, population-based sample and

to link comprehensive information from several population-based national registers with high validity and accuracy (50). Identification of CMA cases through the Special Reimbursement Register can be considered reliable because the requirement for special reimbursement was based on clinical diagnosis made by a pediatrician and was further reviewed against criteria by another clinician. In addition, eligibility for the reimbursement does not depend on a family's socioeconomic situation or area of residence.

The slightly higher point prevalence of CMA in our cohort (approximately 3.4%) compared with international figures of CMA incidence in infants less than 1 year of age (2%–3%) (1), and the prevalence of challenge-proven CMA in children aged 0–4 years (0%–3%) (51), suggest that heterogeneity in the diagnostic procedures among our cohort may exist. For example, some of the cases with severe reactions to cow's milk at a very young age could have received the special reimbursement without undergoing a challenge procedure. The number of these cases is likely to be small, however. Furthermore, we made a special effort to avoid false-positive diagnoses by applying a case definition that included specific criteria for duration of the special reimbursement and number of purchases of special infant formulas. Another limitation of our study is that we did not have information in the registers on parental allergies or mode of infant feeding, which presumably interact and influence the development of CMA (52). However, in previous studies, adjustment for parental allergies or breastfeeding has not substantially changed the associations between maternal or perinatal factors and food allergies (7, 9, 11).

In conclusion, the present data suggest that cesarean section, high number of older siblings, and multiple pregnancy may play a role in the development of CMA, which supports the prenatal and postnatal hypotheses for the development

of allergic diseases. The explanation for the associations observed between maternal background factors and the risk of CMA in the infant is more obscure and may be due to maternal health behavior. Because allergic diseases place a significant burden on the affected children and their parents and result in substantial health care costs (53), prevention is desirable. To develop prevention strategies, it is essential to identify risk and protective factors for these diseases. Although those maternal background and perinatal factors included in the present study are not easily modifiable, identification of such factors may help focus preventive strategies on those children at high risk of developing allergic diseases. Thus, the role of maternal background and perinatal factors in the development of CMA should be further investigated in large epidemiologic cohorts taking into account several possible confounders, especially parental allergies and mode of infant feeding. In addition, research on possible biologic mechanisms behind the associations is essential.

## ACKNOWLEDGMENTS

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This work was supported by the Yrjö Jahnsson Foundation (grant 5663); the Juho Vainio Foundation; and a fellowship from the Doctoral School of Public Health at the University of Tampere, Tampere, Finland, with funding from the Ministry of Education, Helsinki, Finland.

Part of the results of this work were presented as a meeting abstract at the XXVIII Congress of the European Academy of Allergy and Clinical Immunology, Warsaw, Poland, June 6–10, 2009 (Metsälä J, Kilkkinen A, Kaila M, et al. Determinants of cow's milk allergy in childhood—a population-based medical birth register study [abstract]. *Allergy*. 2009;64(suppl 90):198).

Conflict of interest: none declared.

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