# Cesarean section and disease associated with immune function

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**Background: Earlier studies have shown that delivery by cesarean section (CS) is associated with an increased risk of disease associated with immune function in the offspring, but these studies have generally not discriminated between the effect of acute and elective CS.**

**Objective: We sought to further explore these associations using discrimination between the effects of acute versus elective CS.**

**Methods: We performed a population- and national register–based cohort study including all children born in Denmark from January 1997 through December 2012. Hazard ratios for diseases associated with immune function in children delivered by acute and elective CS with vaginal delivery as the reference were calculated by using Cox regression. All analyses were adjusted for gestational age, sex, birth weight, maternal age, maternal smoking during pregnancy, and complications during pregnancy (preeclampsia, eclampsia, hemorrhage, and hyperemesis).**

**Results: A total of 750,569 children aged 0 to 14 years were included. Children delivered by both acute and elective CS had an increased risk of asthma, laryngitis, and gastroenteritis. Children delivered by acute CS had an increased risk of ulcerative colitis and celiac disease, whereas children delivered by elective CS had an increased risk of lower respiratory tract infection and juvenile idiopathic arthritis. The effect of elective CS was higher than the effect of acute CS on the risk of asthma.**

**Conclusion: Children delivered by CS are at increased risk of disease associated with immune function. The effect is mainly on diseases involving the mucosal immune system. (J Allergy Clin Immunol 2016;137:587-90.)**

***Key words:*** *Cesarean section, immune function, microbiome, microbiota, laryngitis, pneumonia, asthma, gastroenteritis, ulcerative colitis, celiac disease, juvenile arthritis*

During the last decades, there has been an increasing incidence of delivery by cesarean section (CS).[1] This increase reflects a widespread notion that CS is lifesaving and prevents injury to both the mother and child. There has also been an increase in CS on maternal request, probably boosted by an increase in fear of childbirth. However, a number of studies have shown that delivery by CS is associated with increased risk of disease in the offspring, such as neonatal respiratory morbidity,[2] respiratory syncytial virus–induced hospitalization,[3] bronchiolitis,[4] asthma,[5,6] gastroenteritis,[7] inflammatory bowel disease,[8] celiac disease,[9] leukemia,[10] and diabetes.[11] Apart from neonatal respiratory morbidity, most of these conditions are thought to originate from a dysfunctional immune system leading to an increased risk of disease. To further explore and characterize the association between delivery by CS and disease involving immune function, such as infections, autoimmune diseases, and malignancies, we performed this population-based cohort study including nearly 800,000 children.

*Abbreviations used*
CS: Cesarean section
ICD-10: International Classification of Diseases, 10th revision

## METHODS

This was a population- and register-based cohort study based on all children born in Denmark from January 1997 through December 2012. Data on maternal age, maternal smoking during pregnancy, complications during pregnancy (preeclampsia, eclampsia, hemorrhage, and hyperemesis), mode of delivery, sex, gestational age at birth, birth weight, neonatal respiratory morbidity, and diagnoses associated with immune function, including gastrointestinal and respiratory tract infections and autoimmune and malignant diseases, were extracted from the Danish National Birth Registry and the Danish National Patient Registry, in which diagnoses and operations are registered according to the International Classification of Diseases, 10th revision (ICD-10). Data were linked by using the unique personal identification number allocated to each person living in Denmark. The study was approved by the Danish Data Protection Agency (no. 2012-41-0910).

### Exposure

Exposure parameters were acute and elective CS (ICD-10 codes KMCA10A-C and KMCA10D-E, respectively).

### Outcome

The following diagnoses were selected as outcome parameters: laryngitis (ICD-10 code J05.0), pneumonia and lower respiratory tract infection (ICD-10 codes J12.0-J15.9 and J20.0-J22.9), asthma (ICD-10 codes J45.0-J45.9), gastroenteritis (ICD-10 codes A08.1 and A09.9), Crohn disease (ICD-10 codes K50.0-K50.9), ulcerative colitis (ICD-10 code K51.0-K51.9), celiac disease (ICD-10 code K90.0), juvenile arthritis (ICD-10 codes M08.0-M08.9), diabetes (ICD-10 codes E10.0-E10.9 and E14.0-E14.9), lymphatic leukemia (ICD-10 codes C91.0-C91.9), myeloid leukemia (ICD-10 codes C92.0-C92.9), malignant lymphoma (ICD-10 codes C81.0-C85.9), and nonhematologic cancer (ICD-10 codes C00.0-C80.9).

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## Statistical methods

Children were followed from the day of birth to an outcome of diagnosis, emigration, death, or the end of follow-up on December 31, 2012, whichever came first. The associations between delivery by acute or elective CS on the one hand and the risk of diseases associated with immune function on the other were analyzed in a Cox proportional hazards model stratified by exact date of birth with vaginal delivery as the reference. Results are reported as hazard ratios with 95% CIs. To avoid children being censored at an outcome of diagnosis, a separate analysis was performed for each of these. Children born at gestational ages of less than 37 weeks and those born as part of multiple births were excluded. In addition, we excluded children with congenital chronic conditions, including all with congenital malformations (Q-diagnoses).

For multivariate analyses, the following prespecified covariates were included: gestational age at birth (weeks), sex (boys and girls), birth weight (≤2500, 2501-3500, 3501-4500, and 4501-6500 g), maternal age (<23, 24-30, 31-37, and ≥38 years), maternal smoking during pregnancy (yes and no), and complications during pregnancy (preeclampsia [ICD-10 codes O14.0-9], (yes and no), eclampsia [ICD-10 codes O15.0-9], (yes and no), hemorrhage [ICD-10 codes O20.0-9], (yes and no), and hyperemesis [ICD-10 codes O21.0-9], [yes and no]).

Statistical analyses were performed with Stata version 11 software (StataCorp, College Station, Tex).

## RESULTS

During the study period, a total of 1,031,424 children were born in Denmark. Of these, 92,062 (8.9%) were delivered by acute CS, and 109,022 (10.6%) were delivered by elective CS. The number of children delivered by CS (both elective and acute) increased from 9,198 (13.6%) in 1997 to 12,704 (21.8%) in 2012. Of the total population, 67,093 children with gestational ages of less than 37 weeks at birth; 73,402 children with congenital chronic conditions, including all with congenital malformations; and 45,539 children delivered as part of multiple births were excluded. In addition, we excluded 7,568 children with missing information on gestational age at birth, 199 children whose gestational ages were recorded as 44 or 45 weeks, and 47,054 because of recorded birth weight less than or greater than 2 SDs from the mean birth weight for all gestational ages included.[12]

Thus 790,569 children aged 0 to 14 years were included in the analysis. Of these, 63,811 (8.1%) were born by elective CS, and 60,319 (7.6%) were born by acute CS. With respect to disease involving immune function, delivery by CS was associated with mucosal infection and inflammation. For asthma, the effect of elective CS was higher than that of acute CS. The estimates for respiratory tract disease did not change after adjusting for neonatal respiratory morbidity. The only condition not affecting the mucosal surfaces that was influenced by delivery by CS was juvenile idiopathic arthritis, in which only elective CS had an effect. There were no associations between CS and Crohn disease, malignant diseases, and diabetes (Table I). A total of 1124 children died during the study period.

## DISCUSSION

To our knowledge, this is the first study that discriminates between the effect of acute and elective CS when looking at the associations between CS and disease associated with immune function in the offspring. We show that both acute and elective CS are associated with laryngitis, asthma, and gastroenteritis; that acute CS is associated with ulcerative colitis and celiac disease; and that elective CS is associated with lower respiratory tract infection and juvenile idiopathic arthritis. In addition, we show that the effect of elective CS on the risk of asthma is greater than that of acute CS.

The strength in our study lies in the population-based design and large sample size, which enabled us to identify the risk of relatively rare diseases, such as ulcerative colitis and juvenile idiopathic arthritis, as affected by mode of birth. In addition, we were able to adjust for multiple confounders in both the mothers and the offspring, such as complications during pregnancy, maternal smoking, and neonatal respiratory morbidity. Furthermore, a potential effect of birth season and birth year was eliminated by matching on date of birth.

Our study has a number of limitations. Thus it was register based, and we made no attempt to validate the diagnostic coding. However, we find it improbable that mode of birth should affect diagnostic coding in the offspring, and therefore differential misclassification is unlikely to affect the relative estimates reported here. Likewise, the reliability of the Danish hospital registers has been demonstrated in numerous studies,[13] and with respect to significant findings, these were all of an increased risk of disease after delivery by CS. Thus in the spectrum of diseases studied, none came out with a decreased risk.

Another limitation is that we did not have data on breast-feeding and therefore were unable to adjust for it. However, an older study from Denmark showed that the rate of breast-feeding among mothers giving birth by CS or vacuum extraction was not affected after discharge,[14] and a worldwide meta-analysis showed a reduced rate of breast-feeding only after elective CS. In addition, once initiated, the rate of breast-feeding was unaffected by CS at the age of 6 months.[15] Therefore lack of breast-feeding cannot explain our findings with respect to diseases associated with acute CS, but we cannot rule out some confounding with respect to the effect of elective CS.

A further limitation is that we could not adjust for maternal asthma because our data originated only from hospitals and we did not have data from general practitioners. Hence, maternal asthma is associated not only with an increased risk of giving birth by CS[16] but also with a wide range of diseases in the offspring.[17] However, the risk of delivery by CS in mothers with asthma is only slightly increased,[16] and because only 6% of pregnant women in Denmark reported asthma,[17] this cannot explain our findings.

Our data must be interpreted with caution because the very large sample size provided us with a statistical power that could detect very small effects, which might not be of clinical significance. Furthermore, the associations found here do not necessarily imply causality. However, assuming causality, it is tempting to speculate that the aberrant microbial colonization acquired perinatally by children delivered by CS might be of importance because our findings were predominantly limited to disease on the mucosal surfaces. Furthermore, this is supported by our finding of a differential effect of acute versus elective CS on asthma, with the latter having the highest effect. Thus in the setting of elective CS, the membranes are usually intact, which is in contrast to the situation in acute CS, where the child might already be colonized with the maternal vaginal microflora *in utero*. In addition, a recent study showed that administration of antibiotics to pregnant women during the last trimester was associated with an increased risk of asthma in the child.[18] With respect to respiratory disease, an earlier study showed an association between transient tachypnea of the newborn and respiratory distress syndrome and later development of asthma,[19] but this is unlikely

**TABLE I.** Hazard ratios for disease associated with immune function in children delivered by CS

| | Delivery | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Vaginal | Elective CS | | | | | Acute CS | | | | | |
| | | Crude | | Adjusted | | | Crude | | Adjusted | | | |
| Full cohort (n = 790,569) | No. (%) | HR | 95% CI | HR | 95% CI | No.* (%) | HR | 95% CI | HR | 95% CI | No.† (%) | *P* value‡ |
| No. | 666,439 | | | | | 63,811 | | | | | 60,319 | |
| Laryngitis (ICD-10 code J05.0) | 18,498 (2.8) | 1.23 | 1.18-1.29 | 1.19 | 1.14-1.25 | 2,097 (3.2) | 1.18 | 1.13-1.24 | 1.14 | 1.09-1.20 | 1,970 (3.3) | .84 |
| Pneumonia and lower respiratory tract infection (ICD-10 codes J12.0-15.9 and J20.0-22.9) | 39,524 (5.9) | 1.30 | 1.26-1.34 | 1.20 | 1.16-1.24 | 4,757 (7.5) | 0.99 | 0.96-1.03 | 1.01 | 0.97-1.04 | 3,610 (5.9) | **<.01** |
| Asthma (ICD-10 codes J45.0-9 and J46.9) | 37,630 (5.6) | 1.26 | 1.22-1.30 | 1.24 | 1.20-1.28 | 4,212 (6.6) | 1.07 | 1.03-1.11 | 1.06 | 1.02-1.10 | 3,595 (5.9) | **<.01** |
| Gastroenteritis (ICD-10 codes A08.1 and A09.9) | 24,332 (3.7) | 1.22 | 1.17-1.27 | 1.18 | 1.13-1.23 | 2,723 (4.3) | 1.20 | 1.15-1.25 | 1.22 | 1.17-1.27 | 2,617 (4.3) | .54 |
| Crohn disease (ICD-10 codes K50.0-9) | 288 (0.04) | 0.86 | 0.54-1.39 | 0.84 | 0.51-1.37 | 18 (0.03) | 1.02 | 0.67-1.55 | 0.96 | 0.63-1.47 | 23 (0.04) | .34 |
| Ulcerative colitis (ICD-10 codes K51.0-9) | 338 (0.04) | 0.81 | 0.50-1.32 | 0.74 | 0.45-1.23 | 18 (0.03) | 1.45 | 1.01-2.09 | 1.47 | 1.02-2.12 | 32 (0.05) | **.03** |
| Celiac disease (ICD-10 codes K90.0) | 264 (0.04) | 0.81 | 0.51-1.29 | 0.69 | 0.43-1.12 | 19 (0.03) | 1.42 | 0.99-2.05 | 1.52 | 1.06-2.20 | 32 (0.05) | **.043** |
| Juvenile arthritis (ICD-10 codes M08.0-9) | 1,380 (0.21) | 1.23 | 1.10-1.47 | 1.25 | 1.04-1.51 | 132 (0.21) | 0.99 | 0.82-1.20 | 0.99 | 0.82-1.20 | 114 (0.19) | .48 |
| Diabetes (ICD-10 codes E10.0-9 and E14.0-9 | 1,282 (0.19) | 1.03 | 0.84-1.26 | 0.93 | 0.75-1.15 | 100 (0.16) | 1.04 | 0.86-1.27 | 1.05 | 0.87-1.28 | 108 (0.18) | .34 |
| Lymphatic leukemia (ICD-10 codes C91.0-9) | 218 (0.03) | 0.96 | 0.60-1.55 | 1.03 | 0.62-1.70 | 18 (0.03) | 1.24 | 0.81-1.90 | 1.20 | 0.78-1.85 | 23 (0.04) | .34 |
| Myeloid leukemia (ICD-10 codes C92.0-9) | 47 (0.01) | 0.98 | 0.36-2.72 | 0.92 | 0.32-2.66 | 4 (0.01) | 1.50 | 0.65-3.51 | 1.57 | 0.67-3.67 | 6 (0.01) | .47 |
| Malignant lymphoma (ICD-10 codes C81.0-85.9) | 56 (0.01) | 0.69 | 0.22-2.20 | 0.62 | 0.19-2.06 | 3 (0.004) | 0.89 | 0.32-2.45 | 0.84 | 0.30-2.32 | 4 (0.001) | .65 |
| Nonhematologic cancer (ICD-10 codes C00.0-80.9) | 391 (0.06) | 0.91 | 0.63-1.33 | 0.92 | 0.62-1.36 | 29 (0.05) | 0.80 | 0.54-1.18 | 0.78 | 0.53-1.17 | 26 (0.04) | .85 |

Values in boldface indicate statistical significance.
*HR*, Hazard ratio.
*Number of children delivered by elective CS.
†Number of children delivered by acute CS.
‡For comparison of adjusted HR for elective versus acute CS.

to explain our findings because adjustment for neonatal respiratory morbidity did not change the estimates.

The associations between acute CS on the one hand and ulcerative colitis and celiac disease on the other, but not Crohn disease, are only partly in line with other studies. Hence, a Swedish study, which did not discriminate between acute and elective CS and looked only at pediatric Crohn disease, reported an increased risk after CS only in boys,[20] and a study from Germany, which also did not discriminate between acute and elective CS, showed an increased risk of celiac disease after CS but not of inflammatory bowel disease.[9] That the risk of ulcerative colitis and celiac disease in our study was affected only by acute CS and not by elective CS is obscure, but it is in keeping with another Danish study showing an increased risk of inflammatory bowel disease only after acute CS.[8]

The only condition not affecting the mucosal surfaces that was associated with delivery by CS was juvenile idiopathic arthritis, for which only elective CS had an effect. Although the literature on the significance of the microbiome for pediatric rheumatic disease is sparse, this association, which, to our knowledge, has not been reported before, might also be explained by an aberrant microbiome. Thus one study in patients with juvenile idiopathic arthritis showed that 4 of 12 bacteria studied with DNA probes in subgingival plaques were less frequently present in these patients.[21] In addition, there is growing evidence that the microbiome is of importance for pathogenesis in both patients with adult rheumatoid arthritis and in those with ankylosing spodylitis.[22-24]

Our study could not confirm an effect of CS on the risk of childhood leukemia, as reported in a recent Danish study, which spanned over a longer time period but did not discriminate between acute and elective CS.[10] However, in addition to other outcomes, we also used other adjustments. Moreover, the discrimination between the effect of acute and elective CS might be crucial because these events represent 2 completely different exposure parameters. Thus, as mentioned, the newborn delivered by elective CS does not acquire microbial colonization from the birth canal, and furthermore, infants delivered by elective CS have not been exposed to labor. Hence, labor is thought to promote the action of various cytokines,[25] some of which might have long-lasting effects on the immune system.[26]

In conclusion, we have shown that delivery by CS is associated with mucosal infection and inflammation and with juvenile idiopathic arthritis. We hypothesize that our findings can be explained in part by a disturbed immune function induced by

the aberrant microbial colonization present in children delivered by CS.

**Clinical implications: Children delivered by CS are at increased risk of disease associated with immune function. The effect is mainly on diseases involving the mucosal immune system.**

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