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ORIGINAL RESEARCH ARTICLE

Delivery mode and risk of gastrointestinal disease in the offspring

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Abstract

Introduction: The global increase of individuals born by cesarean section with reported levels up to 20% of all deliveries, makes it important to study cesarean section and possible associations that can increase risk of subsequent diseases in children. The aim of the study was to evaluate if cesarean section is associated with increased risk of gastrointestinal disease later in life in a large population-based cohort.

Material and methods: In this national population-based cohort study including all full-term individuals registered in the Medical Birth Register in Sweden between 1990 and 2000, type of delivery (exposure) was collected from the Medical Birth Register. The study population was followed until 2017 with regards to the outcomes: inflammatory bowel disease (Crohn's disease or ulcerative colitis), appendicitis, cholecystitis, or diverticulitis registered in the Swedish National Patient Register. Cox proportional-hazards models compared disease-free survival time between exposed and unexposed.

Results: The final study population consisted of 1 102 468 individuals of whom 11.6% were delivered by cesarean section and 88.4% were vaginally delivered. In univariate analysis, cesarean section was associated with Crohn's disease (hazard ratio [HR] 1.13, 95% confidence interval [CI] 1.02–1.25), diverticulosis (HR 1.57, 95% CI 1.13–2.18), and cholecystitis (HR 1.16, 95% CI 1.05–1.28). However, the increased risk only remained for Crohn's disease after adjustment for confounders (HR 1.14, 95% CI 1.02–1.27). No associations between delivery mode and appendicitis, ulcerative colitis, cholecystitis, or diverticulosis were found in the multivariate analysis.

Conclusions: Cesarean section is associated with Crohn's disease later in life, but no other association between delivery mode and gastrointestinal disorders later in life could be found.

KEYWORDS
appendicitis, cesarean section, Crohn's disease, delivery mode, inflammatory bowel disease

Abbreviations: CD, Crohn's disease; CI, confidence interval; CS, cesarean section; HR, hazard ratio; IBD, inflammatory bowel disease; ICD, International Classification of Diseases; IQR, interquartile range; MBR, Medical Birth Register; NBHW, National Board of Health and Welfare; NPR, Swedish National Patient Register; SD, standard deviation.

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1 | INTRODUCTION

The number of individuals born by cesarean section (CS) is increasing globally, with reported levels up to 20% of all deliveries.[1–5] This has encouraged the interest of a possible impact on health later in life in the offspring being born by CS. One suggested significant factor in this context has been early exposure of offspring to bacteria. Although there is no consensus, if intrauterine life is sterile, then being born by CS or vaginal delivery may have an impact on the gut bacterial colonization of the newborn.[6–8] Infants born by vaginal delivery are primarily colonized by bacteria from the birth canal, consisting of bacterial flora mainly from the intestinal tract, unlike infants born by CS, who have an increased prevalence of skin flora at first colonization.[7,9]

Disrupted gut colonization (dysbiosis) of a newborn may be explained by CS delivery, use of perinatal antibiotics, and type of diet (breast milk or formula).[10–17] Dysbiosis can in turn adversely affect the gut development of the host defense and predispose to inflammation rather than to homeostasis, which may lead to increased susceptibility to diseases later in life.[9,18] Previous studies suggest that infants delivered by CS are at increased risks of disorders involving the immune system, such as asthma and allergies, type 1 diabetes, celiac disease, obesity, immune deficiencies, and leukemia and other malignancies affecting young people.[10,11,19–26] Others have investigated the potential association between mode of delivery and gastrointestinal disease such as inflammatory bowel disease (IBD).[23,27–29] However, as previous studies are small and results are incoherent, there is a need to further investigate potential associations between delivery mode and gastrointestinal diseases in which gastrointestinal dysbiosis has been suggested as a possible mediator, such as IBD, appendicitis, cholecystitis, and diverticulitis, using large population-based register data.

We hypothesized that an early altered gastrointestinal microbial dysbiosis in individuals born by CS is associated with an increased risk for gastrointestinal diseases later in life. Hence, the aim of the study was to assess whether CS is associated with increased risks for IBD, appendicitis, cholecystitis, or diverticulitis later in life.

Key message

The global increase of cesarean section makes it important to study the effect of delivery mode for the offspring. This national cohort study concludes that cesarean section is associated with Crohn's disease in the offspring.

2 | MATERIAL AND METHODS

2.1 | Study design and participants

We conducted a national population-based cohort study including all full-term individuals (gestational weeks 37–42) born and registered in the Medical Birth Register (MBR) in Sweden between January 1, 1990 and December 31, 2000. The exposure, type of delivery, was collected from the MBR. The study population was observed until December 31, 2017 with regards to International Classification of Diseases (ICD) diagnoses for assessment of the outcomes: gastrointestinal disease, registered in the Swedish National Patient Register (NPR). A flow chart for the cohort is shown in Figure 1.

2.2 | Registers and data sources

Linkages of several population-based registers, held by the National Board of Health and Welfare (NBHW)and Statistics Sweden, provided diagnostic details and follow up until December 31, 2017. All linkages were performed through personal identification numbers, which identify every resident in Sweden.[30] The MBR, held by the NBHW, contains prospectively collected maternal and newborn data from antenatal care clinics, obstetric clinics, and maternity wards on all pregnancies and deliveries in Sweden since 1973.

Correlation between register data and original medical records, and the validity of included study exposures have been shown to be excellent.[31]

The NPR, also maintained by the NBHW, contains prospectively collected information on all in-hospital admissions in Sweden since 1987. This register also contains all outpatient specialist care since 2001 and is considered highly reliable and valid.[32] The data included in the register are sex, age, primary and secondary diagnoses, surgical procedures, and dates of admission and discharge. The ICD has

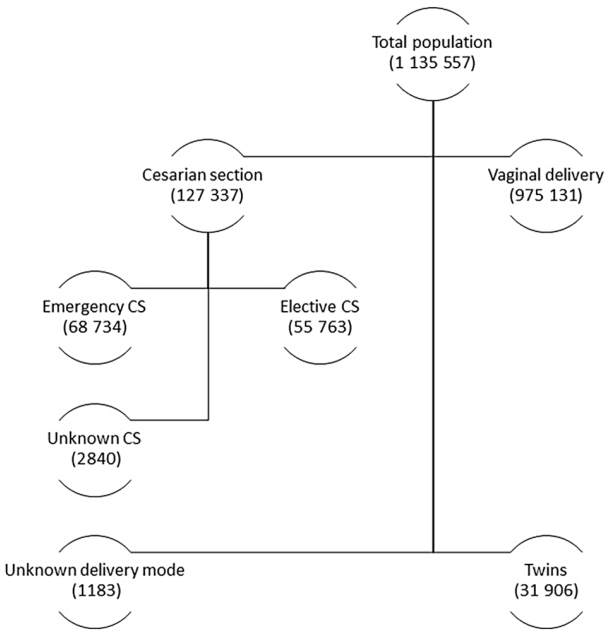

FIGURE 1 Flow chart for the cohort

been modified over the years: ninth revision (ICD-9) in 1987–1996 and 10th revision (ICD-10) since 1997.

Statistics Sweden holds the Swedish Register of Education, started in 1985 including the highest educational level of inhabitants between 16 and 74 years of age.

2.3 | Variables

Exposure data on delivery mode were obtained from the MBR and categorized into CS and vaginal delivery. The exposure CS was also subcategorized into emergency CS or elective CS, where emergency CS was defined as delivery starting with labor (spontaneous and induced) and ending with CS, and elective CS was defined as CS before onset of labor.

Outcomes of gastrointestinal diseases were identified through the NPR based on relevant ICD codes; appendicitis (ICD-9: 540–542, ICD-10: K35, K36.9, K37); IBD (ICD-9: 555, 556, ICD-10: K50-51); colonic diverticular disease (ICD-9: 562, ICD-10: K57); and cholecystitis (ICD-9: 574–575, ICD-10: K80). According to Jakobsson et al, for a diagnosis of IBD, at least two separate IBD diagnoses were needed and the latest subtype of IBD decided either for ulcerative colitis (one or more ulcerative colitis diagnoses and ulcerative colitis as most recent IBD diagnosis) or Crohn's disease (one or more Crohn's disease diagnoses and Crohn's disease as the most recent IBD diagnosis).[33]

Other variables of interest for the study and used in the multivariate analysis included information on maternal characteristics such as maternal age, parity, self-reported smoking habits at the first visit to the antenatal care clinic, former CS, and singleton or multiple pregnancy, obtained from the MBR. Information on offspring characteristics including gestational age, sex and birthweight was also collected from the MBR. Birthweight for gestational age was estimated according to the sex-specific Swedish reference curve for normal fetal growth.[34] A normal birthweight for gestational age was defined as a birthweight between the 3rd and 97th centiles. Below the 3rd centile was categorized as small for gestational age. Data on associated congenital malformations and chromosomal abnormalities were obtained from either the NPR or the MBR using the following diagnostic codes: ICD-10: Q00–99, ICD-9: 740–759. Data on perinatal illness were collected from the NPR: ICD-10: P0–99, ICD-9: 760–779.

Highest parental education level was collected from the Swedish Register of Education and was categorized into three levels: 1: 9 years of compulsory school or less, 2: between 10 and 12 years of schooling, and 3: 13 years or more of schooling.

Missing data are shown as NA (not available) and only complete cases have been used in the analysis. Dates of death and emigration were retrieved from Statistics Sweden and used to censor individuals who died or emigrated before the end of follow up.

Multiple pregnancies ($n = 31\,906$) were excluded from the study because of the risk of prenatal delivery associated with low birthweight and different treatment early in life. Unknown delivery mode ($n = 1183$) was not included in the analysis.

2.4 | Statistical analyses

The association between exposed and unexposed individuals was analyzed using the R program.[35] Categorical data were presented as frequencies or proportions with standard deviation or interquartile range (IQR) and continuous data were presented as median and range. A Cox proportional-hazards regression model was used, and effects were presented as hazard ratio (HR) with 95% confidence interval (CI), with attained age as the underlying time-scale. Potential confounders were identified based on the Directed Acyclic Graphs concept, and the adjusted regression model was adjusted for birthweight, congenital malformations, maternal body mass index, maternal smoking, highest parental education level, perinatal illness, and small for gestational age (see Supporting Information Figure S1).[36]

2.5 | Ethics statement

This study was based on Swedish register data from the Swedish NBHW, which anonymized all patient information. Ethical approval for the study was granted by the Regional Ethical Review Board (2018/7151–32) in Stockholm on October 1, 2018.

3 | RESULTS

Baseline demographics are shown in Table 1. The final study population consisted of 1 102 468 individuals, of whom 11.6% were delivered by CS and 88.4% were vaginally delivered. There were 46.7% females and 53.3% males in the CS group compared with 48.9% females and 51.1% males in the vaginally delivered group. The median gestational age was 38 weeks (IQR 38–40 weeks) in the CS group compared with 40 weeks (IQR 39–41 weeks) in the vaginally delivered group. A larger proportion of congenital malformations and perinatal illness was seen in the CS delivered group compared with the vaginally delivered group.

The median time in years to diagnosis of appendicitis was 15.1 (IQR 10.9–19.0) in the CS group compared with 15.3 (IQR 11.1–19.2) among the vaginally delivered group. For Crohn's disease the median time was 16.9 (IQR 14.1–19.9) in the CS group compared with 17.4 (IQR 14.2–20.4), and for ulcerative colitis the time was 17.8 (IQR 14.6–20.6) compared with 18.2 (IQR 15.2–21.2). For the diagnosis of cholecystitis, median time was 20.8 (IQR 18.1–23.2) in the CS group compared with 21.0 (IQR 18.0–23.4).

The association between CS and later development of gastrointestinal outcome is shown in Table 2. In univariate analysis, individuals born by CS had a significantly increased risk of Crohn's disease (HR 1.13, 95% CI 1.02–1.25), diverticulosis (HR 1.57, 95% CI 1.13–2.18), and cholecystitis (HR 1.16, 95% CI 1.05–1.28), compared with vaginally born individuals. However, the increased risk only remained for Crohn's disease after adjustment for confounders (HR 1.14, 95% CI 1.02–1.27). No association between CS and appendicitis or ulcerative colitis was found in univariate and multivariate analyses.

TABLE 1 Baseline demographics of all deliveries during the study period categorized to all cesarean sections and vaginal delivery

	CS ($n = 127\,337$)	VD ($n = 975\,131$)
Maternal age (years), mean ± SD	30.0 ± 5.3	28.5 ± 5.0
Maternal weight (kg), median (IQR)	65.0 (58.0–74.0)	64.00 (58.0–71.0)
Maternal smoking, *n* (%)		
Yes	23 296 (18.3)	169 015 (17.3)
No	95 147 (74.7)	750 722 (77.0)
NA[a]	8894 (7.0)	55 394 (5.7)
Former CS, *n* (%)		
Yes	36 588 (28.7)	40 789 (4.2)
No	86 198 (67.7)	891 128 (91.4)
NA	4551 (3.6)	43 214 (4.4)
Gestational age (weeks), median (IQR)	38.0 (38.0–40.0)	40.0 (39.0–41.0)
Sex, *n* (%)		
Female	59 471 (46.7)	476 936 (48.9)
Male	67 866 (53.3)	498 194 (51.1)
NA	0	1
Birthweight (g), mean ± SD	3345 ± 793	3577 ± 519
Small for gestational age, *n* (%)		
Yes	9018 (7.1)	18 160 (1.9)
No	117 311 (92.1)	953 239 (97.8)
NA	1008 (0.8)	3732 (0.4)
Congenital malformations, *n* (%)	8018 (6.3)	34 161 (3.5)
Perinatal illness, *n* (%)	24 398 (19.2)	50 641 (5.2)
Deaths, *n* (%)	2380 (1.9)	7582 (0.8)
Parents highest educational level, *n* (%)		
1: ≤9 years	4399 (3.5)	33 161 (3.4)
2: 10–12 years	57 032 (44.8)	433 866 (44.5)
3: ≥13 years	65 516 (51.5)	504 622 (51.7)
NA	390 (0.3)	3482 (0.4)

Abbreviations: CS, cesarean section; NA, not available; VD, vaginal delivery.

[a]Missing data are shown as NA in the table.

Of the 127 337 individuals born by CS, 43.8% had an elective intervention. When comparing this subgroup with the individuals who were vaginally delivered, the risk for Crohn's disease increased to HR 1.16 (95% CI 1.01–1.34) in the univariate analysis and to HR 1.18 (95% CI 1.01–1.37) in the multivariate analysis (Table 3). No other significant result was found in this analysis. In Table 4, individuals with emergency CS ($n = 68\,734$ newborns) were compared with vaginally delivered newborns, showing increased risk for diverticulosis (HR 1.63, 95% CI 1.06–2.5) and for cholecystitis (HR 1.22, 95% CI 1.07–1.39) but these results were not significant in the multivariate analysis.

4 | DISCUSSION

In this national cohort of 1 102 468 full-term newborns born between 1990 and 2000, an association between delivery mode and Crohn's disease was shown, as well as in subgroup analysis for elective CS and vaginal delivery but not for emergency CS compared with vaginal delivery. For other gastrointestinal outcomes, such as appendicitis, ulcerative colitis and cholecystitis, no associations were found.

The possible impact on health of CS delivery compared with vaginal delivery is not well studied but is of great importance because the incidence of CS is increasing. Establishment of the gut microbiota may be affected and disturbed by CS delivery, the method of feeding, antibiotic treatment, gestational age, and environmental factors. Among them, CS is suggested to be one of the major factors in the early-life disruption of the neonatal gut microbiota.[37] There are observations suggesting that early-life aberrations in gut microbiota may have long-lasting consequences that have been associated with increased risk of asthma, allergies, type 1 diabetes, celiac disease, and immune deficiencies, which may suggest an increased risk for inflammatory-mediated disease.[10–17] An immediate risk of infections such as necrotizing enterocolitis and sepsis resulting from an altered gut microbiota has also been reported.[38] In an attempt to change the neonatal gut microbiome, CS-delivered infants have been exposed to their mother's vaginal fluids at birth and longitudinally followed to assess whether the gut microbiome developed more similarly to that of vaginally born babies than of unexposed CS-delivered infants.[39] Similar to vaginally delivered babies, the gut microbiome of these newborns during the first 30 days of life was enriched in vaginal bacteria, which were underrepresented in the unexposed CS-delivered infants.

Probiotics have been used in newborns; an application of two probiotic bacteria during the first days of life after CS resulted in quick and abundant colonization by days 5 and 6, with high populations of *Lactobacillus rhamnosus* and *Bifidobacterium breve*.[40]

In this study, we chose to assess the impact of delivery mode and the possible risk for several relatively common gastrointestinal disorders where disrupted diversity of gastrointestinal flora has been discussed as a risk factor: appendicitis, Crohn's disease, ulcerative colitis, diverticulitis, and cholecystitis. As the individuals in our cohort were born between 1990 and 2000 and followed until 2017, we mainly aimed to study gastrointestinal diseases that affect a young population, such as appendicitis and IBD. We also included cholecystitis and diverticulitis, although these disorders are quite rare at a young age, to assess if these rare cases could be connected to our study exposure. Our study showed an increased risk for developing Crohn's disease, but no other associations were found. As CS may affect the infant microbiota, an association between CS and IBD risk has been postulated, but in the population-based study of Bernstein et al,[29] no association between the mode of delivery and IBD could be found.[27,29,41–43] The reason for increased risk for Crohn's disease and not for ulcerative colitis in our study needs to be investigated further, but this finding may

TABLE 2 Gastrointestinal outcome; hazard ratio and 95% confidence interval for individuals born by cesarean section compared with vaginal delivery

	CS *n* = 127 337	VD *n* = 975 131	Crude HR (95% CI)	Adjusted HR (95% CI)
Appendicitis, *n* (%)	4356 (3.4)	34 803 (3.6)	1.00 (0.97–1.03)	1.02 (0.99–1.05)
Crohn's disease, *n* (%)	431 (0.3)	3048 (0.3)	1.13 (1.02–1.25)	1.14 (1.02–1.27)
Ulcerative colitis, *n* (%)	367 (0.3)	3126 (0.3)	0.94 (0.85–1.05)	0.95 (0.84–1.06)
Diverticulosis, *n* (%)	42 (0.03)	223 (0.02)	1.57 (1.13–2.18)	1.37 (0.96–1.95)
Cholecystitis, *n* (%)	455 (0.4)	3270 (0.3)	1.16 (1.05–1.28)	1.08 (0.97–1.20)

Abbreviations: CI, confidence interval; CS, cesarean section; HR, hazard ratio; VD, vaginal delivery.

TABLE 3 Gastrointestinal outcome; hazard ratio and 95% confidence interval for individuals born by elective cesarean section compared with vaginal delivery

	Elective CS *n* = 55 763	VD *n* = 975 131	Crude HR (95% CI)	Adjusted HR (95% CI)
Appendicitis, *n* (%)	1856 (3.3)	34 803 (3.6)	0.97 (0.93–1.02)	1.00 (0.95–1.05)
Crohn's disease, *n* (%)	194 (0.3)	3048 (0.3)	1.16 (1.01–1.34)	1.18 (1.01–1.37)
Ulcerative colitis, *n* (%)	164 (0.3)	3126 (0.4)	0.97 (0.83–1.13)	0.97 (0.82–1.15)
Diverticulosis, *n* (%)	16 (0.03)	223 (0.02)	1.39 (0.83–2.3)	1.11 (0.64–1.91)
Cholecystitis, *n* (%)	187 (0.3)	3270 (0.3)	1.11 (0.96–1.28)	1.02 (0.87–1.19)

Abbreviations: CI, confidence interval; CS, cesarean section; HR, hazard ratio; VD, vaginal delivery.

TABLE 4 Gastrointestinal outcome; hazard ratio and 95% confidence interval for individuals born by emergency cesarean section compared with vaginal delivery

	Emergency CS *n* = 68 734	VD *n* = 975 131	Crude HR (95% CI)	Adjusted HR (95% CI)
Appendicitis, *n* (%)	2366 (3.4)	34 803 (3.6)	1.01 (0.97–1.05)	1.02 (0.98–1.07)
Crohn's disease, *n* (%)	224 (0.3)	3048 (0.3)	1.10 (0.96–1.26)	1.11 (0.96–1.28)
Ulcerative colitis, *n* (%)	196 (0.3)	3126 (0.4)	0.94 (0.82–1.09)	0.95 (0.81–1.10)
Diverticulosis, *n* (%)	23 (0.03)	223 (0.02)	1.63 (1.06–2.5)	1.48 (0.95–2.30)
Cholecystitis, *n* (%)	253 (0.4)	3270 (0.3)	1.22 (1.07–1.39)	1.12 (0.98–1.29)

Abbreviations: CI, confidence interval; CS, cesarean section; HR, hazard ratio; VD, vaginal delivery.

support the suggestions that the underlying mechanism of Crohn's disease may be more sensitive to gut microbiota differences than ulcerative colitis. Appendectomy has also been shown to protect against ulcerative colitis but to increase the risk of Crohn's disease, with the hypotheses that the removal of the appendix might influence the gut microbiota and hence also the mucosal immune system in such a way as to reduce the risk of ulcerative colitis but increase the risk of Crohn's disease.[44–46]

As there may be a difference in the use of preoperative or peroperative antibiotic treatment during an elective CS compared with an emergency CS we performed subgroup analysis in which we confirmed the association with Crohn's disease when comparing elective CS but not when comparing emergency CS with vaginal delivery. The underlying mechanisms to this difference also need further studies, but our hypothesis is that individuals born by emergency CS may have been exposed to vaginal flora during the beginning of the delivery compared with those born by elective CS, who have no exposure to vaginal flora. This could also strengthen the hypothesis that dysbiosis in the microbiota is a risk factor for Crohn's disease.

The etiology of appendicitis is unclear but there are speculations of the impact on for example *Bacteroides* species, which indicate the involvements of the microbiome in appendicitis.[47,48] In this study we could not find any association with type of delivery and risk for appendicitis. For diverticulitis there are no known associations with being born by CS, but there are also data that suggest the microbiome as a possible factor for the pathophysiology.[49,50]

Strengths of our study include the completeness of the data prospectively collected on mode of delivery, maternal background factors, perinatal characteristics, and gastrointestinal diseases for the study outcome. As the data are based on prospectively collected data from a nationwide cohort with excellent coverage, the outcome should be highly generalizable in other high-income settings. Also, the likelihood for data inclusion in the register is the same for both modes of delivery.

However, there are inherent limitations in register-based studies with residual confounding due to factors not recorded in the used registers. For example, information on the use of perinatal antibiotics, type of diet (breastfeeding or formula), possible hereditary factors as well as body mass index and diabetes would have improved the current study design. Unfortunately, we did not have information on these variables from the registers. Furthermore, a sibling study would have provided the opportunity to study the association between delivery mode and gastrointestinal disease, with adjustment for genetic predisposition, and other lifestyle and environmental

factors shared within families. Unfortunately, the data used in this study were identified based on the offspring, so mother and siblings could not be identified.

Nevertheless, potential confounders were identified based on the Directed Acyclic Graphs concept, and the final model was adjusted for maternal smoking, birthweight, gestational age, small for gestational age, congenital malformations, perinatal illness, and highest parental educational level.

In this study, we attempted to assess potential long-term effects of being born by CS. We found an association between delivery mode and Crohn's disease later in life, but no association with the other assessed gastrointestinal diseases. Further studies are needed to confirm our data but also to understand the possible underlying mechanisms.

5 | CONCLUSION

Cesarean section is associated with Crohn's disease later in life, but no other association between delivery mode and gastrointestinal disorders later in life could be found.

AUTHOR CONTRIBUTIONS

ALG and UOG conceived the presented idea. ALG and CH received the data and processed it. EH, AKÖ, and ALG verified the analytical methods. ALG and CH supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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