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Cesarean section and offspring's risk of multiple sclerosis: a Danish nationwide cohort study

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Abstract

Background: Apart from a recent study reporting a 2- to 3-fold increased risk of multiple sclerosis (MS) among women and men who were delivered by Cesarean section (C-section), little attention has been given to the possible association between mode of delivery and the risk of MS.

Objectives: We studied the association between C-section and risk of MS, in a cohort of 1.7 million Danes born from 1973 to 2005.

Methods: Information on C-section and MS was obtained from the Danish Medical Birth Register and the Danish MS Register, respectively. The association between C-section and MS was evaluated by means of MS incidence rate ratios (RR) with 95% confidence intervals (CI) obtained in log-linear Poisson regression analyses.

Results: There were 930 cases of MS in the study cohort, of whom 80 (9%) were delivered by C-section. Overall, we found there was no significant association between C-section and risk of MS (RR = 1.17; 0.92–1.46). Analyses stratified by sex revealed no unusual risk of MS for women (RR = 1.08: 0.80–1.42) nor men (RR = 1.37: 0.91–1.98). A supplementary sibling-matched Cox regression analysis likewise suggested there was no excess risk of MS in persons delivered by C-section (HR = 1.03; 0.63–1.69).

Conclusions: Mode of delivery appears to be unimportant in relation to MS development in the offspring.

Keywords

Multiple sclerosis, immunology, mode of delivery, C-section, offspring, disease risk

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Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system that affects approximately 2.5 million people worldwide. The etiology of MS remains unknown, but increasing incidence rates of MS suggest the existence of environmental risk factors.[1]

The frequency of Cesarean section (C-section) has increased markedly in many Western Countries,[2] including Denmark. Between 1982 and 2011, the proportion of Danish children delivered by C-section increased from 11% to 29%.[3,4] C-section may have some undesirable long-term consequences for the newborn child. Newborns delivered by C-section are not exposed to maternal vaginal and fecal bacteria at birth, but mainly to skin bacteria, and as such the normal colonization pattern of the fetal intestine is delayed and disturbed.[5] It has been suggested that this disturbs the normal development of the immune system, accompanied by an increased risk of immune-mediated diseases[6] such as asthma, allergies and certain autoimmune conditions.[5,7–10]

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Little attention has been given to the possible role of C-section in the etiology of MS. A case-control study based on 449 MS cases recruited from the Isfahan Multiple Sclerosis Society database and 900 of their healthy siblings reported a 2.3–2.7 fold increased risk of MS among the persons delivered by C-section, as compared to their vaginally-delivered siblings.[11] Information about mode of delivery and other perinatal characteristics were; however, based on self-reports, which may have increased the risk of recall bias.

In the present study, we assessed the association between being delivered by C-section and the risk of developing MS later, in a nation-wide register-based cohort study that included all individuals born in Denmark from 1973 to 2005.

Materials and methods

The study cohort

By means of data from the Danish Civil Registration System (CRS), a continuously updated demographic register, covering the entire Danish population since 1968,[12] we identified all singleton births occurring between 1 January 1973 and 31 December 2005. The CRS includes information about the date of birth and vital status, and for the children born since the mid-1950s, information about their parents and siblings. All the information in the CRS is linked to the individual's unique 10-digit personal identifier (the CRS number). To ensure virtually complete information on perinatal factors, we restricted the study cohort to children born in Denmark by Danish-born parents. The study cohort was subsequently linked to the Danish Medical Birth Register (MBR), using the CRS number as key. The MBR was established in 1968 and it was computerized in 1973.[13] The MBR has data on all the live births and stillbirths by women with permanent residence in Denmark and contains detailed information about each childbirth, including: date of birth, birth weight, birth length, single or multiple birth, gestational age, malformations and mode of delivery (vaginal birth versus C-section).

MS outcomes

We identified the MS cases in the study cohort in the Danish Multiple Sclerosis Register, comprising information on all cases of MS in Denmark since 1956, as previously described.[14] In all the analyses, we defined the date of diagnosis and the date of first symptoms as the first of July, in the recorded year of diagnosis and first symptoms, respectively. If the MS patient died or emigrated in the same year he or she was diagnosed with MS or had the first symptoms, the date of diagnosis/first symptoms was defined as the day before death or emigration.

Statistical analyses

The association between mode of delivery on the subsequent risk of MS was analyzed by log-linear Poisson regression models. Incidence rate ratios with accompanying 95% confidence intervals (CI) were used as measures of relative risk (RR). Each cohort member was followed from the date of birth or 1 January 1977, whichever came later, until the study end on 31 December 2007, the person's death, emigration or their diagnosis/first symptoms of MS, whichever came first. RRs were adjusted for age (1-year intervals) and calendar period (1-year intervals). In order to control for potential confounding, the following variables were included as covariates in the Poisson regression model. Birth weight in grams was categorized into five groups (≤ 2500, 2501–3000, 3001–3500, 3501–4000, ≥ 4001), gestational age into two groups (< 37, ≥ 37 weeks) and birth order into four groups (1 = first born, 2 = second born, 3, ≥ 4). Finally, age-specific RRs were calculated for four different age groups (0–19, 20–24, 25–29, 30–35 years).

Robustness analyses

Theoretically, the preferred mode of delivery may differ between healthy women and those with MS. Thus, in a robustness analysis, we examined for possible effect modification of the RR by the maternal MS status (yes, no) at the time of delivery. The completeness and validity of the Danish Hospital Discharge Register concerning the diagnosis of MS is considered to be slightly lower than the Danish Register of Multiple Sclerosis;[14,15] however, the Danish Hospital Discharge Register is updated until 2011. We therefore performed a second robustness analysis, in which we identified MS outcomes in the Danish Hospital Discharge Register between 1977 and 2011, using ICD8 code 340 and ICD10 code G35. A third robustness analysis was carried out to address the findings reported in the recent study by Maghzi et al.[11] Specifically, we performed a sibling-stratified Cox regression analysis of the effect of C-section on MS risk, stratified on the mother's identity and using age as the underlying time scale. Hazard ratios (HRs) were further controlled for sex, birth weight (≤ 2500, 2501–3000, 3001–3500, 3501–4000, ≥ 4001 grams), gestational age (< 37, ≥ 37 weeks), birth order (1, 2, 3, ≥ 4) and birth cohort in 1-year intervals, using cubic splines restricted to be linear in the tails.[16]

Results

The cohort of individuals born from 1973 to 2005 consisted of 1,727,747 persons, of whom 86.2% were born vaginally and 12.4% by C-section. We excluded the remaining 1.4% without information about mode of delivery.

Table 1. Relative risk (RR) of multiple sclerosis in the age span 0–34 years for C-section versus vaginal born children, according to sex and age at MS-diagnosis or appearance of first symptoms, recorded in the Danish Register of Multiple Sclerosis.

			Year of diagnosis				Year of first symptoms			
	Person years/1000		Cases				Cases			
	CS	Vaginal	CS	Vaginal	RR[a]	95% CI	CS	Vaginal	RR[a]	95% CI
Total										
Overall	3189	28,189	80	850	1.17	0.92–1.46	82	863	1.18	0.93–1.48
By age (years)										
0–19	2722	22,551	17	110	1.43	0.83–2.32	25	200	1.28	0.82–1.90
20–24	278	2986	32	299	1.19	0.81–1.69	39	349	1.34	0.94–1.84
25–29+	148	1946	26	328	1.11	0.72–1.62	15	254	0.88	0.50–1.42
30+	41	705	5	113	0.81	0.29–1.78	3	60	0.93	0.23–2.51
Test for homogeneity					*P = 0.71*				*P = 0.53*	
Female										
Overall	1495	13,800	51	594	1.08	0.80–1.42	52	604	1.09	0.81–1.43
By age (years)										
0–19	1275	11,038	8	78	0.98	0.43–1.91	15	143	1.10	0.62–1.82
20–24	131	1463	23	216	1.20	0.76–1.81	27	256	1.28	0.84–1.87
25–29+	70	953	17	225	1.07	0.63–1.69	8	164	0.74	0.33–1.40
30+	19	346	3	75	0.74	0.18–1.99	2	41	0.92	0.15–3.00
Test for homogeneity					*P = 0.86*				*P = 0.58*	
Male										
Overall	1694	14,389	29	256	1.37	0.91–1.98	30	259	1.40	0.94–2.03
Men										
0–19	1447	11,513	9	32	2.44	1.09–4.93	10	57	1.69	0.81–3.17
20–24	147	1523	9	83	1.18	0.55–2.22	12	93	1.50	0.78–2.64
25–29+	78	993	9	103	1.19	0.56–2.23	7	90	1.11	0.47–2.24
30+	22	359	2	38	0.92	0.15–3.00	1	19	0.93	0.05–4.49
Test for homogeneity					*P = 0.42*				*P = 0.83*	

CI: confidence interval; CS: C-section; C-section: Cesarean section; MS: multiple sclerosis; Pyrs: Person years at risk; RR: relative risk.
Follow-up period 1977–2007; birth cohort 1973–2005.
[a]Adjusted for birth order, gestational age, birth weight, age, calendar period.
RR for the total cohort of female and males also adjusted for sex. The RR in each row represents a separate analysis. Onset of MS defined as either year of diagnosis or year of first symptoms.

During follow-up, 645 women and 285 men were diagnosed with MS. Overall, we observed no effect of C-section on the subsequent risk of MS (RR = 1.17; 95% CI: 0.92–1.46) when adjusted for age, calendar period, birth order, birth weight and gestational age. There was a suggestion of an increased risk of MS development before age 20 years, among those delivered by C-section (RR = 1.43; 0.83–2.32), but this was not a statistically-significant finding (Table 1); and a test for possible statistical interaction between mode of delivery and attained age was not statistically significant ($p = 0.71$). Further stratification by both sex and attained age suggested an elevated risk of MS at a young age (before age 20) in men delivered by C-section (RR = 2.44; 1.09–4.93). In contrast, mode of delivery was not associated with MS risk in women overall nor in specific age groups (Table 1). Repeating the analyses using the date of first MS symptoms to define MS outcomes revealed essentially similar results; however, in that analysis we observed no increased risk of MS before age 20 years among men delivered by C-section (IRR = 1.69; 0.81–3.17) (Table 1).

Robustness analyses

The number of MS cases in offspring of mothers with MS was too small ($n = 3$) to enable a thorough evaluation of possible effect modification by maternal MS status at the time of delivery. Nevertheless, it seemed appropriate to conclude that maternal MS had little impact, if any, on our findings. In a robustness analysis, based on the MS cases identified in the Danish National Patient Register through 2011, RRs were practically unchanged (Table 2). Finally, in a sibling-matched Cox regression analysis including 990,113 mothers and their children, we found no indication of an association between mode of delivery and MS risk in offspring overall (HR = 1.03; 0.63–1.69), nor separately for

Table 2. Relative risk (RR) of multiple sclerosis in the age span 0–38 years for C-section versus vaginally born children, according to sex and age at MS-diagnosis, recorded in the Danish National Patient Register.

	Person years/1000		Cases			
	CS	Vaginal	CS	Vaginal	RR[a]	95% CI
Total						
Overall	4110	34,568	138	1473	1.07	0.90–128
By age (years)						
0–19	3320	25,852	25	161	1.37	0.88–2.05
20–24	395	3821	44	408	1.08	0.78–1.45
25–29+	247	2750	41	493	0.97	0.69–1.32
30+	147	2144	28	411	1.04	0.69–1.49
Test for homogeneity					*P = 0.65*	
Female						
Overall	1928	16,929	88	1053	0.99	0.79–1.22
By age (years)						
0–19	1556	12,656	12	114	0.98	0.51–1.70
20–24	186	1871	31	299	1.07	0.72–1.53
25–29	117	1349	28	349	0.96	0.64–1.38
30+	70	1054	17	291	0.92	0.54–1.45
Test for homogeneity					*P=0.96*	
Male						
Overall	2182	17,639	50	420	1.27	0.93–1.70
By age (years)						
0–19	1765	13,197	13	47	2.18	1.13–3.92
20–24	209	1950	13	109	1.10	0.59–1.89
25–29	130	1401	13	144	1.00	0.54–1.70
30+	78	1091	11	120	1.30	0.66–2.31
Test for homogeneity					*P = 0.31*	

CI: Confidence interval; CS: C-section; MS: multiple sclerosis; Pyrs: Person years at risk; RR: relative risk
Follow-up 1977–2011; birth cohort 1973–2008.
[a]Adjusted for birth order, gestational age, birth weight, age, calendar period.
RR for the total cohort of female and males also adjusted for sex. The RR in each row represents a separate analysis.

female (HR = 0.79 (0.43–1.44)) or male (HR = 1.37 (0.75–2.53) offspring.

Discussion

In the present large cohort study of Danes followed for several decades, we found no evidence of an increased risk of MS among persons delivered by C-section compared to those delivered vaginally. The only possible exception was a significant association linking C-section to an increased risk of MS before an age of 20 years in men, but not women, a finding that was not substantiated in a robustness analysis using an alternative definition to identify MS cases in the cohort, nor in a sibling-matched analysis.

Our findings are in contrast to those reported in a recent case-control study from Iran. The authors reported a 2.7-fold (95% CI: 1.3–5.6) increased risk of MS among women and a 2.3-fold (95% CI: 0.9–5.6) increased risk among men delivered by C-section. The Iranian study was based on MS patients (n = 449) and their healthy siblings (n = 900), and relied on self-reports on the mode of delivery, gestational age and birth order.[11] The use of siblings as controls is a recognized method to reduce potential confounding by genetic, socioeconomic[17,18] or other shared family factors. Our finding of no association between mode of delivery and MS risk in a large-scale cohort study and in a supplementary sibling-matched analysis based on information from nationwide Danish registers covering several decades did however suggest that the remarkable observations by Maghzi et al. may be due to chance, bias or methodological limitations.

As mentioned previously, the only exception to the overall null association between C-section and risk of MS was an increased risk of MS before age 20 years, in men born by C-section. Although this finding could theoretically be causal in nature, our robustness analyses lent no strong support for this.

Bias or chance is probably the most obvious explanation for the observed association. Childhood-onset MS is rare[19] and the correct diagnosis is made difficult by the highly variable symptoms of MS among children and the existence of other pediatric demyelinating[20] and neurological

conditions resembling MS, some of which[21,19] even show a slight male predominance among younger children. Taken together with the fact that children delivered by C-section, compared to vaginally delivered children, are more often in contact with the health care system,[5] differential diagnostic problems among boys in combination with surveillance bias could contribute to the observed spurious association between C-section and risk of MS among younger males.

Only persons born in Denmark to Danish-born parents were included in our study. Our findings may, therefore, not be generalizable to other populations. Likewise, because our study cohort was rather young, these findings may not apply to older populations. We excluded all offspring in the study cohort who had no information on mode of delivery; however, we consider this limitation to be of only theoretical importance, as only 1.4% of the underlying study base was excluded due to missing information.

In summary, our results did not support previous findings of a 2- to 3-fold increased risk of MS among persons delivered by C-section. In our study, the mode of child delivery appeared to be unimportant in relation to the risk of MS development.

Conflict of interest

The authors declare that there are no conflicts of interest.

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