



Prisopgave i Klinisk Psykiatri

Effect of Mode of Birth on development of Mental Disorders in the Offspring: a nationwide Danish Cohort Study

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Keystrokes (excluding title, author list, references and tables): 17.473

INTRODUCTION

Caesarean section is the chosen mode of delivery at every fifth birth in Denmark¹ and increasing rates of Caesarean sections worldwide has led to investigations of the long-term effects of Caesarean section on the offspring's health.²⁻⁴ Moreover, being born by Caesarean section has been found to decrease the diversity of the offspring's microbiota during the first years of life.⁴⁻⁶ The gut microbiota is hypothesized to be involved in regulation of mental health through the bidirectional microbiota-gut-brain link and several studies suggests that inflammatory pathophysiological mechanisms might play a role in the development of mental disorders.^{7,8} Thus it has been proposed that differences in microbiota induced by Caesarean section could increase the risk of mental disorders. Furthermore, being born by Caesarean section have been associated with increased risk of developing obesity,⁹ allergy,¹⁰ asthma¹¹ and type 1 diabetes,¹² which are also associated with increased risks of mental disorders.

Prior studies on the association between Caesarean section and mental disorders have focused on specific mental disorders with conflicting results. A recent systematic review and meta-analysis on 40 case-control and 25 observational studies found increased risks of ADHD and Autism in children born by Caesarean section compared to vaginal birth but less than 3 studies on each outcome had controlled for parental psychiatric history.¹³ The review included studies on different mental disorders with data on a total of 186,295 cases, but the studies had a high level of unexplainable heterogeneity. On the other hand, two large Danish cohort studies found no association between the mode of delivery and the development of Attention Deficit Hyperactive Disorder (ADHD) and Autism Spectrum Disorders in the offspring.^{14,15} The conflicting results may be due to differences in study designs, insufficient adjustment for confounding and inappropriate adjustment for variables on the causal pathway such as those leading to the birthweight paradox.¹⁶ Parental infections could be an example of this since it has been found to increase the risk of both Caesarean

delivery and mental disorders and may hence cause confounding.^{7,8} Additionally, infections in the child and also treatment with antibiotics can affect the gut microbiota and thus might have an impact if increased risks of mental disorders would be due to Caesarean section induced microbiome changes.¹⁷

No prior study has investigated the association between mode of delivery and risk of the entire spectrum of mental disorders. We aimed to investigate this by estimating the risk in the presence of multiple confounders such as parental infections, socio-economic status and psychiatric family history in the presence of competing risks in a nationwide setting with up to 36 years of follow-up. Moreover, we secondarily investigated if exposure to infections after birth altered the risk of mental disorders in individuals exposed to Caesarean section.

Table 1: Baseline Characteristics of Study Population at Time of Birth: Caesarean Section and Vaginal Delivery groups

	Caesarean Section (n=364.908)	Vaginal Delivery (n=1.831.779)	Total (n=2.196.687)
Censoring			
Death ¹	4160 (1.1%)	11471 (0.6%)	15631 (0.7%)
Diagnosis of Mental Disorder	6268 (1.7%)	38084 (2.1%)	44352 (2.0%)
Lost to follow-up	24047 (6.6%)	154954 (8.5%)	179001 (8.1%)
Years of follow-up			
Mean (SD)	14.8 (9.7)	17.5 (9.9)	17.0 (10.0)
Offspring Sex			
Male	171978 (47.1%)	897576 (49.0%)	1069554 (48.7%)
Female	192930 (52.9%)	934203 (51.0%)	1127133 (51.3%)
Birth Decade			
1980s	67763 (18.6%)	477687 (26.1%)	545450 (24.8%)
1990s	89372 (24.5%)	574749 (31.4%)	664121 (30.2%)
2000s	131620 (36.1%)	509725 (27.8%)	641345 (29.2%)
2010s	76153 (20.9%)	269618 (14.7%)	345771 (15.7%)
Parental Age at birth (years)			
Maternal Mean (SD)	30.1 (5.1)	28.7 (4.9)	29.0 (5.0)
Paternal Mean (SD)	32.6 (6.1)	31.5 (5.8)	31.7 (5.9)
Maternal highest education			
Secondary School	84075 (23.5%)	480065 (26.8%)	564140 (26.2%)
High School	22213 (6.2%)	125653 (7.0%)	147866 (6.9%)
Vocational School	123239 (34.4%)	595293 (33.2%)	718532 (33.4%)
Short higher education	16307 (4.5%)	72430 (4.0%)	88737 (4.1%)
Medium higher education	31141 (8.7%)	137124 (7.6%)	168265 (7.8%)
Long higher education	74661 (20.8%)	352764 (19.7%)	427425 (19.9%)
Bachelor's degree	6777 (1.9%)	31262 (1.7%)	38039 (1.8%)

Paternal highest education			
Secondary School	76326 (21.4%)	412793 (23.2%)	489119 (22.9%)
High School	17697 (5.0%)	92119 (5.2%)	109816 (5.1%)
Vocational School	157514 (44.3%)	781839 (43.9%)	939353 (43.9%)
Short higher education	19610 (5.5%)	87061 (4.9%)	106671 (5.0%)
Medium higher education	38351 (10.8%)	179050 (10.1%)	217401 (10.2%)
Long higher education	40718 (11.4%)	201632 (11.3%)	242350 (11.3%)
Bachelor's degree	5714 (1.6%)	26918 (1.5%)	32632 (1.5%)
Maternal income²			
Mean (SD)	130.0 (165.9)	114.0 (85.5)	116.7 (103.5)
Paternal income²			
Mean (SD)	157.6 (248.7)	137.6 (172.7)	140.9 (187.6)
Maternal work status			
Employed	257194 (70.7%)	1259819 (69.0%)	1517013 (69.3%)
In education	9584 (2.6%)	53777 (2.9%)	63361 (2.9%)
Not in workforce	80633 (22.2%)	400636 (21.9%)	481269 (22.0%)
Unemployed	16435 (4.5%)	111007 (6.1%)	127442 (5.8%)
Paternal work status			
Employed	319447 (88.3%)	1587918 (87.4%)	1907365 (87.6%)
In education	5152 (1.4%)	28796 (1.6%)	33948 (1.6%)
Not in workforce	19792 (5.5%)	97861 (5.4%)	117653 (5.4%)
Unemployed	17387 (4.8%)	102045 (5.6%)	119432 (5.5%)
Maternal History of severe infections³			
0 infections	229191 (62.8%)	1312060 (71.6%)	1541251 (70.2%)
1 infection	72404 (19.8%)	307508 (16.8%)	379912 (17.3%)
>1 infection	63313 (17.4%)	212211 (11.6%)	275524 (12.5%)
Paternal History of severe infections³			
0 infections	278385 (76.3%)	1458669 (79.6%)	1737054 (79.1%)
1 infection	52377 (14.4%)	236694 (12.9%)	289071 (13.2%)
>1 infection	34146 (9.4%)	136416 (7.4%)	170562 (7.8%)
Maternal infections during pregnancy⁴			
0 infections	346440 (94.9%)	1784781 (97.4%)	2131221 (97.0%)
1 infection	14106 (3.9%)	35551 (1.9%)	49657 (2.3%)
≥1 infection	4362 (1.2%)	11447 (0.6%)	15809 (0.7%)
Paternal infections during pregnancy⁴			
0 infections	362078 (99.2%)	1817808 (99.2%)	2179886 (99.2%)
≥1 infection	2830 (0.8%)	13971 (0.8%)	16801 (0.8%)
Maternal psychiatric History			
0	355556 (97.4%)	1795462 (98.0%)	2151018 (97.9%)
≥1	9352 (2.6%)	36317 (2.0%)	45669 (2.1%)
Paternal Psychiatric History			
0	357580 (98.0%)	1797845 (98.1%)	2155425 (98.1%)
≥1	7328 (2.0%)	33934 (1.9%)	41262 (1.9%)
Birth order/number birth⁵			
1	183132 (50.2%)	794075 (43.4%)	977207 (44.5%)
2	123582 (33.9%)	700498 (38.2%)	824080 (37.5%)
>2	58179 (15.9%)	337151 (18.4%)	395330 (18.0%)

Litter size⁵			
1	325550 (89.2%)	1797763 (98.1%)	2123313 (96.7%)
2	37703 (10.3%)	33863 (1.8%)	71566 (3.3%)
>2	1640 (0.4%)	98 (0.0%)	1738 (0.1%)

Abbreviations: SD = Standard deviation.

¹Death is handled as a competing risk in analyses and does not include children who died on their first day. ²In Danish kroner (DKK) multiplied by 1000. ³Includes all infections requiring hospitalization earlier than 35 weeks before delivery. ⁴Includes all infections requiring hospitalization in the period between delivery and 35 weeks prior. The registers only include data on hospital-infections since 1977. For the earliest subjects we only have 3 years of history of severe infections for parents. ⁵Includes all biological children from the mother.

MATERIAL AND METHODS

Study design and participants

The present study is a nationwide observational cohort study covering the entire Danish population. Data was obtained from Danish nationwide registers by use of the unique personal registration number assigned to all Danes at birth by the Danish Civil Registration System,¹⁸ permitting linkage between the national registers and including information on parents and siblings from 1968. We identified all individuals born in Denmark between January 1st, 1980, and December 31st, 2015. We excluded individuals who died during their first day or with missing parental identification. All individuals were followed from birth to outcome (see below), emigration, death or end of follow-up on December 31st, 2016, whichever came first.

Exposure: Procedures of mode of delivery

Caesarean sections were identified as ICD coded Caesarean section procedures matched to offspring within 5 days of birth from the Danish National Patient Register, where information on all patient contacts since 1977 are registered.¹⁹ Births not identified as “Caesarean Section” were categorized as “Vaginal Birth”. Where possible, we categorized Caesarean sections as “acute” or “planned” and “prelabour” or “intrapartum”. It was not possible to identify pre-delivery indications for Caesarean section.

Outcome: Mental disorders

Mental disorders were identified through the Danish Psychiatric Central Research Register, which holds information on all in-patient contacts in psychiatric hospitals since 1969.²⁰ For a broad assessment of the risk of mental disorders, we identified as the primary outcome any mental disorder (ICD-10: F00-99 or ICD-8: 290-315) that was diagnosed during an in-patient admission. Secondly, we identified specific diagnostic groups (see Table 2).

Confounders and covariates

Data on the following covariates at childbirth were available for the adjusted analyses: Sex and birth year for both parents and offspring, birth decade, number of siblings and birth order.¹⁹ As proxies for socioeconomic status (SES) or genetic susceptibility of mental disorders we adjusted for parental highest educational degree,²¹ parental work status¹⁸ and parental history of mental disorders (ICD-10: F00-99 or ICD-8: 290-315) prior to childbirth since 1969.²⁰ We also adjusted for paternal and maternal Charlson Comorbidity Index²³ and the number of severe infections requiring hospital admission prior to birth of offspring, as well as the number of paternal and maternal severe infections requiring hospital admission 35 weeks prior to the day of birth.¹⁹

Statistical analyses

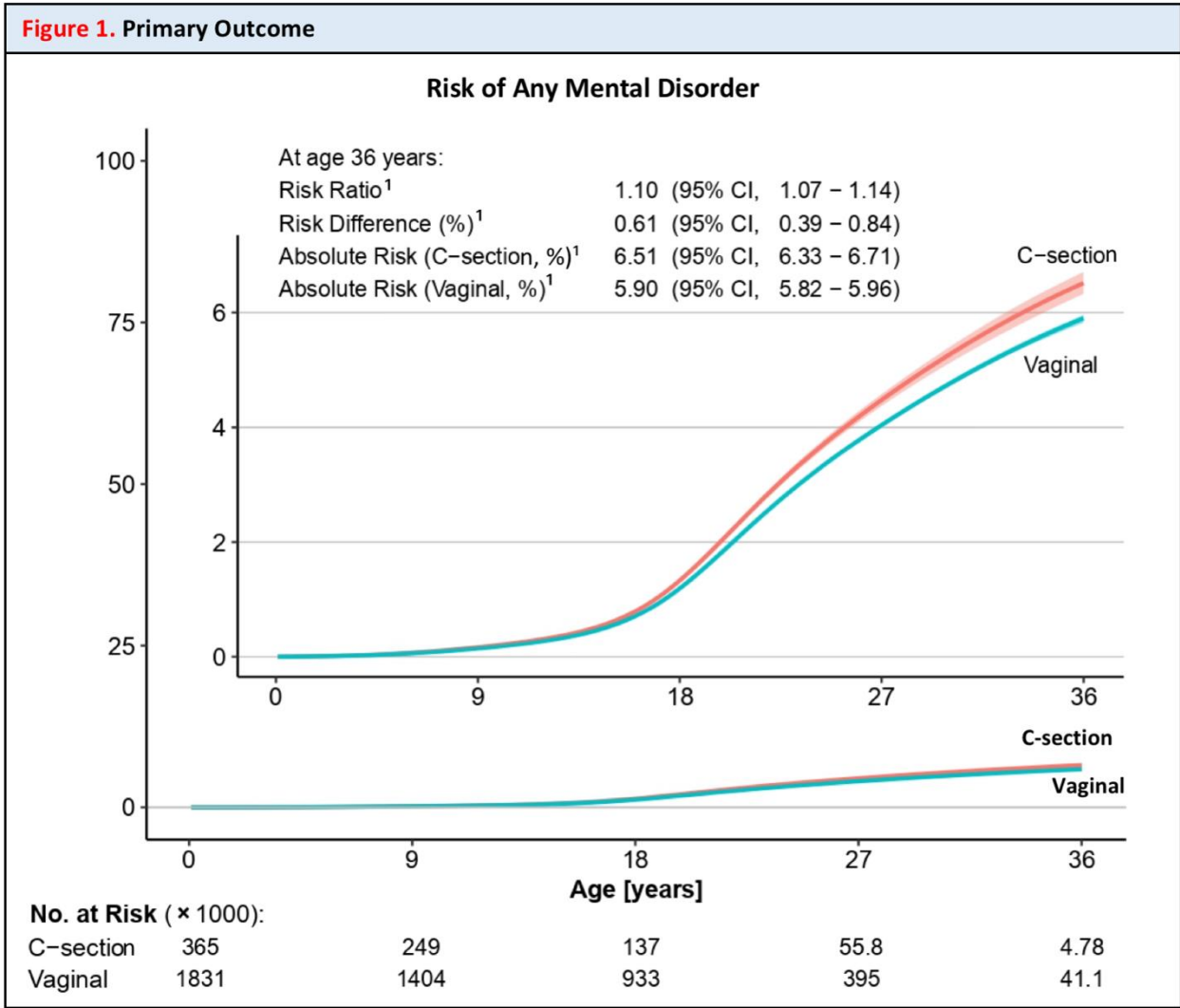
The primary analysis evaluated relative and absolute risk contrasts based on estimated risk functions (cumulative incidence) by mode of delivery for developing serious mental disorders requiring treatment or diagnosis at a psychiatric hospital standardized to the joint distribution of confounders. The hazard of mental disorders was estimated using a logistic regression with inverse probability weighting to adjust for confounding.^{24–26} Delivery-specific 6-degree cubic splines were used to model the hazard in monthly intervals over subject age with linear effect of calendar time

coded as year of birth with additive effects of all confounders as coded in Table 1. Our analyses were not adjusted for post-birth variables (Apgar score, birthweight etc.) to avoid adjusting for variables on the causal pathway and thereby avoiding the bias known as the birthweight paradox.¹⁶ Missing baseline information was rare (<3%) and affected subjects were excluded from the analyses. Death was treated as a competing event and the cumulative incidence of mental disorder was estimated by integration of the case-specific hazard for mental disorders using the Nelson-Aalen method²⁷ and 95% confidence intervals were estimated with the two-sample percentile bootstrap method using 1000 bootstrap samples.

Under assumptions of exchangeability conditional on the observed confounders, positivity, no measurement bias, correct specifications of the exposure model and noninformative censoring²⁸ the risk difference and risk ratio for Caesarean section versus vaginal delivery can be interpreted as the causal effect on the additive and relative scales of delivery mode on the risk of mental disorder. Secondary analyses were conducted for the mode of delivery regarding the risk of specific mental disorders. Additionally, analyses were conducted on intrapartum versus prelabour Caesarean section and acute versus planned Caesarean section. We further analysed the risk of any mental disorder from birth adjusted to number of infections requiring hospital contact by age 10 in the offspring grouped as 0, 1, 2, 3 or >3 infections. All secondary analyses used methods similar to the primary analysis.

All statistical analyses were performed using R software (version 3.6.1; R Development Core Team, 2019).

Figure 1. Risk of Any Mental Disorder in Offspring by Mode of Delivery grouped as either Caesarean Section or Vaginal Delivery Among 2,196,687 Individuals



Abbreviations: C-section = caesarean section; C-section = caesarean section; Vaginal = Vaginal Delivery; 95%-CI = 95% confidence interval; No. = Number. ¹The analyses were adjusted for age, gender, birth decade, parental educational level, parental income, parental work status, parental hospitalizations for infections, Charlson comorbidity index, parental mental disorders, birth order and litter size.

RESULTS

The cohort consisted of 2,196,687 children born January 1st, 1980 to December 31st, 2015, with 38.5 million observation-years of follow-up from January 1st, 1980 to December 31st, 2016 (see Table 1 for characteristics of the study population). A total of 364,908 (16.6%) children were born by Caesarean section while 1,831,779 (83.4%) were born by vaginal delivery. A total of 44,352 (2.0%) individuals were diagnosed with a mental disorder during admission to a psychiatric facility

during the study period, of which 6,268 (14.1%) had been exposed to birth by Caesarean section and 38,084 (85.9%) had been exposed to vaginal delivery. During our study period, Caesarean section increased from 10.4% in 1980 to 19.2% in 2016. All analyses presented below are adjusted for all covariates presented in Table 1.

Caesarean section and the Risk of Any Treated Mental Disorder

The primary analysis showed that children exposed to birth by Caesarean section had a small increased risk of 10% for any treated mental disorder (Risk Ratio (RR), 1.10; 95% CI, 1.07-1.14) compared with children born vaginally (Figure 1). The absolute risk of developing a mental disorder at age 36 for Caesarean section was 6.51 % (95% CI, 6.33-6.71) and the absolute risk at age 36 for children born vaginally was 5.90 % (95% CI, 5.82-5.96) resulting in a small absolute risk difference of 0.61% (95% CI, 0.39-0.84) (Figure 1).

Caesarean section and the Risk of Specific Mental Disorders

Caesarean section was associated with a 49% increased risk of Intellectual Disability (RR, 1.49; 95% CI, 1.24-1.75) but with a small risk difference of 0.09% (RD, 0.09; 95% CI, 0.05-0.14) compared with children born vaginally (Table 2). The risk of developing neurotic, stress-related and somatoform disorders was increased by 17% (RR, 1.17; 95% CI, 1.11-1.24) with a small risk difference of 0.46% (RD, 0.46; 95% CI, 0.29-0.63). The risk of schizophrenia and related disorders was increased by 9% (RR, 1.09; 95% CI, 1.01-1.18) with a small risk difference of 0.12% (RD, 0.12; 95% CI, 0.01-0.23). The risk of specific personality disorders was increased by 14% (RR, 1.14; 95% CI, 1.05-1.24) with a small risk difference of 0.15% (RD, 0.15; 95% CI, 0.06-0.27). The risk of autism spectrum disorders (ASD) was increased by 14% (RR, 1.14; 95% CI, 1.01-1.29) with a small risk difference of 0.04% (RD, 0.04; 95% CI, 0.00-0.09) (Table 2).

Table 2. Risk of Specific Categories of Mental Disorders and Specific Disorders in Offspring After Exposure to Birth by Caesarean Section or Vaginal Delivery

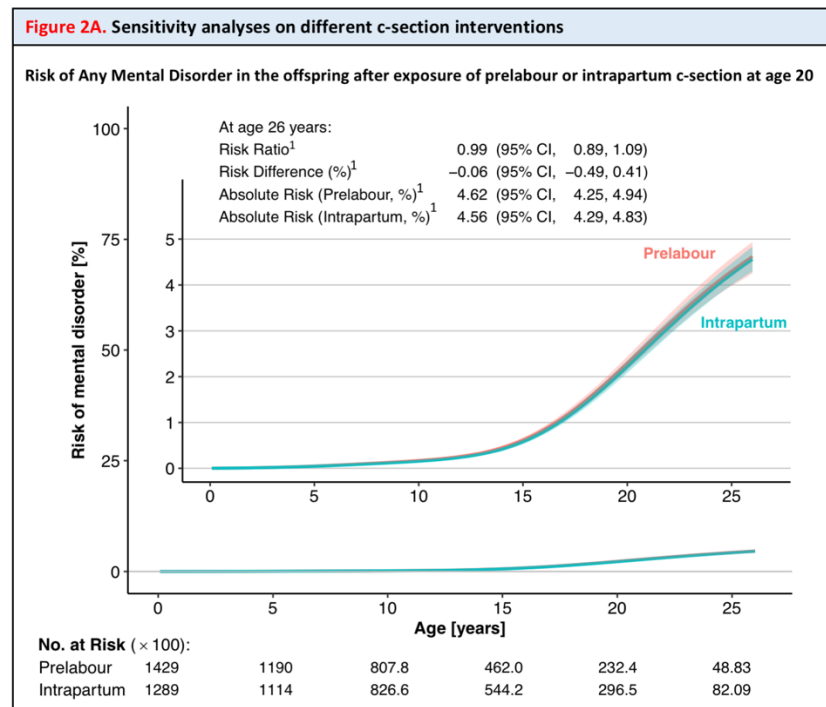
Subgroup ¹	Risk Ratio ²	RR (95% CI) ²	AR (95% CI) ² C-section	AR (95% CI) ² Vaginal	RD [%] (95% CI) ²	Cases ³ C-section	Cases ³ Vaginal
Schizophrenia and related disorders		1.09 (1.01-1.18)	1.42 (1.31-1.53)	1.30 (1.26-1.34)	0.12 (0.01-0.23)	1374	8300
➤ Schizophrenia		1.07 (0.97-1.18)	0.80 (0.73-0.88)	0.75 (0.72-0.78)	0.05 (-0.02-0.13)	769	4693
Mood disorders		1.06 (0.98-1.13)	1.89 (1.76-2.02)	1.79 (1.74-1.84)	0.10 (-0.03-0.24)	1628	10308
➤ Single and recurrent depressive disorder		1.07 (0.99-1.16)	1.60 (1.49-1.72)	1.50 (1.45-1.54)	0.10 (-0.01-0.23)	1409	8890
➤ Bipolar disorder		1.01 (0.82-1.22)	0.34 (0.28-0.41)	0.34 (0.31-0.36)	0.00 (-0.06-0.07)	251	1530
Neurotic, stress-related and somatoform disorders		1.17 (1.11-1.24)	3.16 (2.99-3.33)	2.70 (2.63-2.76)	0.46 (0.29-0.63)	2787	16483
➤ Obsessive-compulsive disorder (OCD)		1.10 (0.89-1.33)	0.24 (0.19-0.28)	0.21 (0.20-0.23)	0.02 (-0.02-0.07)	249	1391
Eating disorders		1.03 (0.90-1.17)	0.34 (0.29-0.38)	0.32 (0.31-0.34)	0.01 (-0.03-0.05)	457	2694
Specific personality disorders		1.14 (1.05-1.24)	1.25 (1.15-1.36)	1.10 (1.07-1.13)	0.15 (0.06-0.27)	1125	6975
Intellectual Disability		1.49 (1.24-1.75)	0.28 (0.23-0.33)	0.19 (0.17-0.20)	0.09 (0.05-0.14)	287	1443
Autism spectrum disorders (ASD)		1.14 (1.01-1.29)	0.36 (0.32-0.40)	0.31 (0.30-0.33)	0.04 (0.00-0.09)	571	2891
Behavioural and emotional disorders*		1.04 (0.96-1.13)	0.88 (0.82-0.95)	0.85 (0.82-0.88)	0.03 (-0.04-0.11)	1260	7473
➤ Attention deficit hyperactive disorder (ADHD)		0.97 (0.87-1.08)	0.60 (0.54-0.66)	0.61 (0.59-0.64)	-0.02 (-0.08-0.05)	688	4336

*...with onset usually occurring in childhood and adolescence Abbreviations: RR = Risk ratio; AR = Absolute risk; RD = Risk Difference; C-section = caesarean section; Vaginal = Vaginal Delivery; 95%-CI = 95% confidence interval.¹ The definition of the specific diagnostic codes that the subgroups exist of are listed in supplementary information that is available on request from authors. ²The analyses were adjusted for age, gender, birth decade, parental educational level, parental income, parental work status, parental hospitalizations for infections, Charlson comorbidity index, parental mental disorders, birth order and litter size. ³Cases = number of subjects with diagnosis of any mental disorder

Sensitivity Analyses

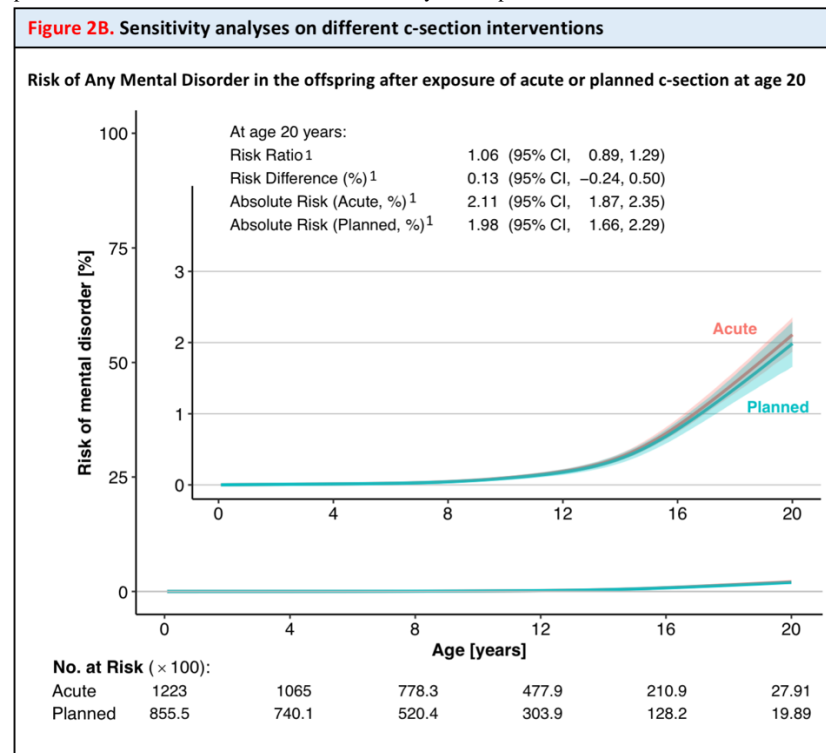
There was no difference in risk of mental disorders for children exposed to prelabour Caesarean section (RR, 0.99; 95% CI, 0.89-1.09) compared with intrapartum Caesarean section (Figure 2A). Moreover, we found no difference in risk of mental disorders for children exposed to acute Caesarean section (RR, 1.06; 95% CI, 0.89-1.29) compared with children born by planned Caesarean section (Figure 2B).

Figure 2. (A) Risk of any mental disorder in the offspring depending on the type of caesarean section grouped as acute or planned caesarean section (B) Risk of any mental disorder in the offspring depending on the type of caesarean section grouped as intrapartum or prelabour caesarean section



Abbreviations: C-section = caesarean section; Vaginal = Vaginal delivery; 95%-CI = 95% confidence interval.

¹The analyses were adjusted for age, gender, birth decade, parental educational level, parental income, parental work status, parental hospitalizations for infections, Charlson comorbidity index, parental mental disorders, birth order and litter size.

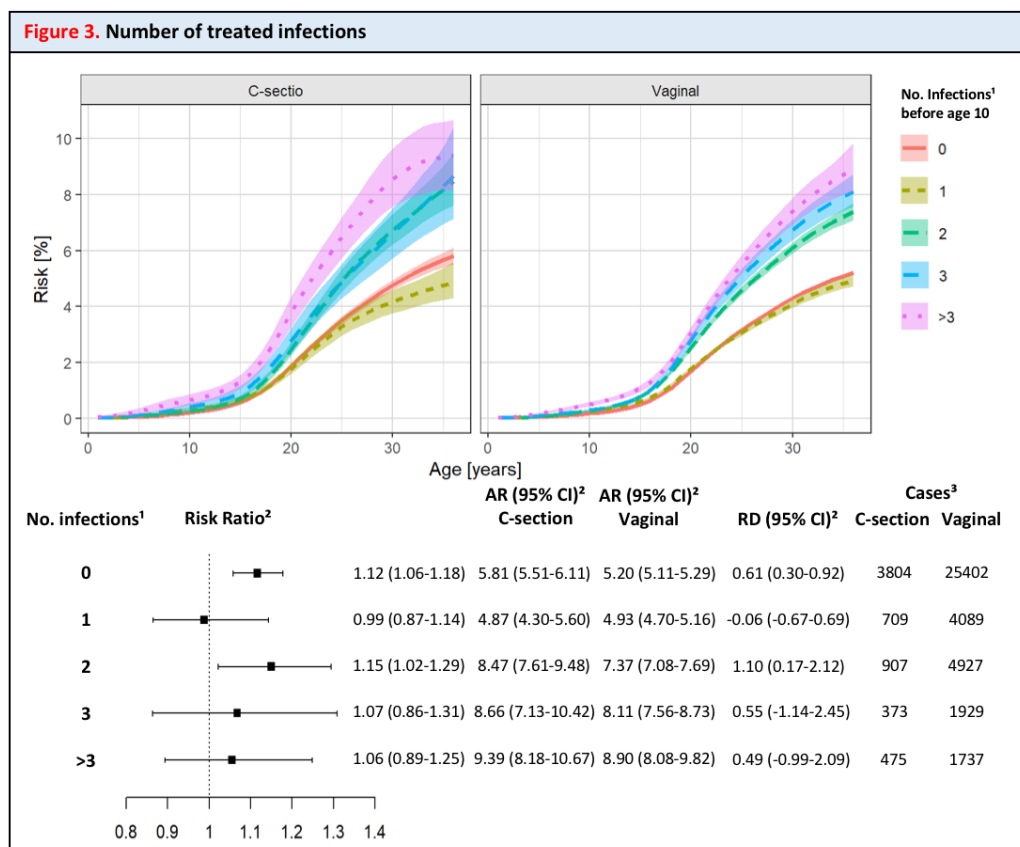


Abbreviations: C-section = caesarean section; Vaginal = Vaginal delivery; 95%-CI = 95% confidence interval.

¹The analyses were adjusted for age, gender, birth decade, parental educational level, parental income, parental work status, parental hospitalizations for infections, Charlson comorbidity index, parental mental disorders, birth order and litter size.

Children delivered by Caesarean section more often had a hospitalization for infection (135,438/364,908 (37.1%)) before age 10 than children born by vaginal delivery (549,569/1,831,779 (30.0%)). Among children born by Caesarean section there was an increase in the absolute risks of developing mental disorders from 5.81 % (95% CI, 5.51-6.11) among individuals without hospitalization for infection to 9.39 % (95% CI, 8.18-10.64) for individuals with three or more hospitalizations for infections. Among children born by vaginal delivery the absolute risks of developing mental disorders increased from 5.20 % (95% CI, 5.51-6.11) among individuals without hospitalization for infection to 8.90 % (95% CI, 8.08-9.82) among individuals with three or more hospitalizations for infections (Figure 3).

Figure 3. Risk of Any Mental Disorder in Offspring After Exposure to Birth by Caesarean Section or Vaginal Delivery with Exposure of Number of Treated Infections requiring hospitalization in the Offspring before age 10



Abbreviations: AR = Absolute risk; RD = Risk Difference; C-section = caesarean section; Vaginal = Vaginal Delivery; 95%-CI = 95% confidence interval; No. = Number. ¹Includes all types of infections requiring hospitalization, that the offspring has required before the age of 10.

²The analyses were adjusted for age, gender, birth decade, parental educational level, parental income, parental work status, parental hospitalizations for infections, Charlson comorbidity index, parental mental disorders, birth order and litter size. ³Cases = number of subjects with diagnosis of any mental disorder

DISCUSSION

In this nationwide population-based observational cohort study of over 2 million children Caesarean section was associated with a small increased relative risk of 10% of being hospitalized with a mental disorder compared with those born vaginally with a small absolute risk difference of 0.61% between the two exposure groups. The clinical relevance of this small excess risk is limited and may be explained by unmeasured confounding such as exposure to hypoxia or other factors causing foetal distress prior to birth. Although there is evidence that the microbiota composition is different in individuals born by Caesarean section in the first years of life,⁴⁻⁶ this normalizes in early childhood and may be the reason why it does not cause a differential risk of developing a mental disorder. We compared intrapartum Caesarean section to prelabour Caesarean section to look at a proxy of whether the child had been in contact with the maternal vaginal microbiota. Intrapartum Caesarean section is likely to cause rupture of membranes allowing contact between maternal vaginal microbiota and the child but there was no difference in the risk of mental disorders when comparing to prelabour Caesarean section with the child presumably being delivered in intact membranes. Additionally, the risk of mental disorders did not depend on the severity of the Caesarean section analysed in the comparison of planned Caesarean section versus acute Caesarean section, which might indicate differences in the level of a stressful environment for both the child and the parents during birth. When looking at specific mental disorders, we particularly found that Caesarean section was associated with a 49% increased risk of being diagnosed with intellectual disability and a 17% increased risk of neurotic, stress-related and somatoform disorders; however, with small risk differences between the two exposure groups and nonnegligible uncertainty. Exposure to Caesarean section was associated with more infections in children than vaginal delivery, but when comparing children with or without infections there were no differential risk difference associated with Caesarean section.

Our nationwide study represents the first study to date investigating the association between mode of delivery and the risk of all as well as specific mental disorders in offspring. Previous studies have reported conflicting results^{14,15,29–32} when investigating the risk of specific mental disorders following delivery by Caesarean section, with some studies indicating that the risk of Obsessive Compulsive Disorder³⁰, Autism^{33,34} and ADHD^{32,35} may be increased. In contrast, two recent studies based on the Danish nationwide registers showed no increased risk of both Autism¹⁵ and ADHD¹⁴ after being born by Caesarean section. The previous literature has been difficult to compare due to differences in study designs in previous studies regarding inclusion of confounders and statistical choices. This was also emphasized in a recent meta-analysis that showed high statistical heterogeneity between the included studies.¹³ Of interest is also the comparison of Caesarean section without medical indication (at maternal request) with voluntary vaginal delivery. Such an analysis is complicated by the lack of reliable information in the registries on indications for actual and planned delivery method. To account for these potential unobserved confounders, several studies have used a sibling-comparison design to adjust for within-familial confounding. The design assumes that the exposure and outcome of an individual does not affect the exposure and outcome of the individuals' siblings, which will likely lead to bias.³⁶ Several of the previous studies used the stratified Cox model to adjust for within-familial confounding.^{29–31,35} Our present study aimed to target potential confounders without using a sibling-model, in order to not disguise potential carry-over effects leading to bias. We fitted our statistical model based on previously identified confounders, that add confounding to the relationship between mode of delivery and mental disorders.

Strengths and limitations

Our findings are strengthened by several factors such as the prospective design and the well-validated nationwide registers of the entire Danish population minimizing the risk of selection and recall bias. Another strength is that we evaluated the previously used confounders in the literature and because of the birth-weight paradox¹⁶ we did not adjust for birth variables that may lie on the causal pathway, such as birth weight, gestational period and Apgar score, that was adjusted for in several previous studies.^{29–33,35,37} For our outcome measure, we chose to only include in-patient contacts for consistency throughout the study period because the registers hold data on out-patient and emergency room contacts since 1995 only. If we had included out-patient contacts the absolute risks would have been higher. A limitation of this study is that there is not specific information in the registers on the indications of a planned Caesarean section; however, we found no difference in the risks when comparing the different types of Caesarean sections, which indicates that the indications behind the Caesarean section are of less importance to our result.

CONCLUSIONS

Birth by Caesarean section was associated with a small increased risk of mental disorder in the offspring; however, this may be explained by unmeasured confounding and the risk difference of 0.61% is unlikely to be of substantial clinical relevance. Furthermore, we find no clinically meaningful difference between exposure to intrapartum or prelabour Caesarean section and acute or planned Caesarean section on the risk of mental disorders, thus Caesarean section induced alterations of the gut microbiota may only have a limited impact on the risk of developing mental disorders.

References

1. Bliddal, M., Broe, A., Pottgard, A., Olsen, J. & Langhoff-Roos, J. The Danish Medical Birth Register. *Eur. J. Epidemiol.* **33**, 27–36 (2018).
2. Keag, O. E., Norman, J. E. & Stock, S. J. Long-term risks and benefits associated with cesarean delivery for mother, baby, and subsequent pregnancies: Systematic review and meta-analysis. *PLoS Med.* **15**, e1002494 (2018).
3. Robson, S. J., Vally, H., Abdel-Latif, M. E., Yu, M. & Westrupp, E. Childhood Health and Developmental Outcomes After Cesarean Birth in an Australian Cohort. *Pediatrics* **136**, e1285-93 (2015).
4. Sandall, J. *et al.* Short-term and long-term effects of caesarean section on the health of women and children. *Lancet (London, England)* **392**, 1349–1357 (2018).
5. Jakobsson, H. E. *et al.* Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. *Gut* **63**, 559–566 (2014).
6. Azad, M. B. *et al.* Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *BJOG* **123**, 983–993 (2016).
7. Kohler-Forsberg, O. *et al.* A Nationwide Study in Denmark of the Association Between Treated Infections and the Subsequent Risk of Treated Mental Disorders in Children and Adolescents. *JAMA psychiatry* **76**, 271–279 (2019).
8. Orlovskaya, S. *et al.* Association of Streptococcal Throat Infection With Mental Disorders: Testing Key Aspects of the PANDAS Hypothesis in a Nationwide Study. *JAMA psychiatry* **74**, 740–746 (2017).
9. Kuhle, S., Tong, O. S. & Woolcott, C. G. Association between caesarean section and childhood obesity: a systematic review and meta-analysis. *Obes. Rev.* **16**, 295–303 (2015).
10. Keag, O. E., Norman, J. E. & Stock, S. J. Long-term risks and benefits associated with cesarean delivery for mother, baby, and subsequent pregnancies: Systematic review and meta-analysis. *PLoS Med.* (2018). doi:10.1371/journal.pmed.1002494
11. Huang, L. *et al.* Is elective cesarean section associated with a higher risk of asthma? A meta-analysis. *J. Asthma* **52**, 16–25 (2015).
12. Cardwell, C. R. *et al.* Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia* **51**,

726–735 (2008).

13. Zhang, T. *et al.* Association of Cesarean Delivery With Risk of Neurodevelopmental and Psychiatric Disorders in the Offspring: A Systematic Review and Meta-analysis. *JAMA Netw. open* **2**, e1910236 (2019).
14. Axelsson, P. B. *et al.* Investigating the effects of cesarean delivery and antibiotic use in early childhood on risk of later attention deficit hyperactivity disorder. *J. Child Psychol. Psychiatry*. **60**, 151–159 (2019).
15. Axelsson, P. B. *et al.* Relation Between Infant Microbiota and Autism?: Results from a National Cohort Sibling Design Study. *Epidemiology* **30**, 52–60 (2019).
16. Hernandez-Diaz, S., Schisterman, E. F. & Hernan, M. A. The birth weight ‘paradox’ uncovered? *Am. J. Epidemiol.* **164**, 1115–1120 (2006).
17. Martin, R. *et al.* Early-Life Events, Including Mode of Delivery and Type of Feeding, Siblings and Gender, Shape the Developing Gut Microbiota. *PLoS One* **11**, e0158498 (2016).
18. Pedersen, C. B. The Danish Civil Registration System. *Scand. J. Public Health* **39**, 22–25 (2011).
19. Andersen, T. F., Madsen, M., Jorgensen, J., Mellekjoer, L. & Olsen, J. H. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan. Med. Bull.* **46**, 263–268 (1999).
20. Mors, O., Perto, G. P. & Mortensen, P. B. The Danish Psychiatric Central Research Register. *Scand. J. Public Health* **39**, 54–57 (2011).
21. Jensen, V. M. & Rasmussen, A. W. Danish Education Registers. *Scand. J. Public Health* **39**, 91–94 (2011).
22. Baadsgaard, M. & Quitzau, J. Danish registers on personal income and transfer payments. *Scand. J. Public Health* **39**, 103–105 (2011).
23. Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* **40**, 373–383 (1987).
24. Cole, S. R., Hudgens, M. G., Brookhart, M. A. & Westreich, D. Risk. *Am. J. Epidemiol.* **181**, 246–250 (2015).
25. Robins, J. M., Hernan, M. A. & Brumback, B. Marginal structural models and causal inference in epidemiology. *Epidemiology* **11**, 550–560 (2000).
26. Hernan, M. A. *et al.* Observational studies analyzed like randomized experiments: an

application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology* **19**, 766–779 (2008).

27. Andersen, P. K., Geskus, R. B., de Witte, T. & Putter, H. Competing risks in epidemiology: possibilities and pitfalls. *Int. J. Epidemiol.* **41**, 861–870 (2012).
28. Hernán, M. A. & Robins, J. M. *Causal Inference: What If*. Boca Raton: Chapman & Hall/CRC. (2020).
29. Curran, E. A. *et al.* Association Between Obstetric Mode of Delivery and Autism Spectrum Disorder: A Population-Based Sibling Design Study. *JAMA psychiatry* **72**, 935–942 (2015).
30. Brander, G. *et al.* Association of Perinatal Risk Factors With Obsessive-Compulsive Disorder: A Population-Based Birth Cohort, Sibling Control Study. *JAMA psychiatry* **73**, 1135–1144 (2016).
31. O'Neill, S. M. *et al.* Birth by Caesarean Section and the Risk of Adult Psychosis: A Population-Based Cohort Study. *Schizophr. Bull.* **42**, 633–641 (2016).
32. Sucksdorff, M. *et al.* Lower Apgar scores and Caesarean sections are related to attention-deficit/hyperactivity disorder. *Acta Paediatr.* **107**, 1750–1758 (2018).
33. Bilder, D., Pinborough-Zimmerman, J., Miller, J. & McMahon, W. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. *Pediatrics* **123**, 1293–1300 (2009).
34. Curran, E. A. *et al.* Research review: Birth by caesarean section and development of autism spectrum disorder and attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *J. Child Psychol. Psychiatry.* **56**, 500–508 (2015).
35. Curran, E. A. *et al.* Obstetric mode of delivery and attention-deficit/hyperactivity disorder: a sibling-matched study. *Int. J. Epidemiol.* **45**, 532–542 (2016).
36. Sjolander, A., Frisell, T., Kuja-Halkola, R., Oberg, S. & Zetterqvist, J. Carryover Effects in Sibling Comparison Designs. *Epidemiology* **27**, 852–858 (2016).
37. Polo-Kantola, P. *et al.* Obstetric risk factors and autism spectrum disorders in Finland. *J. Pediatr.* **164**, 358–365 (2014).