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Association of Perinatal Risk Factors With Obsessive-Compulsive Disorder
A Population-Based Birth Cohort, Sibling Control Study

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IMPORTANCE Perinatal complications may increase the risk of obsessive-compulsive disorder (OCD). Previous reports were based on small, retrospective, specialist clinic–based studies that were unable to rigorously control for unmeasured environmental and genetic confounding.

OBJECTIVE To prospectively investigate a wide range of potential perinatal risk factors for OCD, controlling for unmeasured factors shared between siblings in the analyses.

DESIGN, SETTING, AND PARTICIPANTS This population-based birth cohort study included all 2 421 284 children from singleton births in Sweden from January 1, 1973, to December 31, 1996, who were followed up through December 31, 2013. From the 1 403 651 families in the cohort, differentially exposed siblings from the 743 885 families with siblings were evaluated; of these, 11 592 families included clusters of full siblings that were discordant for OCD. Analysis of the data was conducted from January, 26, 2015, to September, 5, 2016.

EXPOSURES Perinatal data were collected from the Swedish Medical Birth Register and included maternal smoking during pregnancy, labor presentation, obstetric delivery, gestational age (for preterm birth), birth weight, birth weight in relation to gestational age, 5-minute Apgar score, and head circumference.

MAIN OUTCOMES AND MEASURES Previously validated OCD codes (*International Statistical Classification of Diseases and Health Related Problems, Tenth Revision*, code F42) in the Swedish National Patient Register.

RESULTS Of 2 421 284 individuals included in the cohort, 17 305 persons were diagnosed with OCD. Of these, 7111 were men (41.1%). The mean (SD) age of individuals at first diagnosis of OCD was 23.4 (6.5) years. An increased risk for OCD remained after controlling for shared familial confounders and measured covariates (including sex, year of birth, maternal and paternal age at birth, and parity), for smoking 10 or more cigarettes per day during pregnancy (hazard ratio [HR], 1.27; 95% CI, 1.02-1.58), breech presentation (HR, 1.35; 95% CI, 1.06-1.71), delivery by cesarean section (HR, 1.17; 95% CI, 1.01-1.34), preterm birth (HR, 1.24; 95% CI, 1.07-1.43), birth weight 1501 to 2500 g (HR, 1.30; 95% CI, 1.05-1.62) and 2501 to 3500 g (HR, 1.08; 95% CI, 1.01-1.16), being large for gestational age (HR, 1.23; 95% CI, 1.05-1.45), and Apgar distress scores at 5 minutes (HR, 1.50; 95% CI, 1.07-2.09). Gestational age and birth weight followed inverse dose-response associations, whereby an increasingly higher risk for OCD was noted in children with a shorter gestational age and lower birth weight. We also observed a dose-response association between the number of perinatal events and increased OCD risk, with HRs ranging from 1.11 (95% CI, 1.07-1.15) for 1 event to 1.51 (95% CI, 1.18-1.94) for 5 or more events.

CONCLUSIONS AND RELEVANCE A range of perinatal risk factors is associated with a higher risk for OCD independent of shared familial confounders, suggesting that perinatal risk factors may be in the causal pathway to OCD.

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With much of the current focus on the discovery of genetic factors conferring risk for development of obsessive-compulsive disorder (OCD), environmental risk factors have received relatively little attention. Because environmental factors are at least as important as genetic factors in the development of OCD,[1,2] the identification of such risk factors should be viewed as a research priority.

At the present time, to our knowledge, there are no robust environmental risk factors known to play a causal role in the development of OCD. Previous OCD studies[3] have had several important methodologic weaknesses, including the predominant use of retrospective designs and recruitment of patients from specialist clinics, limiting the confidence in the data and generalizability of the findings. The success of gene by environment interaction studies depends on high-quality epidemiologic methods, including a detailed objective assessment of environmental exposures.[4]

Complications in the perinatal period, including delivery by cesarean section, delivery using vacuum extraction, preterm birth, and low birth weight, have been associated with a range of psychiatric disorders, such as schizophrenia,[5] bipolar disorder,[6,7] autism spectrum disorder,[8,9] and attention-deficit/hyperactivity disorder (ADHD).[9,10] Few studies,[3,11-17] most of which were retrospective, indicate that perinatal complications may also play a role in OCD, but the methodologic weaknesses of those studies preclude firm conclusions.

Most research into risk factors for mental disorders has primarily relied on adjusting for statistical covariates to account for confounding but has generally not taken familial effects into account.[18] Perinatal factors may exhibit a spurious association with a disorder, not representing a causal link but instead being explained by unmeasured confounders, such as parental mental health, social adversity, or maternally transmitted inherited factors.[19] Family-based study designs provide a better control for such unmeasured environmental and genetic factors; comparison of full siblings raised in the same family but discordant for the exposure automatically excludes confounding of all shared environmental and a substantial proportion of genetic factors.[20]

In this longitudinal, population-based cohort study, we aimed to explore the potential causal link between OCD and a range of perinatal factors. Unlike previous studies,[3] which tended to explore a limited number of risk factors at a time, we investigated a broad range of exposures and controlled for measured covariates, specifically, year of birth, sex, maternal and paternal age at birth, and parity. A sibling comparison design was used to further control for shared familial confounders.

Key Points

Question Do adverse perinatal events increase the risk for obsessive-compulsive disorder (OCD)?

Findings In a population-based birth cohort study of 2.4 million children in Sweden, maternal smoking during pregnancy, breech presentation, delivery by cesarean section, preterm birth, low birth weight, being large for gestational age, and Apgar distress scores were associated with a higher risk of developing OCD, independently of shared familial confounders. A dose-response association was identified for a number of perinatal events, with a higher risk for OCD noted in individuals with a greater number of events.

Meaning The findings of this study are important for the understanding of the cause of OCD and will inform future studies on gene by environment interaction and epigenetics.

Methods

Study Population

The study cohort, consisting of all 2 421 284 live singleton births in Sweden from January 1, 1973, through December 31, 1996, was followed up until first diagnosis of OCD (available from 1997, when the *International Statistical Classification of Diseases and Health Related Problems, Tenth Revision* was introduced[21]), migration, death, or end of follow-up (December 31, 2013), whichever came first. The data were obtained by linking individuals through their unique personal identification numbers[22] from the following population-based registers: (1) the Swedish Medical Birth Register,[23] which includes data on more than 99% of all pregnancies and deliveries in Sweden since 1973; (2) the Swedish Multi-generation Register,[24] with information about kinship going back to 1932, containing information on 100% of mothers and 98% of fathers of index persons born after 1961; (3) the Swedish National Patient Register,[25] which covers all inpatient hospital admissions since 1969 and outpatient care since 2001; (4) the Migration Register,[26] providing information about migration in and out of Sweden; and (5) the Cause of Death Register,[27] with information on dates and causes of all deaths since 1961. Information from the Cause of Death Register and the Migration Register was used to calculate censoring time. For the sibling comparison analysis, we identified a subsample of 743 885 families with at least 2 full siblings (ie, siblings sharing the same biological mother and father) during the same time period from the Swedish Multi-generation Register.

Ethics approval and waiver of informed consent was obtained from the Regional Ethical Review Board in Stockholm. The requirement for informed consent was waived because the study was register based and data on the included individuals were deidentified.

Exposures

Information about all prenatal exposures was retrieved from the Swedish Medical Birth Register. Unless otherwise specified, information was available from January 1, 1973, to December 31, 2013.

Maternal Smoking During Pregnancy

Information on maternal smoking during pregnancy collected at the first antenatal visit is available in the Swedish Medical Birth Register from 1982, marking the start of cohort inclusion for this exposure (n = 1 547 271). The information is categorized as no daily smoking, 1 to 9 cigarettes per day, and 10 or more cigarettes per day.

Labor Presentation and Obstetric Delivery

Labor presentation was divided into normal presentation, breech presentation, and other malpresentations. Obstetric delivery was divided into 3 hierarchical categories: cesarean section, assisted vaginal delivery (use of forceps or vacuum extraction), and unassisted vaginal delivery.

Gestational Age and Birth Weight

Gestational age and birth weight were analyzed in 2 ways. In the first method, data were evaluated as continuous variables with linear and quadratic terms included. Gestational age was distributed as every week and birth weight was distributed as every 250 g. In the second analysis, gestational age was categorized as very preterm birth (gestational age <32 weeks), preterm birth (32-36 weeks), term birth (37-41 weeks), and postterm birth (≥42 weeks), and birth weight was categorized as 1500 g or less (very low birth weight), 1501 to 2500 g (low birth weight), 2501 to 3500 g, 3501 to 4500 g (normal birth weight [reference category]), and more than 4500 g (high birth weight). Small for gestational age and large for gestational age were defined as a birth weight of more than 2 SDs below and above the mean weight for gestational age, respectively, according to the Scandinavian fetal growth curve adjusted for sex.[28]

Apgar Score

The Apgar score[29] of the index neonate at 5 minutes after delivery was categorized as normal (a score of ≥7), distress (4-6), or near death (≤3) in accordance with neonatal practice.[30] The Apgar score is a tool for evaluating heart rate, respiratory effort, reflex irritability, muscle tone, and color after delivery, considered to be 5 useful indicators that could be determined easily without interfering with the care of the infant.

Head Circumference

Small head circumference was defined as head circumference below the 10th percentile for each gestational week, and large head circumference was that above the 90th percentile for each gestational week. These categories were established according to the World Health Organization standards.[31]

Outcome and Covariates

The first instance of a recorded OCD diagnosis in the National Patient Register constituted the outcome. The OCD diagnosis was defined as code F42 according to *ICD-10*, which was introduced in Sweden in 1997. The OCD codes in the National Patient Register are reliable and valid.[32] Data on all potential measured confounders were collected from the Swedish Medical Birth Register (year of birth, sex, parity, and maternal age at childbirth) and the Swedish Multi-generation Register (paternal age at childbirth).

Statistical Analysis

Differences in sociodemographic and clinical variables between OCD cases and non-OCD cases were determined with χ^2 or 2-tailed *t* tests for independent samples. We performed Cox proportional hazards regression analysis to estimate hazard ratios (HRs) and 95% CIs of the association between perinatal factors and OCD. Three different Cox proportional hazards regression models were fitted for all exposure variables: (1) crude associations with OCD were modeled separately for each exposure variable, (2) analysis was adjusted for sex and year of birth, and (3) all measured confounders, as listed above, were adjusted for in the fully adjusted model.

For continuous variables (ie, gestational age and birth weight), we fitted both a linear and quadratic representation. We used the Akaike information criterion to determine which model (ie, linear or linear + quadratic) best fit the data.

The analyses were replicated in a fixed-effects model of the subsample of clusters of all full siblings by using stratified Cox proportional hazards regression models. By design, these models adjust for shared familial confounders[33] and, in particular, for genetic factors and unmeasured shared confounders such as socioeconomic status or stable parental factors. Furthermore, we adjusted for all measured confounders, which typically vary between siblings.

To confirm that the associations were not entirely explained by comorbid conditions, we performed sensitivity analyses in subgroups in which all individuals with comorbid conditions were excluded from analysis. These conditions were organized in 3 clusters: organic disorders (ie, organic brain disorder and epilepsy), psychotic disorders (ie, schizophrenia and bipolar disorder), and neuropsychiatric disorders (ie, ADHD, pervasive developmental disorders, and mental retardation). All disorders were defined as at least 1 registered diagnosis in the National Patient Register according to their *ICD-10* code (eTable 1 in the Supplement). These models adjusted for all measured confounders. In addition, we performed a sensitivity analysis on a subsample born in 1987 or later and applied the same models, including the sibling comparison, to examine whether the extended follow-up time for the oldest subsample of the cohort until the introduction of *ICD-10* in 1997 was a source of bias.

A post hoc Cox proportional hazards regression analysis was used to determine the association between the number of adverse perinatal events and the risk for OCD. All analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

Results

Descriptive Statistics

Descriptive characteristics of the study population are presented in **Table 1**. In total, 2 421 284 individuals were included in the cohort; of these, 17 305 were diagnosed with OCD during the study period, resulting in a Kaplan-Meier estimated prevalence of 1.32% at age 40 years (eFigure in the Supplement). The mean (SD) age at first diagnosis of OCD was 23.4 (6.5) years. The individuals with OCD differed significantly from those without OCD in several aspects. For instance, the proportion of women was significantly higher compared with men among persons with OCD (58.9% vs 41.1%; $P < .001$). Those with OCD also had more comorbid disorders than did those without OCD (37.9% vs 5%; $P < .001$). Of the 743 885 families with at least 2 children, 11 592 (15.6%) included full siblings discordant for OCD.

Table 1. Descriptive Characteristics of Study Population

Variable	No. (%)	
	Individuals Without OCD	Individuals With OCD[a]
Singleton births	2 403 979 (99.3)	17 305 (0.7)
Follow-up time, mean (SD), y[b]	27.9 (7.9)	23.4 (6.5)
Sex[b]		
Male	1 236 992 (51.5)	7111 (41.1)
Female	1 166 848 (48.5)	10 194 (58.9)
Age of mothers at birth of index person, mean (SD), y[b]	27.6 (5.1)	28.1 (5.4)
Missing	0	0
Age of fathers at birth of index person, mean (SD), y[b]	31 (5.9)	31.5 (6.3)
Missing	19 386 (0.8)	129 (0.8)
Parity[b]		
1	1 005 218 (41.8)	7529 (43.5)
2	882 048 (36.7)	6037 (34.9)
3	369 326 (15.4)	2546 (14.7)
≥4	147 387 (6.1)	1193 (6.9)
Missing	0	0
Maternal smoking during pregnancy[b,c]		
No daily smoking	1 056 510 (68.8)	7686 (66.4)
1-9 Cigarettes per day	215 487 (14)	1687 (14.6)
≥10 Cigarettes per day	132 294 (8.6)	1184 (10.2)
Missing	131 401 (8.6)	1022 (8.8)
Labor presentation[b]		
Normal	1 685 751 (70.1)	11 489 (66.4)
Breech	51 873 (2.2)	455 (2.6)
Other malpresentation	76 127 (3.2)	554 (3.2)
Missing	590 228 (24.5)	4807 (27.8)
Obstetric delivery[b]		
Unassisted vaginal	1 979 096 (82.3)	13 948 (80.6)
Cesarean section	246 853 (10.3)	1987 (11.5)
Assisted vaginal[d]	143 640 (6)	1162 (6.7)
Missing	34 390 (1.4)	208 (1.2)
Gestational age, mean (SD), wk[b]	39.5 (1.9)	39.4 (1.9)
Gestational age, wk[e]		
<32	14 968 (0.6)	132 (0.8)
32-36	105 057 (4.4)	889 (5.1)
37-41	2 058 650 (85.6)	14 758 (85.3)
≥42	218 172 (9.1)	1476 (8.5)
Missing	7132 (0.3)	50 (0.3)
Birth weight, mean (SD), g[b]	3514 (554.5)	3483.5 (572.3)
Birth weight, g		
≤1500	12 690 (0.5)	112 (0.7)
1501-2500	73 076 (3)	633 (3.7)
2501-3500	1 071 877 (44.6)	8031 (46.4)
3501-4500	1 167 229 (48.6)	7928 (45.8)
>4500	72 757 (3)	541 (3.1)
Missing	6350 (0.3)	60 (0.3)
Birth weight in relation to gestational age[f]		
Small	78 684 (3.3)	606 (3.5)
Normal	2 238 704 (93.1)	15 967 (92.3)
Large	72 591 (3)	619 (3.6)
Missing	14 000 (0.6)	113 (0.6)
Apgar score at 5 min[g]		
≥7	2 155 955 (89.7)	15 662 (90.5)
4-6	18 323 (0.7)	151 (0.9)
≤3	6377 (0.3)	42 (0.2)
Missing	223 324 (9.3)	1450 (8.4)
Head circumference[b,h]		
Small	121 345 (5.1)	991 (5.7)
Normal	2 101 622 (87.4)	15 065 (87.1)
Large	122 427 (5.1)	831 (4.8)
Missing	58 585 (2.4)	418 (2.4)
Comorbidity		
Organic disorders[b,i]	28 721 (1.2)	613 (3.5)
Psychotic disorders[b,j]	28 615 (1.2)	2606 (15.1)
Neuropsychiatric disorders[b,k]	79 517 (3.3)	4820 (27.9)
Any organic, psychotic or neuropsychiatric disorder[b]	120 941 (5)	6551 (37.9)
Affective and anxiety disorders[b,l]	214 261 (8.9)	12 212 (70.6)

Abbreviation: OCD, obsessive-compulsive disorder.

[a] Kaplan-Meier estimate of expected prevalence at age 40 y: 1.32% (eFigure in the Supplement).

[b] $P < .001$ determined with χ^2 or independent, 2-tailed t test.

[c] Data available from 1982 (n = 1 547 271).

[d] Use of forceps or vacuum extraction.

[e] Less than 32 weeks indicates very preterm; 32 to 36 weeks, preterm; 37 to 41 weeks, term; and 42 weeks or longer, postterm.

[f] Small for gestational age indicates 2 SDs below mean birth weight for gestational age; large, 2 SDs above mean birth weight for gestational age.

[g] Score of 7 or higher indicates normal; 4 to 6, distress; and 3 or lower, near death.

[h] Small circumference indicates less than 10th percentile per gestational week; large, greater than 90th percentile per gestational week.

[i] Organic brain disorder and epilepsy.

[j] Schizophrenia and bipolar disorder.

[k] Attention-deficit/hyperactivity disorder, autism, and mental retardation.

[l] Mood disorders (except bipolar disorder) and anxiety disorders (except OCD).

Maternal Smoking During Pregnancy

Maternal smoking of 10 cigarettes or more per day during pregnancy was associated with an increased risk of offspring OCD both in the fully adjusted model (HR, 1.20; 95% CI, 1.13-1.28) and in the sibling comparison model (HR, 1.27; 95% CI, 1.02-1.58) (**Table 2**) compared with offspring of mothers who did not smoke during pregnancy. Maternal smoking of 1 to 9 cigarettes per day during pregnancy exhibited only a small increased risk for OCD in the offspring compared with nonsmoking mothers (HR, 1.06; 95% CI, 1-1.12). The risk remained but with lower precision in the sibling comparison (HR, 1.06; 95% CI, 0.89-1.26).

Table 2. Association Between Perinatal Events and OCD

Perinatal Event	Hazard Ratio (95% CI)			
	Unadjusted Model	Partially Adjusted[a]	Adjusted[b]	Full Sibling Comparison[b]
Maternal smoking during pregnancy[c]				
No daily smoking	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1-9 Cigarettes per day	0.97 (0.92-1.03)	1.04 (0.98-1.09)	1.06 (1.00-1.12)	1.06 (0.89-1.26)
≥10 Cigarettes per day	1.09 (1.03-1.16)	1.18 (1.11-1.25)	1.20 (1.13-1.28)	1.27 (1.02-1.58)
Labor presentation				
Normal	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Breech	1.35 (1.23-1.48)	1.30 (1.18-1.42)	1.26 (1.15-1.39)	1.35 (1.06-1.71)
Other malpresentation	1.10 (1.01-1.20)	1.05 (0.97-1.14)	1.05 (0.96-1.14)	1.11 (0.93-1.33)
Obstetric delivery				
Unassisted vaginal	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Cesarean section	1.24 (1.18-1.29)	1.15 (1.10-1.21)	1.09 (1.04-1.15)	1.17 (1.01-1.34)
Assisted vaginal	1.19 (1.12-1.27)	1.18 (1.11-1.25)	1.12 (1.05-1.19)	1.07 (0.94-1.22)
Gestational age, wk[d]				
<32	1.78 (1.50-2.12)	1.67 (1.40-1.98)	1.61 (1.35-1.91)	1.46 (0.97-2.19)
32-36	1.22 (1.14-1.31)	1.22 (1.14-1.31)	1.20 (1.12-1.28)	1.24 (1.07-1.43)
37-41	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
≥42	0.82 (0.78-0.87)	0.97 (0.92-1.03)	0.97 (0.92-1.03)	0.98 (0.88-1.09)
Birth weight, g[e]				
≤1500	1.42 (1.09-1.84)	1.18 (0.90-1.56)	1.15 (0.87-1.51)	1.72 (0.94-3.14)
1501-2500	1.05 (0.95-1.15)	1.13 (1.02-1.24)	1.10 (1-1.21)	1.30 (1.05-1.62)
2501-3500	1.02 (0.98-1.05)	1.04 (1.01-1.08)	1.03 (1.00-1.07)	1.08 (1.01-1.16)
3501-4500	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
>4500	1.18 (1.08-1.29)	1.17 (1.07-1.27)	1.17 (1.07-1.27)	1.14 (0.96-1.35)
Birth weight in relation to gestational age[f]				
Not small	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Small	1.00 (0.92-1.08)	1.13 (1.04-1.22)	1.10 (1.02-1.20)	1.13 (0.94-1.35)
Not large	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Large	1.26 (1.17-1.37)	1.20 (1.11-1.30)	1.20 (1.11-1.30)	1.23 (1.05-1.45)
Apgar score at 5 min[g]				
≥7	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
4-6	1.18 (1.01-1.39)	1.33 (1.14-1.57)	1.28 (1.09-1.51)	1.50 (1.07-2.09)
≤3	1.27 (0.94-1.72)	1.42 (1.05-1.92)	1.40 (1.03-1.90)	1.68 (0.79-3.56)
Head circumference[h]				
Small	1.03 (0.97-1.10)	1.08 (1.01-1.15)	1.07 (1.00-1.14)	0.96 (0.84-1.09)
Normal	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Large	0.97 (0.90-1.04)	1.05 (0.97-1.12)	1.03 (0.96-1.11)	1.01 (0.88-1.16)

Abbreviation: OCD, obsessive-compulsive disorder.

[a] Model adjusted for sex and year of birth.

[b] Model adjusted for sex, year of birth, age of mother and father, and parity.

[c] Data available from 1982 (n = 1 547 271).

[d] Less than 32 weeks indicates very preterm; 32 to 36 weeks, preterm; 37 to 41 weeks, term; and 42 weeks or longer, postterm.

[e] All models adjusted additionally for gestational age, both linear and quadratic terms.

[f] Small for gestational age indicates 2 SDs below mean birth weight for gestational age; large, 2 SDs above mean birth weight for gestational age.

[g] Score of 7 or higher indicates normal; 4 to 6, distress; and 3 or lower, near death.

[h] Small circumference indicates less than 10th percentile per gestational week; large, greater than 90th percentile per gestational week.

Labor Presentation

Breech presentation was associated with an increased risk for OCD (fully adjusted model: HR, 1.26; 95% CI, 1.15-1.39; sibling comparison: HR, 1.35; 95% CI, 1.06-1.71) compared with normal presentation (Table 2). A similar association was not found for other malpresentations, neither in the fully adjusted model nor the sibling comparison model (Table 2).

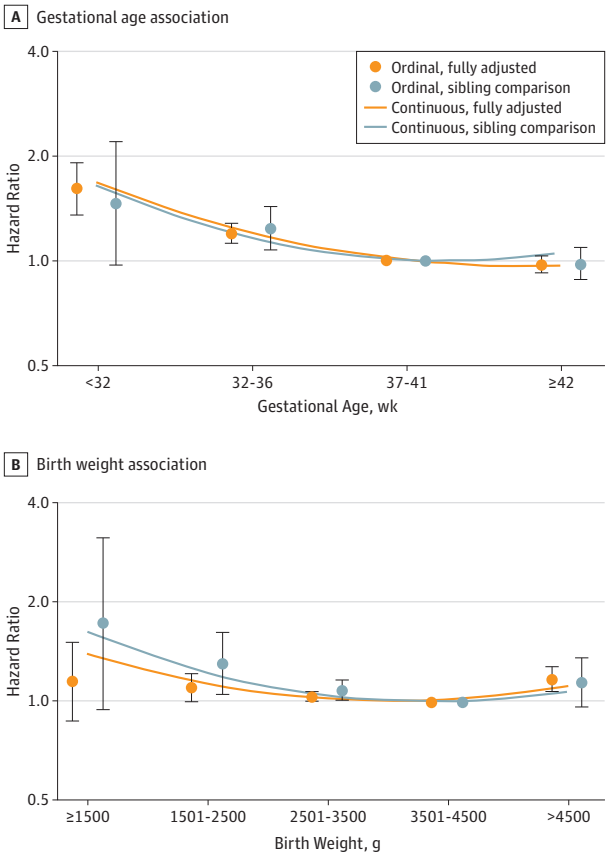
Obstetric Delivery

There was a slightly increased risk of OCD among individuals delivered by cesarean section (HR, 1.09; 95% CI, 1.04-1.15) and assisted vaginal delivery (HR, 1.12; 95% CI, 1.05-1.19) compared with unassisted vaginal delivery in the fully adjusted model (Table 2). In the sibling comparison models, these estimates remained similar in magnitude but had lower precision; the association with cesarean section remained statistically significant (HR, 1.17; 95% CI, 1.01-1.34), whereas the association with assisted vaginal delivery did not (HR, 1.07; 95% CI, 0.94-1.22) (Table 2).

Gestational Age

There was an inverse association between gestational age and OCD that remained when we adjusted for potential confounders (Table 2). Compared with those with term birth, the risk for OCD in individuals with very preterm birth (<32 weeks) was higher (HR, 1.61; 95% CI, 1.35-1.91) than in individuals with preterm birth (32-36 weeks: HR, 1.20; 95% CI, 1.12-1.28), indicating a dose-response association (**Figure**, A). The continuous

Figure. Association Between Gestational Age and Obsessive-Compulsive Disorder (OCD) and Between Birth Weight and OCD



Analysis of data as ordinal and continuous variables in fully adjusted, baseline, population-wide estimate and sibling comparison models for gestational age (reference group, 37-41 weeks) (A) and birth weight (reference group, 3501-4500 g) (B) in determination of the risk for OCD in offspring born in Sweden between January 1, 1973, and December 31, 1996. Error bars indicate 95% CI. The y-axis uses a log scale.

representation of gestational age displayed a pattern similar to that of the ordinal representation (Figure, A). The results of the sibling comparison yielded similar estimates but with lower precision (very preterm birth: HR, 1.46; 95% CI, 0.97-2.19; and preterm birth: HR, 1.24; 95% CI, 1.07-1.43) (Table 2 and Figure, A).

Birth Weight

The ordinal representation of birth weight showed an inverse association with OCD that remained when we adjusted for all measured confounders as well as gestational age (known to correlate with birth weight[34]) (Table 2). Both low and high birth weight were associated with a slightly increased risk for OCD (eg, low birth weight [1501-2500 g]: HR, 1.10; 95% CI, 1-1.21; and high birth weight [>4500 g]: HR, 1.17; 95% CI, 1.07-1.27). The continuous representation mirrored these results (Figure, B).

The results from the sibling comparison models yielded higher estimates for low birth weights but with lower precision and followed a clearer dose-response association, with the highest risk for very low birth weight (≤1500 g) (HR, 1.72; 95% CI, 0.94-3.14) (Table 2 and Figure, B). The estimate for high birth weight (>4500 g) remained similar in magnitude (HR, 1.14; 95% CI, 0.96-1.35). Analyses of both small- and large-for-gestational age individuals followed the same pattern in both the magnitude and precision of the estimates (Table 2).

Apgar Score

At 5 minutes after delivery, infants with Apgar scores at distress (scores 4-6) or near-death (≤3) levels had an increased risk of OCD in both the fully adjusted model (HR, 1.28; 95% CI, 1.09-1.51; and HR, 1.4; 95% CI, 1.03-1.90, respectively) and the sibling comparison model (HR, 1.50; 95% CI, 1.07-2.09; and HR, 1.68; 95% CI, 0.79-3.56, respectively) (Table 2) compared with infants with normal Apgar scores. However, the precision was low in the sibling comparison, especially for near-death scores, which did not remain statistically significant.

Head Circumference

The small association between small head circumference and OCD in the fully adjusted model (HR, 1.07; 95% CI, 1-1.14) did not remain in the sibling comparison (HR, 0.96; 95% CI, 0.84-1.09) (Table 2). No association between large head circumference and OCD was observed.

Sensitivity Analyses

The pattern of results remained largely unchanged when individuals with comorbid disorders were excluded from the analyses (**Table 3**). Evaluation of the subsample of individuals born in 1987 or later (without an extended follow-up time until the introduction of *ICD-10*) revealed a similar pattern but with lower precision (eTable 2 in the Supplement); one exception was the association for breech presentation, which did not remain in the sibling comparison.

Post Hoc Analyses: Number of Perinatal Events

A dose-response association between the number of adverse perinatal events and increased risk for OCD was observed. Hazard ratios ranged from 1.11 (95% CI, 1.07-1.15) for 1 event to 1.51 (95% CI, 1.18-1.94) for 5 or more events (**Table 4**).

Discussion

In this large study of the entire Swedish population, we found that several perinatal factors were associated with a higher risk of developing OCD, confirming and extending the results of the few previous small and often retrospective studies.[3,11-17] These associations largely remained when genetic and environmental factors shared by siblings were taken into account, confounders were strictly controlled, and relevant comorbidities were excluded. The associations for preterm birth and low birth weight were further supported by dose-response associations consistent with causal inference. A dose-response association was also identified for the number of perinatal events, whereby the higher the number of events, the greater the risk of OCD.

Table 3. Association Between Perinatal Events and OCD With Common Comorbid Disorders Excluded[a]

Perinatal Event	Hazard Ratio (95% CI)			
	Excluding Organic Disorders[b]	Excluding Psychotic Disorders[c]	Excluding Neuropsychiatric Disorders[d]	Excluding Any Neuropsychiatric, Psychotic, or Organic Disorder
Maternal smoking during pregnancy[e]				
No daily smoking	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1-9 Cigarettes per day	1.05 (1.00-1.11)	1.03 (0.97-1.09)	0.98 (0.92-1.05)	0.96 (0.90-1.03)
≥10 Cigarettes per day	1.20 (1.13-1.28)	1.19 (1.11-1.27)	1.12 (1.04-1.21)	1.10 (1.01-1.19)
Labor presentation				
Normal	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Breech	1.25 (1.14-1.38)	1.22 (1.10-1.35)	1.28 (1.14-1.43)	1.23 (1.09-1.39)
Other malpresentation	1.04 (0.95-1.14)	1.05 (0.95-1.15)	1.05 (0.95-1.16)	1.03 (0.93-1.15)
Obstetric delivery				
Unassisted vaginal	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Cesarean section	1.09 (1.04-1.15)	1.08 (1.02-1.13)	1.04 (0.98-1.10)	1.03 (0.96-1.09)
Assisted vaginal	1.13 (1.06-1.20)	1.12 (1.05-1.20)	1.14 (1.06-1.22)	1.13 (1.05-1.23)
Gestational age, wk[f]				
<32	1.48 (1.23-1.78)	1.51 (1.24-1.83)	1.49 (1.20-1.85)	1.36 (1.07-1.74)
32-36	1.18 (1.10-1.27)	1.18 (1.10-1.27)	1.12 (1.03-1.22)	1.10 (1.00-1.20)
37-41	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
≥42	0.96 (0.91-1.01)	0.96 (0.91-1.02)	0.94 (0.88-1.00)	0.92 (0.86-0.99)
Birth weight, g[g]				
≤1500	1.15 (0.86-1.54)	1.20 (0.89-1.63)	1.09 (0.78-1.54)	1.19 (0.82-1.73)
1501-2500	1.11 (1.01-1.23)	1.11 (1.00-1.24)	1.03 (0.91-1.15)	1.05 (0.92-1.19)
2501-3500	1.03 (0.99-1.06)	1.03 (1.00-1.07)	1.01 (0.97-1.05)	1.00 (0.96-1.04)
3501-4500	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
>4500	1.17 (1.07-1.28)	1.19 (1.08-1.30)	1.15 (1.04-1.28)	1.17 (1.04-1.31)
Birth weight in relation to gestational age[h]				
Not small	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Small	1.10 (1.01-1.20)	1.08 (0.99-1.18)	1.00 (0.90-1.10)	0.97 (0.87-1.09)
Not large	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Large	1.21 (1.12-1.32)	1.22 (1.11-1.33)	1.23 (1.12-1.36)	1.24 (1.12-1.37)
Apgar score at 5 min[i]				
≥7	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
4-6	1.27 (1.08-1.50)	1.25 (1.04-1.49)	1.22 (1.00-1.49)	1.17 (0.94-1.46)
≤3	1.34 (0.97-1.85)	1.45 (1.05-2.01)	1.61 (1.14-2.26)	1.50 (1.02-2.21)
Head circumference, cm[j]				
Small	1.06 (0.99-1.13)	1.06 (0.99-1.14)	1.01 (0.93-1.09)	1.00 (0.91-1.08)
Normal	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Large	1.03 (0.95-1.10)	1.03 (0.95-1.11)	1.05 (0.96-1.14)	1.05 (0.96-1.15)

Abbreviation: OCD, obsessive-compulsive disorder.

[a] Model adjusted for sex, year of birth, age of mother and father, and parity.

[b] Organic brain disorder and epilepsy.

[c] Schizophrenia and bipolar disorder.

[d] Attention-deficit/hyperactivity disorder, autism, and mental retardation.

[e] Data available from 1982 (n = 1 547 271).

[f] Less than 32 weeks indicates very preterm; 32 to 36 weeks, preterm; 37 to 41 weeks, term; and 42 weeks or longer, postterm.

[g] Adjusted additionally for gestational age, both linear and quadratic terms.

[h] Small for gestational age indicates 2 SDs below mean birth weight for gestational age; large, 2 SDs above mean birth weight for gestational age.

[i] Score of 7 or higher indicates normal; 4 to 6, distress; and 3 or lower, near death.

[j] Small circumference indicates less than 10th percentile per gestational week; large, greater than 90th percentile per gestational week.

The specific mechanism linking OCD and maternal smoking, complicated birth, preterm birth, fetal growth, and distress at birth remains to be identified. However, these findings are in line with the fetal programming hypothesis, positing that adaptation to the fetal environment may lead to adverse effects in subsequent life.[35,36] An adverse fetal environment or insult (eg, hypoxia-ischemia, white matter injury, reduced blood flow, malnutrition, and differences in development of the serotonergic system) has been observed[37-39] to affect brain development. It also has been shown[39,40] that variations in fetal growth are associated with brain development well into childhood and adolescence. Research into differences in brain structure and function between people with and without the associations identified in the present study may reveal the mediating biological pathways.

Rather than being unique to OCD, many of these perinatal risk factors may be shared across a range of neuropsychiatric disorders. For instance, using similar family designs, studies have shown associations between low birth weight and ADHD and autism[9,10,41] as well as between gestational age and autism, ADHD, and psychotic or bipolar disorders.[7] These findings contradict the widely held notion that,

Table 4. Post Hoc Analyses

No. of Perinatal Events[a]	No. (%)[b]		Hazard Ratio (95% CI)		
	Individuals Without OCD	Individuals With OCD	Unadjusted Model	Partially Adjusted[c]	Adjusted[d]
0	1 519 653 (63.2)	10 286 (59.4)	1 [Reference]	1 [Reference]	1 [Reference]
1	604 512 (25.1)	4679 (27)	1.18 (1.14-1.22)	1.14 (1.10-1.18)	1.11 (1.07-1.15)
2	190 379 (7.9)	1562 (9)	1.28 (1.22-1.35)	1.24 (1.17-1.31)	1.20 (1.13-1.26)
3	61 340 (2.6)	533 (3.1)	1.40 (1.28-1.53)	1.35 (1.23-1.47)	1.30 (1.19-1.42)
4	21 117 (0.9)	182 (1.1)	1.54 (1.33-1.78)	1.39 (1.20-1.61)	1.34 (1.15-1.55)
≥5	6978 (0.3)	63 (0.4)	1.94 (1.51-2.48)	1.61 (1.25-2.06)	1.51 (1.18-1.94)

Abbreviation: OCD obsessive-compulsive disorder.

[a] All measured perinatal events are included. The events were defined as follows: heavy (≥10 cigarettes per day) maternal smoking during pregnancy, any labor presentation other than normal, any obstetric delivery other than unassisted vaginal delivery, gestational age less than 37 weeks, birth weight 2500 g or less, being small or large for gestational age, Apgar score less than 7, and small or large head circumference. Maternal smoking during pregnancy was included even though the variable was not introduced in the Swedish Medical Birth Register until 1982, but running analyses on the entire cohort excluding smoking, and on a subsample of those born from 1982 and later, revealed virtually no differences in the estimates.

[b] $P < .001$ determined using χ^2 analysis.

[c] Adjusted for sex and year of birth.

[d] Adjusted for sex, year of birth, age of mother and father, and parity.

although mental disorders share genetic risk factors, the contribution of environmental risk factors is largely disorder specific.[42-44] One exception to this lack of specificity may be our finding of an increased risk of OCD in children exposed to maternal smoking during pregnancy. This finding was unexpected since other family-based studies[20,45] have suggested that the causal inference between maternal smoking during pregnancy and a range of adverse outcomes in offspring (eg, ADHD, criminality, academic achievement, drug use, adolescent antisocial behavior, adolescent psychological functioning, suicidal behavior, childhood conduct problems, and intellectual abilities) has been overstated. The results of the present study indicate a relatively small, yet robust association between maternal smoking during pregnancy and OCD, even after controlling for familial confounding. If replicated, these findings may have important implications for future research, for example, using relevant animal models.

To our knowledge, this is the first study examining a broad range of perinatal risk factors for OCD using a large, population-based cohort with prospectively collected data during pregnancy and at the time of birth. By comparing clusters of full siblings discordant for OCD, we could control for many (unmeasured) shared familial confounders (genetic and environmental). The validity and reliability of the Swedish *ICD-10* codes for OCD have been well established.[32]

Some limitations of the study need to be considered. The cohort is weighted toward more severe cases and does not represent the totality of all patients with OCD in Sweden. There are missing cases because many individuals do not seek help, coverage of the Swedish National Patient Register between 1997 and 2001 is incomplete, and patients diagnosed with OCD by general practitioners and other nonspecialists are not included. Sibling comparisons can help in inferring, but not proving, causality and have lower statistical power compared with population-based estimates.[33] Furthermore, sibling comparison designs are sensitive to random measurement error in the exposure and may be biased owing to variables shared by siblings that are related to the exposure but not the outcome.[20,46] The sibling comparison also assumes that there are no carryover effects from one pregnancy to a later pregnancy.[46,47] Adjusting for parity addresses this limitation, but just partially. Monozygotic twin comparison studies could cement these findings further, controlling also for potential evocative genetic and more shared environmental factors, but would be limited to exposures that are not shared by monozygotic twins.

Conclusions

In the present study, we found that perinatal factors, especially maternal smoking during pregnancy, breech presentation, cesarean section, preterm birth, low birth weight, being large for gestational age, and Apgar distress scores, were associated with a higher risk of developing OCD independent of shared familial confounders and several other measured covariates. A dose-response association was also identified for the number of perinatal events, with an increasingly higher number of events associated with a greater risk for OCD. The findings are important for the understanding of the cause of OCD and will inform future studies of gene by environment interaction and epigenetics. If the finding is replicated, the association between maternal smoking during pregnancy and OCD may emerge as an interesting disorder-specific risk factor for evaluation in future research.

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