

Prenatal and Early Childhood Infections and Subsequent Risk of Obsessive-Compulsive Disorder and Tic Disorders: A Nationwide, Sibling-Controlled Study

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ABSTRACT

BACKGROUND: Postinfectious autoimmune processes are hypothesized to be causally related to both obsessive-compulsive disorder (OCD) and tic disorders, but current evidence is conflicting. This study examined whether prenatal maternal (and paternal, as an internal control) infections and early childhood infections in the offspring (i.e., during the first 3 years of life) were associated with a subsequent risk of OCD and Tourette syndrome or chronic tic disorder (TS/CTD).

METHODS: Individuals exposed to any prenatal maternal infection ($n = 16,743$) and early childhood infection ($n = 264,346$) were identified from a population-based birth cohort consisting of 2,949,080 singletons born in Sweden between 1973 and 2003 and were followed through 2013. Cox proportional hazard regression models were used to estimate hazard ratios (HRs). Sibling analyses were performed to control for familial confounding.

RESULTS: At the population level, and after adjusting for parental psychiatric history and autoimmune diseases, a significantly increased risk of OCD and TS/CTD was found in individuals exposed to prenatal maternal (but not paternal) infections (OCD: HR, 1.33; 95% CI, 1.12–1.57; TS/CTD: HR, 1.60; 95% CI, 1.23–2.09) and early childhood infections (OCD: HR, 1.19; 95% CI, 1.14–1.25; TS/CTD: HR, 1.34; 95% CI, 1.24–1.44). However, these associations were no longer significant in the sibling analyses.

CONCLUSIONS: The results do not support the hypothesis that prenatal maternal or early-life infections play a direct causal role in the etiology of either OCD or TS/CTD. Instead, familial factors (e.g., genetic pleiotropy) may explain both the propensity to infections and the liability to OCD and TS/CTD.

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Postinfectious autoimmune responses are hypothesized to contribute to the development of neuropsychiatric disorders, such as obsessive-compulsive disorder (OCD) or tic disorders, although current evidence is conflicting (1,2). For example, group A streptococcus infections have been linked to the acute-onset and exacerbation of OCD and/or tic disorder symptoms in prepubertal individuals, leading to the proposal of the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) syndrome (3). However, conclusive evidence supporting the association between group A streptococcus infections, OCD, and tics has remained elusive (4–10). Some evidence emerging from population-based studies partially supports the PANDAS hypothesis (11–13), but none of these studies was able to establish causality or to demonstrate a clear temporal association between infections and the onset or exacerbation of OCD and tics.

One powerful strategy to test the postinfectious autoimmune hypothesis could be to focus on infections that occur

very early in life (i.e., in utero and early childhood), a period considered critical for neurodevelopment (1,14). By definition, this approach would ensure that the infection precedes the onset of OCD or tics. A maternal immune activation model has been hypothesized to explain the possible link between a dysregulated immune system in utero and impaired child development (1,15–20). Previous research has linked prenatal infections to increased risk of several neurodevelopmental and psychiatric disorders, including autism spectrum disorder (21), attention-deficit/hyperactivity disorder (22,23), depression (24), and psychosis (25–27), but similar studies have yet to be conducted in OCD and Tourette syndrome or chronic tic disorder (TS/CTD). Similarly, we are not aware of previous population-based studies exploring the role of early childhood infections (i.e., during the first 3 years of life) and the subsequent risk of either OCD or TS/CTD.

In this nationwide birth cohort study, we investigated whether exposure to prenatal maternal infections and early childhood (i.e., during the first 3 years of life) infections in the

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offspring were associated with a subsequent risk of OCD and TS/CTD. As an internal control, we also examined the associations between prenatal paternal infections and the outcomes of interest. We systematically adjusted for potential confounders, such as parental psychopathology and autoimmune diseases. The latter are strongly associated with both OCD and TS/CTD (2,28–31). We also used a discordant sibling design to test whether the potential association between infections, OCD, and TS/CTD is independent of unmeasured familial factors (e.g., genetic factors).

METHODS AND MATERIALS

Ethical approval was obtained from the Regional Ethical Committee in Stockholm (2013/862-31/5). The requirement for informed consent was waived because the study was register based and data on the included individuals were pseudonymized.

Data Sources

Using the unique personal identification number assigned to each Swedish resident (32), we linked several national registers: 1) the Medical Birth Register (33), which holds data on more than 99% of all pregnancies and deliveries in Sweden since 1973, including information on antenatal care of the mother and the pediatric examination of the newborns; 2) the National Patient Register (NPR) (34), which covers inpatient hospital admissions since 1969 and outpatient specialist care since 2001, with diagnoses based on the ICD-8 (1969–1986), ICD-9 (1987–1996), and ICD-10 (1997–2013) revisions; 3) the Total Population Register (35), which contains information about emigration since 1961 and immigration since 1969 from and to Sweden; 4) the Cause of Death Register (36), which includes dates and causes of more than 99% of all deaths of Swedish residents since 1961; and 5) the Multi-Generation Register (37), which provides information on each resident's family pedigree among those born in Sweden after 1933 and those ever registered as residents in Sweden after 1960.

Study Population

In this birth cohort study, all 3,041,379 singletons born in Sweden between January 1, 1973, and December 31, 2003, were identified. Individuals who emigrated ($n = 32,741$), died before age 3 ($n = 17,679$) or had missing data on their gestational age ($n = 7604$) or the mother's ($n = 4506$) or father's ($n = 29,769$) identification number were excluded. The final cohort consisted of 2,949,080 individuals who were followed from the age of 3 until the date of diagnosis of OCD or TS/CTD, emigration, death, or end of the follow-up (December 31, 2013) whichever came first. For the sibling analyses, sets of full siblings were identified within the final cohort.

Variables

Exposures. Prenatal maternal infections were defined as any viral or bacterial infection requiring hospitalization occurring during the pregnancy period, which was calculated by subtracting the offspring's birthdate and the gestational age in days. As an internal comparison, we also extracted data on paternal infections during the index pregnancy period because they are unlikely to be associated with the outcomes.

Early childhood infections were defined as any viral or bacterial infection requiring hospitalization that occurred during the first 3 years of life. Data on infections were obtained from the NPR and were later divided into any infection (i.e., viral or bacterial), viral infection, and bacterial infection (see ICD codes in Table S1).

Outcomes. Diagnoses of OCD and TS/CTD were obtained from the NPR (38). OCD outcomes were identified as the first instance of a recorded OCD diagnosis made after the age of 6 (to avoid diagnostic misclassification) using ICD codes 300.3 in ICD-8, 300D in ICD-9, or F42 in ICD-10. The ICD codes for OCD in the NPR have excellent inter-rater reliability ($\kappa = 0.98$) and good validity (positive predictive value = 0.72) (38). TS/CTD outcomes were identified using an algorithm including ICD-8 code 306.2, ICD-9 code 307C, or ICD-10 codes F95.0, F95.1, F95.2, F95.8, and F95.9; if the diagnosis was made after the age of 3. This algorithm excludes those with only transient tics (i.e., tic symptoms lasting < 1 year) and has shown excellent inter-rater reliability ($\kappa = 1$) and high validity (positive predictive value = 0.92) (38).

Covariates. Offspring's birth year, sex, and maternal age at delivery were collected from the Medical Birth Register. From the Multi-Generation Register, we identified the offspring's registered father and his age at the birth of the index person. From the NPR, we identified maternal and paternal psychiatric history prior to the birth of the index person to control for parental psychopathology, using ICD-8 and ICD-9 codes 290–315 and ICD-10 codes F00–F99. In addition, to control for parental autoimmunity, we identified lifetime maternal records of autoimmune diseases using a list of ICD codes for 40 autoimmune diseases (see ICD codes in Table S2) previously used in population-based studies (28,39).

Statistical Analysis

Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals of the risk of OCD and TS/CTD separately in the offspring exposed to prenatal or early childhood infections, with attained age as the underlying time scale. We fitted 3 different Cox regression models for all exposure variables: Model 1 adjusted for offspring's birth year, sex, and maternal and paternal ages at birth of the index offspring; model 2 further adjusted for maternal and paternal psychiatric history; and model 3 further adjusted for lifetime maternal and paternal autoimmune diseases. Robust standard errors were used to account for the familial clustering in the analyses.

To explore the role of familial confounding, sibling analyses using stratified Cox proportional hazards regression models were performed. These analyses, by design, account for about 50% of the genetic background and all the shared environment within each set of full siblings. Siblings who were differently exposed to prenatal maternal or early childhood infections contributed to the risk estimates in the analysis. The sibling analyses adjusted for offspring's birth year and sex. The unadjusted cumulative incidence for each exposure and outcome was plotted using Kaplan-Meier survival estimates for the main cohort and the sibling cohort.

Data were analyzed from October 7, 2021, to March 4, 2022. $p < .05$ was considered statistically significant. Statistical analyses were conducted using SAS software (version 9.4; SAS Institute) and R (version 4.0.5; R Foundation).

RESULTS

Cohort Characteristics

Table 1 summarizes the characteristics of the full cohort. Among 2,949,080 individuals, we identified 16,743 (0.6%) exposed to any prenatal maternal infection and 264,346 (9.0%) exposed to any early childhood infection. At the end of the follow-up, a total of 18,888 offspring received at least one diagnosis of OCD (median age at first diagnosis, 21.8 years; interquartile range, 10.4), and 5479 received at least one diagnosis of TS/CTD (median age at first diagnosis, 12.7 years; interquartile range, 7.2) (Table 1).

Exposure to Prenatal Maternal Infections

We identified 135 (0.79%) offspring exposed to any prenatal maternal infection and 18,893 (0.64%) unexposed offspring who later received a diagnosis of OCD during the follow-up period. The corresponding figures for offspring who later developed TS/CTD were 56 (0.33%) exposed and 5423 (0.18%) unexposed offspring. The Kaplan-Meier estimated cumulative incidence of OCD at the end of the study period was 1.98% (95% CI, 1.57%–2.39%) in offspring exposed to any prenatal maternal infection, compared with 1.42% (95% CI, 1.39%–1.45%) in unexposed offspring (Figure 1A). The cumulative incidence of TS/CTD at the end of the study period was 0.75% (95% CI, 0.17%–1.32%) in offspring exposed to any prenatal maternal infection, compared with 0.26% (95% CI, 0.25%–0.27%) in unexposed individuals (Figure 1C).

Results for the associations between prenatal maternal infections and the risk of OCD and TS/CTD are presented in Table 2. In the minimally adjusted models (model 1), offspring exposed to any prenatal maternal infection had an increased risk of OCD (HR, 1.34; 95% CI, 1.13–1.59) and TS/CTD (HR,

1.64; 95% CI, 1.26–2.13), compared with unexposed offspring. Model 2 additionally adjusted for parental psychiatric history and produced similar results as model 1, although the magnitude of the associations was slightly attenuated. In model 3, where parental autoimmune diseases were additionally adjusted for, all associations remained robust: offspring exposed to any prenatal maternal infection had an increased risk of OCD (HR, 1.33; 95% CI, 1.12–1.57) and TS/CTD (HR, 1.60; 95% CI, 1.23–2.09), compared with unexposed offspring. When looking at different infection agents, and after adjusting for all measured confounders (model 3), only bacterial, but not viral, infections were associated with increased risk of OCD (HR, 1.32; 95% CI, 1.06–1.64) and TS/CTD (HR, 1.71; 95% CI, 1.25–2.33).

Exposure to Prenatal Paternal Infections

Prenatal paternal infections during the index pregnancy period were not significantly associated with risk of either OCD or TS/CTD in any of the 3 models (Table 2).

Exposure to Early Childhood Infections

We identified 1983 (0.75%) offspring exposed to any early childhood infection and 16,905 (0.63%) unexposed offspring who later received a diagnosis of OCD; we also identified 748 (0.28%) exposed and 4730 (0.18%) unexposed individuals who received a diagnosis of TS/CTD. The Kaplan-Meier estimated cumulative incidence of OCD at the end of the study period was 1.95% (95% CI, 1.76%–2.14%) in offspring exposed to any early childhood infection, compared with 1.38% (95% CI, 1.36%–1.41%) in unexposed offspring (Figure 1B). The cumulative incidence of TS/CTD at the end of the study period was 0.41% (95% CI, 0.37%–0.46%) in offspring exposed to any early childhood infection, compared with 0.25% (95% CI, 0.24%–0.26%) in unexposed individuals (Figure 1D).

Results for the association between early childhood infections and the risk of OCD and TS/CTD are presented in Table 2. In the minimally adjusted models (model 1), offspring exposed to any early childhood infection had an increased risk

Table 1. Descriptive Characteristics of the Birth Cohort (N = 2,949,080)

Characteristic	Prenatal Maternal Infections		Early Childhood Infections	
	Unexposed, n = 2,932,337	Exposed, n = 16,743	Unexposed, n = 2,684,734	Exposed, n = 264,346
Male Offspring	1,506,849 (51.4%)	8564 (51.1%)	1,365,396 (50.9%)	150,017 (56.8%)
Distribution of Years of Birth				
1973–1983	1,014,282 (34.6%)	5218 (31.2%)	968,397 (36.1%)	51,103 (19.3%)
1984–1993	1,042,900 (35.6%)	5162 (30.8%)	918,494 (34.2%)	129,568 (49.0%)
1994–2003	875,155 (29.8%)	6363 (38.0%)	797,843 (29.7%)	83,675 (31.7%)
Age of Mothers at Birth of Index Offspring, Years	28.02 ± 5.12	27.00 ± 5.57	28.02 ± 5.12	27.99 ± 5.19
Age of Fathers at Birth of Index Offspring, Years	30.87 ± 5.98	30.17 ± 6.54	30.87 ± 5.98	30.85 ± 6.07
Lifetime Maternal Autoimmune Diseases	270,348 (9.2%)	2353 (14.1%)	245,011 (8.8%)	27,690 (10.5%)
Lifetime Paternal Autoimmune Diseases	214,265 (7.3%)	1355 (8.1%)	196,049 (7.3%)	15,571 (5.9%)
Maternal Psychiatric History	73,740 (2.5%)	1237 (7.4%)	64,270 (2.4%)	10,707 (4.1%)
Paternal Psychiatric History	71,506 (2.4%)	779 (4.7%)	63,318 (2.4%)	8967 (3.4%)

Values are presented as n (%) or mean ± SD.

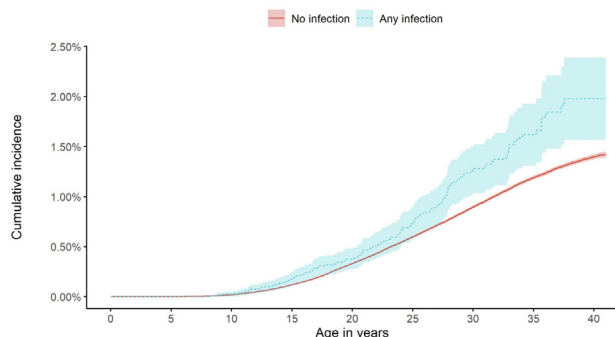
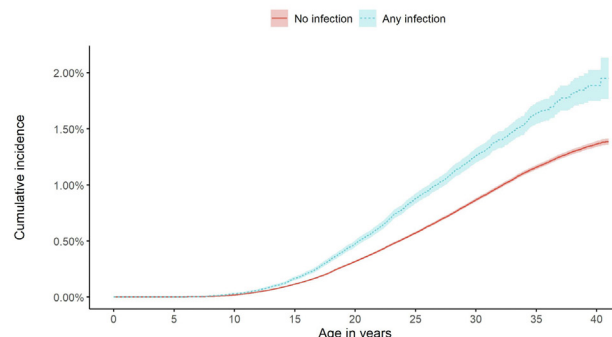
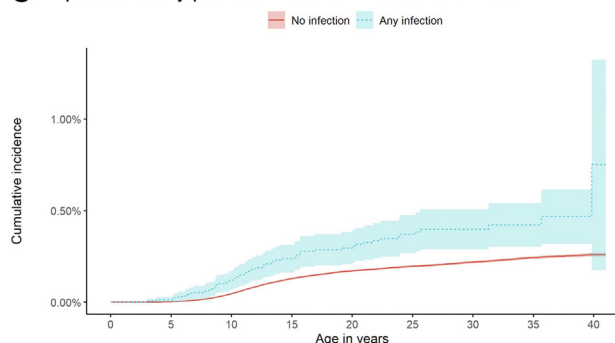
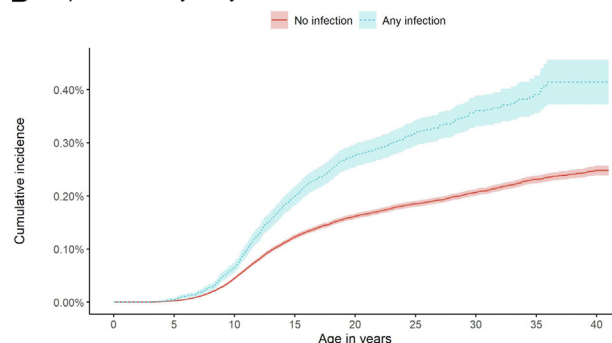
A Exposure to any prenatal maternal infection and OCD**B** Exposure to any early childhood infection and OCD**C** Exposure to any prenatal maternal infection and TS/CTD**D** Exposure to any early childhood infection and TS/CTD

Figure 1. Cumulative incidence for obsessive-compulsive disorder (OCD) and Tourette syndrome or chronic tic disorder (TS/CTD) in individuals exposed vs. unexposed to prenatal (**A, C**) or childhood (**B, D**) infections.

of OCD (HR, 1.19; 95% CI, 1.14–1.25) and TS/CTD (HR, 1.35; 95% CI, 1.25–1.45), compared with unexposed offspring. Adjusting for parental psychiatric history (model 2) did not change the results (i.e., overlapping confidence interval). In the fully adjusted models (model 3), individuals exposed to any early childhood infection had an increased risk of OCD (HR, 1.19; 95% CI, 1.14–1.25) and TS/CTD (HR, 1.34; 95% CI, 1.24–1.44), compared with unexposed individuals. Both bacterial and viral infections were associated with increased risk of OCD (for viral infections: HR, 1.24; 95% CI, 1.17–1.31; for bacterial infections: HR, 1.22; 95% CI, 1.13–1.32) and TS/CTD (for viral infections: HR, 1.36; 95% CI, 1.24–1.51; for bacterial infections: HR, 1.34; 95% CI, 1.17–1.53).

Sibling Analyses

Clusters of full siblings discordant for the exposures were identified, consisting of 10,720 offspring exposed to prenatal maternal infections and their 16,234 unexposed siblings, and 178,715 offspring exposed to early childhood infections and their 242,119 unexposed siblings. The Kaplan-Meier estimated cumulative incidence of OCD and TS/CTD in exposed versus unexposed clusters of siblings are shown in Figure 2. In the sibling analyses, which also adjusted for offspring's birth year and sex, neither exposure to prenatal maternal infections nor exposure to early childhood infections remained significantly associated with an increased risk of OCD or TS/CTD (Table 3).

DISCUSSION

This population-based birth cohort study followed nearly 3 million individuals from birth up to 4 decades to investigate the associations between prenatal maternal infections and early childhood (before age 3) infections with the subsequent risk of OCD and TS/CTD in the offspring. Four main findings emerged from this study.

First, after adjusting for all measured confounders, we found that prenatal maternal infections, in general, were associated with increased risk of OCD (33%) and TS/CTD (60%). However, further analyses revealed that associations were limited to bacterial, but not viral, infections. Prenatal bacterial infections have previously been associated with several other psychiatric disorders, such as autism spectrum disorder (18%) (40), attention-deficit/hyperactivity disorder (29%–51%) (22,23), and psychotic disorders (80%) (25). Because, in our cohort, severe viral infections during pregnancy were relatively rare, these specific analyses may have been underpowered.

Second, prenatal paternal infections were not associated with increased risk of OCD or TS/CTD. Consistent results were found in a Danish register-based cohort study, where it was shown that paternal infections during pregnancy were not associated with any mental disorder regardless of the timing of the infections during the pregnancy, in- or outpatient treatments for the infections, or total number of infections (41). Because paternal infections during the index pregnancy are unlikely to directly interfere with fetal development, the increased risk of OCD and TS/CTD when exposed to maternal,

Table 2. Risk of OCD and TS/CTD in Offspring Exposed to Prenatal Maternal Infections, Prenatal Paternal Infections, and Early Childhood Infections

	Exposed Cohort, <i>n</i> (%)	Unexposed Cohort, <i>n</i> (%)	Model 1 ^a , HR (95% CI)	Model 2 ^b , HR (95% CI)	Model 3 ^c , HR (95% CI)
Risk of OCD					
Prenatal Maternal Infections					
Any infection ^d	135 (0.79%)	18,893 (0.64%)	1.34 (1.13–1.59) ^e	1.26 (1.06–1.50) ^e	1.33 (1.12–1.57) ^e
Viral infections	49 (0.87%)	18,839 (0.64%)	1.33 (1.00–1.76)	1.24 (0.93–1.64)	1.31 (0.99–1.74)
Bacterial infections	83 (0.74%)	18,805 (0.64%)	1.33 (1.07–1.65) ^e	1.26 (1.02–1.57) ^e	1.32 (1.06–1.64) ^e
Prenatal Paternal Infections					
Any infection ^d	44 (0.61%)	18,844 (0.64%)	0.97 (0.72–1.31)	0.92 (0.68–1.23)	0.97 (0.72–1.30)
Viral infections	13 (0.50%)	18,875 (0.64%)	0.80 (0.46–1.38)	0.73 (0.43–1.26)	0.80 (0.46–1.37)
Bacterial infections	27 (0.66%)	18,861 (0.64%)	1.04 (0.72–1.52)	1.01 (0.69–1.47)	1.04 (0.71–1.52)
Early Childhood Infections					
Any infection ^d	1983 (0.75%)	16,905 (0.63%)	1.19 (1.14–1.25) ^e	1.17 (1.12–1.23) ^e	1.19 (1.14–1.25) ^e
Viral infections	1184 (0.79%)	17,704 (0.63%)	1.24 (1.17–1.32) ^e	1.21 (1.14–1.28) ^e	1.24 (1.17–1.31) ^e
Bacterial infections	614 (0.77%)	18,274 (0.63%)	1.22 (1.13–1.33) ^e	1.20 (1.11–1.31) ^e	1.22 (1.13–1.32) ^e
Risk of TS/CTD					
Prenatal Maternal Infections					
Any infection ^d	56 (0.33%)	5423 (0.18%)	1.64 (1.26–2.13) ^e	1.49 (1.15–1.94) ^e	1.60 (1.23–2.09) ^e
Viral infections	12 (0.21%)	5467 (0.19%)	1.13 (0.64–2.00)	1.00 (0.57–1.77)	1.10 (0.62–1.94)
Bacterial infections	40 (0.36%)	5439 (0.18%)	1.74 (1.27–2.37) ^e	1.59 (1.17–2.18) ^e	1.71 (1.25–2.33) ^e
Prenatal Paternal Infections					
Any infection ^d	16 (0.22%)	5463 (0.19%)	1.07 (0.66–1.75)	0.96 (0.59–1.57)	1.05 (0.64–1.72)
Viral infections	6 (0.23%)	5473 (0.19%)	1.12 (0.50–2.50)	0.94 (0.42–2.09)	1.10 (0.49–2.45)
Bacterial infections	9 (0.22%)	5470 (0.19%)	1.10 (0.57–2.11)	1.03 (0.53–1.97)	1.08 (0.56–2.08)
Early Childhood Infections					
Any infection ^d	748 (0.28%)	4730 (0.18%)	1.35 (1.25–1.45) ^e	1.31 (1.21–1.42) ^e	1.34 (1.24–1.44) ^e
Viral infections	433 (0.29%)	5046 (0.18%)	1.38 (1.25–1.52) ^e	1.33 (1.20–1.47) ^e	1.36 (1.24–1.51) ^e
Bacterial infections	223 (0.28%)	5256 (0.18%)	1.35 (1.18–1.54) ^e	1.32 (1.16–1.51) ^e	1.34 (1.17–1.53) ^e

HR, hazard ratio; OCD, obsessive-compulsive disorder; TS/CTD, Tourette syndrome or chronic tic disorder.

^aModel 1 adjusted for offspring birth year, sex, maternal and paternal age at birth of offspring.

^bModel 2 adjusted for, in addition to variables in model 1, maternal and paternal psychiatric disorders.

^cModel 3 adjusted for, in addition to variables in model 2, maternal and paternal autoimmune diseases.

^dFrequency numbers of any infection may be larger than the sum of viral and bacterial infections because they additionally included infections with unknown agents (viral or bacterial).

^eStatistically significant hazard ratio.

but not paternal, infections during pregnancy are potentially in line with a maternal immune activation hypothesis, whereby immune dysregulation in utero is thought to have a deleterious impact on neurodevelopment (42). However, alternative explanations are possible, such as genetic maternal effects (43).

Third, after adjusting for all measured confounders, we found that individuals exposed to early childhood infections before the age of 3 had a 19% increased risk of OCD and 34% for TS/CTD. For both disorders, the risks were similar for bacterial and viral infections. Of note, we were able to detect these associations despite the fact that most streptococcal infections tend to occur later in childhood (44). In addition, adjusting for parental psychiatric history and autoimmune diseases did not change the results, suggesting a minor contribution of these factors to the association between early-life infections and risk of OCD and TS/CTD. Although we have no information on the type of symptom onset (e.g., abrupt vs.

insidious), these findings support the idea that postinfectious autoimmune responses (not limited to streptococcal infections) may play a role in the etiology of OCD and TS/CTD. Nevertheless, these associations do not necessarily indicate a direct causal link between infections and OCD or TS/CTD, among other reasons because these analyses do not adjust for unmeasured familial confounding.

Fourth, in our sibling analyses comparing exposed with unexposed siblings within the same nuclear family, all associations attenuated to the null and were no longer significant, suggesting that unmeasured familial confounding largely explains the associations described in the population analyses. In line with our findings, a contributing role of shared maternal genetic effects in the OCD risk architecture has been suggested (43). Moreover, a familial link between OCD, TS/CTD, pediatric acute-onset neuropsychiatric syndrome, and autoimmune diseases has been well documented (28,45). Genetic

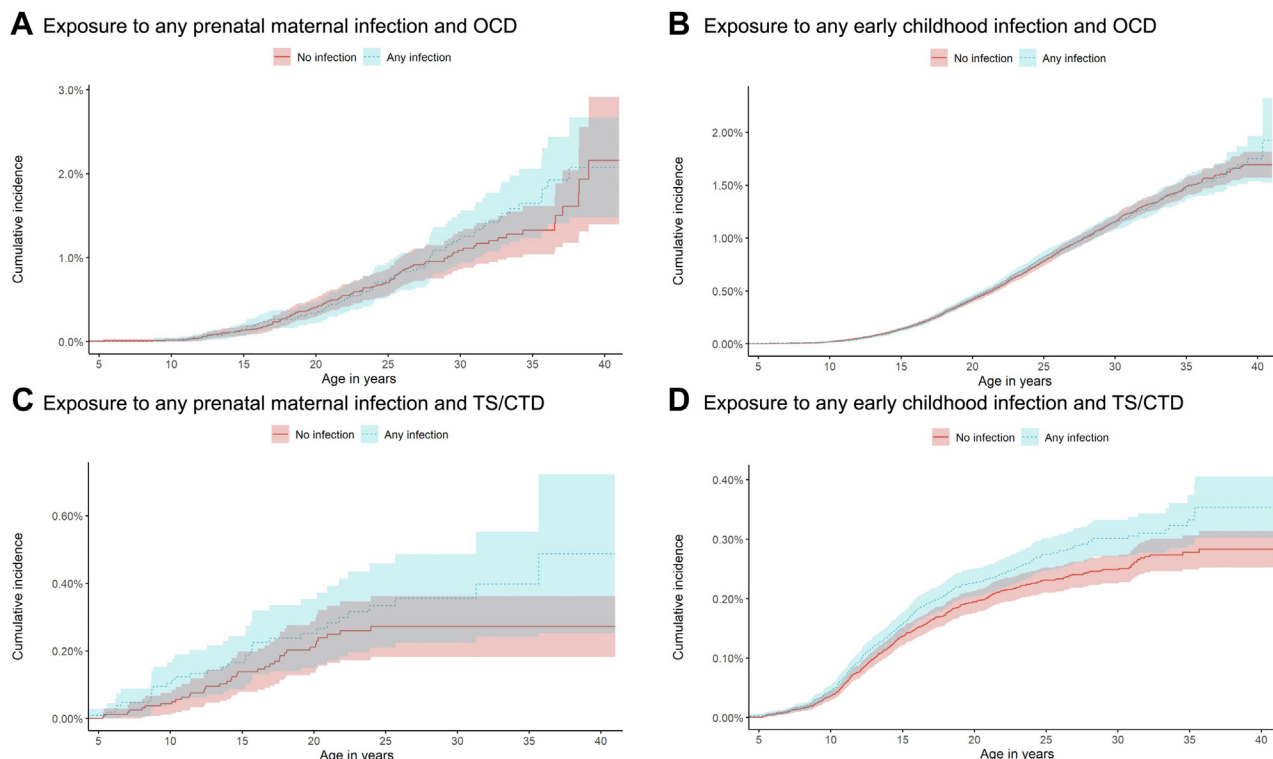


Figure 2. Cumulative incidence for obsessive-compulsive disorder (OCD) and Tourette syndrome or chronic tic disorder (TS/CTD) in siblings who were discordant for exposure to prenatal (A, C) or childhood (B, D) infections.

correlations with immune-related phenotypes have been suggested for both OCD (46,47) and TS/CTD (48–50), although they remain poorly understood, primarily due to the modest size of the current genome-wide association studies of these disorders. Overall, our results do not support the hypothesis that maternal or early-life infections play a direct causal role in the etiology of either OCD or TS/CTD. Instead, the results suggest that familial factors (e.g., genetic pleiotropy) may explain both the propensity to infections and the liability to OCD or TS/CTD. Defects in immunity (innate and adaptive) may lead to increased susceptibility to infections and autoimmune diseases, which may, in turn, provide compromised protection to the host from pathogens and result in physiological conditions (1,39,51). Thus, a double-hit scenario seems most plausible, whereby infections may act as a second hit in people with genetic susceptibility to both immune-related conditions and OCD and TS/CTD (17,52). As the sample

sizes of genomic studies continue to grow, it may be possible to identify the specific coding variants of genes that interact with one another and contribute both to the negative impact of prenatal maternal and/or early-life infections, as well as the individual's vulnerability to develop OCD and/or TS/CTD. One potential challenge will be the recent discovery that mosaic mutations in genes occur very early in development (53).

Strengths and Limitations

The strengths of this study are the use of nationwide population-based data, including nearly 3 million individuals prospectively followed from birth for several decades, which minimizes the risk of selection and recall bias; the long follow-up time, which can capture OCD and TS/CTD cases that had an onset during adolescence and adulthood; the established validity and reliability of the diagnostic codes (38); the use of inpatient data to identify infection status, which minimizes the

Table 3. Risk of OCD and TS/CTD in Offspring Exposed vs. Unexposed to Prenatal Maternal or Early Childhood Infections in the Sibling Cohort

Outcome	Prenatal Maternal Infections			Early Childhood Infections		
	n (%)		HR (95% CI), Adjusted for Offspring's Year of Birth and Sex	n (%)		HR (95% CI), Adjusted for Offspring's Year of Birth and Sex
	Exposed, n = 10,720	Unexposed, n = 16,234		Exposed, n = 178,715	Unexposed, n = 242,119	
OCD	84 (0.78%)	117 (0.72%)	0.92 (0.65–1.30)	1241 (0.69%)	1772 (0.73%)	0.93 (0.85–1.01)
TS/CTD	32 (0.30%)	36 (0.22%)	1.35 (0.77–2.37)	432 (0.24%)	507 (0.21%)	0.97 (0.83–1.13)

HR, hazard ratio; OCD, obsessive-compulsive disorder; TS/CTD, Tourette syndrome or chronic tic disorder.

risk of misclassification of exposure; and the use of sibling comparisons extracted from the full cohort, which allowed us, for the first time, to account for unmeasured familial confounding.

However, the results should be interpreted in light of some limitations. First, although we made an effort to capture all bacterial and viral infections, we did not have data on a few groups of infections (e.g., ear and eye infections). In addition, we could not include fungal or parasitic infections; thus, their associations with OCD and TS/CTD will require study. Second, we had data on diagnoses of infections but no data on what treatments the individuals with these infections received. This may have affected the results because antibiotics and antiviral drugs may affect intestinal microbiota composition and one's health. Third, not all OCD and TS/CTD cases were captured because many affected individuals, particularly those with mild symptoms, do not seek help. Moreover, OCD and TS/CTD cases diagnosed prior to 2001, may be more severe because before 2001 the NPR only registered inpatient diagnoses. Finally, although sibling analyses control for unmeasured shared confounders, they are sensitive to biases introduced by random measurement errors of exposure and unmeasured nonshared confounders within the sibling clusters (54). Carry-over effects may also introduce biases to sibling analyses by affecting the status of exposure from previous pregnancies to later pregnancies or from older siblings to younger siblings (54). This limitation was partially addressed by adjusting for parental autoimmunity in the fully adjusted models.

Conclusions

In this large birth cohort study, prenatal maternal and early childhood infections were associated with an increased risk of subsequent OCD and TS/CTD. However, these associations were no longer significant in sibling analyses, suggesting that unmeasured familial confounding could largely explain the significant associations observed at the population level. Overall, the results do not support the hypothesis that maternal or early-life infections play a direct causal role in the etiology of either OCD or TS/CTD. Instead, familial factors (e.g., genetic pleiotropy) may explain both the propensity to infections and the liability to OCD and TS/CTD.

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