Parental Psychopathology and Tourette Syndrome/Chronic Tic Disorder in Offspring: A Nationwide Case-Control Study

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Objective: To determine the associations between maternal and paternal psychiatric diagnoses and Tourette syndrome (TS)/chronic tic disorder (CT) in a nationwide study.

Method: This nested case-control study linked data derived from three national registers. All singletons born and diagnosed with TS/CT in Finland between January 1991 and December 2010 were identified (n = 1,120) and matched to four controls (n = 4,299). Conditional logistic regression was used to examine the associations between parental psychopathology and TS/CT.

Results: Altogether, 24.9% of patients with TS/CT and 12.0% of controls had a mother with a psychiatric diagnosis. Similarly, 17.9% and 12.9% had a father with a psychiatric diagnosis. Any maternal and any paternal psychiatric diagnosis was associated with offspring TS/CT (odds ratio [OR] 2.3; 95% CI 1.9−2.7 and OR 1.2; 95% CI 1.01−1.5, respectively). The association between maternal psychiatric diagnosis and TS/CT was stronger than that between paternal psychiatric diagnosis and TS/CT ($p < .001$). Maternal personality disorders (OR 3.1, 95% CI 1.9−5.1), anxiety disorders (OR 2.6, 95% CI 1.9−3.5), affective disorders (OR 2.3, 95% CI 1.8−2.9), psychotic disorders (OR 2.0, 95% CI 1.2−3.3), and addiction disorders (OR 1.8, 95% CI 1.1−2.8) were associated with TS/CT. Paternal OCD (OR 6.5, 95% CI 1.1−39.5) and anxiety disorders (OR 1.5, 95% CI 1.1−2.3) were associated with TS/CT.

Conclusion: Parental psychiatric diagnoses (especially in the mother) are associated with diagnosed offspring TS/CT. Further studies are required before the results can be generalized to all children with TS/CT. The associations between maternal psychiatric disorders and TS may reflect both maternal specific environmental and/or genetic influences.

Key words: Tourette syndrome, parental psychiatric diagnoses, risk factor

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Tourette syndrome (TS) and chronic tic disorders (CT) are childhood-onset neurodevelopmental disorders defined by the presence of multiple motor and one or more vocal or either motor or vocal tics persisting for at least 1 year.[1] The etiology of the disorders is complex and involves both multifactorial genetic and environmental factors.[2-4] In addition to chronic tics as the core symptoms of the disorder, 70% to 85% of clinically diagnosed TS is accompanied by other neurodevelopmental or psychiatric disorders.[4,5]

Familial clustering of tic disorders, obsessive-compulsive disorder (OCD), and attention-deficit/hyperactivity disorder (ADHD) has been shown in clinical studies,[5-11] and large nationwide register-based studies have confirmed the clustering of tic disorders and OCD.[4,12] There are fewer studies on parental psychiatric disorders other than OCD and ADHD, but a few clinical studies have reported increased rates of depression and anxiety disorders among family members of individuals with TS.[5,13-16] A study including 1,364 TS-affected persons and their 1,142 first-degree relatives found genetic correlations between mood and anxiety disorders and TS; however, these relationships were mediated by the presence of co-occurring OCD and/or ADHD.[5] A population-based study derived from a pre-birth cohort including 122 children with TS/CT reported an association between self-reported maternal (but not paternal) anxiety and depression and TS/CT.[17] A population-based study including 25 individuals with TS suggested that first-degree relatives of those with TS had more psychiatric diagnoses, mostly tic disorders, ADHD, OCD, and depression, compared with relatives of controls.[18]

A wide range of parental psychiatric disorders has been associated with other neurodevelopmental disorders, for example, autism and ADHD, in epidemiological studies.[19-21] This study aimed to expand the current knowledge of the associations between parental psychopathology and TS/CT in offspring by using a nationwide case-control design. Based on the findings on parental psychopathology and autism and ADHD,[19-21] and previous studies on TS,[5,13-18] we hypothesized the following: that parents of individuals

This article is discussed in an editorial by Dr. Barbara J. Coffey on page 281.

Supplemental material cited in this article is available online.

affected by TS/CT would have higher rates of psychiatric disorders than parents of unaffected controls; and that a wide range of specific parental psychiatric disorders would be associated with TS/CT in offspring.

METHOD

This nested case-control study used data derived from Finnish national registries. A personal identification code (PIC) includes the date of birth, sex, and a unique control number for each person and is assigned to all Finnish citizens. The PIC enabled the identification of patients, controls, and their parents. The data between compatible national registers was linked by the PIC. The sampling frame included all children born in Finland between January 1, 1991, and December 31, 2010 (n = 1,199,112). Children diagnosed with TS or CT during the same time period were identified from the Finnish Hospital Discharge Register (FHDR). The data on parental factors were derived from the Finnish Central Population register (CPR), the FHDR, and the Finnish Medical Birth Register (FMBR). The study was authorized by the Ministry of Social Affairs and Health (STM/1528/2007) and the National Institute of Health and Welfare (THL) with approval from the ethics committee of the hospital district of Southwest Finland. All data were de-identified and based on registries; thus participants, controls, and their parents were not contacted, and informed consent was not required by the ethical review boards that approved the study.

National Registers

The FHDR, established in 1969, covers inpatient wards in somatic and psychiatric hospitals. Since 1998, the outpatient clinics at public hospitals have also been included. The FHDR records primary and subsidiary diagnoses at discharge from the hospital. The information is based on clinical diagnoses, given by the attending clinician using *International Classification of Diseases* (*ICD*) *8th Revision*, from 1969 to 1986, *9th Revision* from 1987 to 1995, and *10th Revision* from 1996 onward. Completeness of the inpatient register is greater than 95%, and positive predictive values for diagnoses of psychiatric disorder have varied from 75% to 100%.[22] The validity of TS diagnoses in the FHDR was shown to be 95%.[23]

Parents of participants and controls were identified from the CPR, which contains personal data about Finnish citizens and other citizens residing permanently in Finland. The data include name, PIC, address, citizenship and native language, family relations, emigration and immigration dates, and countries of origin.

The FMBR, established in 1987 and maintained by THL, includes standardized data on maternal background, pregnancies, prenatal period, and neonatal period for all births in Finland.

Identification of Participants and Controls

Children diagnosed with TS or CT (*ICD-10* codes F95.2 or F95.1 or *ICD-9* codes 3072D or 3072C) without severe or profound mental retardation (*ICD-10* codes F72, F73, and *ICD-9* codes 3181 and 3182) between January 1, 1991, and December 31, 2010, were identified from the FHDR (n = 1,157). Twins (n = 36) or triplets (n = 1) were excluded; thus 1,120 individuals (96.8%) were included in the analyses. Among those with TS/CT, there were 21 individuals (1.9%) diagnosed with comorbid schizophrenia and other psychosis and 79 (7.1%) and 54 (4.8%) diagnosed with affective and anxiety disorders, respectively. The characteristics of the TS/CT sample have been described in detail previously.[23]

The controls, children without any tic disorder diagnoses (*ICD-10* code F95X or *ICD-9* code 3072A–D) or severe or profound mental retardation were identified from the CPR. Each individual with TS/CT was matched to four controls, on date of birth (±30 days), sex, and place of birth. Those who emigrated from Finland (n = 22), who died before diagnosis (n = 21), who were born twins/triplets (n = 131), or who were initially matched to one with TS/CT born as twins/triplets (n = 145) were excluded. The number of the remaining controls was 4,299.

Identification of Parents

All mothers of those with TS/CT and controls were identified from the FMBR. Fathers of individuals with TS/CT and controls were identified from the CPR. A man married to a mother at the time of the child's birth is registered as the child's father. If the mother is not married, paternity is registered by the acknowledgement of the father, and DNA testing for paternity is also available free of charge. In this study, fathers of 1,095 participants (97.8%) with TS/CT and 4,258 controls (99.0%) were identified.

Parental Psychiatric Diagnoses

Parental psychiatric diagnoses were derived from the FHDR. Parents were followed up from January 1969 to December 2010. Psychiatric diagnoses according to *ICD-10*, *ICD-9*, and *ICD-8* codes are listed in Table S1, available online. First, maternal and paternal psychiatric diagnoses were aggregated and categorized as present or absent, respectively. Second, the maternal and paternal psychiatric diagnostic entities were examined separately in the following categories: schizophrenia and other nonaffective psychosis; affective disorders; OCD; anxiety disorders; personality disorders; other psychiatric disorders; and alcohol and other drug addiction or abuse. Due to the often chronic and pervasive nature of schizophrenia, parents diagnosed with schizophrenia and other psychotic disorders were not assigned to other groups, but all other parents could be assigned to several of these groups in case of comorbidity. Furthermore, the sample was stratified by sex; associations between any maternal and any paternal psychiatric diagnoses and TS/CT were examined for females and males. To control for possible prenatal effects of substance abuse, mothers with comorbid alcohol/drug addiction or abuse disorder were excluded from the analyses in an additional model. Furthermore, maternal and paternal psychiatric diagnoses (present/absent) were stratified to diagnoses given before versus after birth of the offspring so that the association between maternal/paternal psychiatric diagnoses given before and after the child's birth could be evaluated. Maternal and paternal psychiatric diagnoses were also pooled together: no psychiatric diagnoses in either parent (reference), maternal psychiatric diagnosis without paternal psychiatric diagnosis, paternal psychiatric diagnosis without maternal diagnosis, and both parents having psychiatric diagnoses.

Maternal and paternal developmental, emotional, and behavioral disorders typically occurring in childhood (i.e., tic disorders, ADHD, autism spectrum disorder [ASD], and other developmental disorders) were examined jointly due to the low numbers of these participants and controls.

Covariates

Covariates were included in the analyses based on their potential association with TS/CT, other neurodevelopmental disorders (e.g., autism) or psychiatric disorders in the literature and/or in this sample. These were as follows: maternal age,[24,25] paternal age,[24,25] maternal socioeconomic status (SES),[24,26] parity, co-occurring maternal/paternal OCD/ADHD/tic disorder,[5] other parent's psychiatric disorders,[24,27] and parental immigration.[28,29] The association between parity and TS in this sample has been reported previously.[30] The associations among maternal age, paternal age,

maternal SES, parental immigration, and TS/CT were tested (see Table S2, available online). Parental age at the time of birth and parental immigration status were obtained from the CPR. Maternal and paternal age were categorized as binary variables: below the median and at or above the median. Parental immigration status was defined by using the mother tongue and the country of birth: parents born abroad and whose mother tongue was other than Finnish were defined as immigrants. Parents born in Finland or who were born abroad but had Finnish as mother tongue were defined as Finnish. Parental immigration status was studied as a binary variable: at least one of the parents is an immigrant (yes/no). Maternal SES at the time of child's birth and parity were obtained from the FMBR. The measure of SES follows national classifications on occupations and socioeconomic group categorized as follows: upper white collar (reference); lower white collar; blue collar; others (e.g., entrepreneurs and persons outside the workforce); and no information on SES. Parity was categorized as a binary maternal variable (0 and ≥1). Other parent's psychiatric disorders and co-occurring OCD/ADHD/tic disorder were categorized as binary variables (present/absent). The associations between covariates and TS/CT are presented in Table S2, available online. The covariates were included in the final models if they showed a trend for association with TS/CT ($p < .10$).

Statistical Analyses

Conditional logistic regression analyses were used to examine the associations between parental psychiatric diagnoses and offspring TS/CT. Initially, the unadjusted odds ratios with 95% CIs were calculated for each category of maternal and paternal psychiatric diagnoses (present/absent). Analyses were first adjusted with the other parent's psychiatric diagnoses only, and thereafter with the covariates. Thereafter, participants with TS/CT and controls were stratified by sex, and unadjusted and adjusted models were examined for females and males separately. The interaction between females and males was also evaluated. In additional analyses, we fitted models in which mothers with comorbid alcohol or other substance abuse disorders were excluded. In addition, both maternal and paternal psychiatric diagnoses were stratified by timing of parent's first diagnosis (i.e., before versus after offspring's birth). To compare the magnitude of risk between any maternal and paternal psychiatric diagnoses and between maternal and paternal anxiety diagnoses, pairwise comparisons between mothers and fathers were conducted. The interaction between maternal and paternal psychiatric diagnoses given before and after the child's birth was evaluated, respectively. Maternal and paternal diagnoses were also pooled together as described earlier. A two-sided p value of $<.05$ was considered statistically significant. Statistical analyses were performed with SAS statistical software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Table 1 shows frequencies of cases and controls in relation to parental psychiatric disorders, and associations between maternal and paternal psychiatric diagnoses and offspring TS/CT. Maternal and paternal age, maternal SES, parity, other parent's psychiatric disorder, and co-occurring maternal/paternal OCD/ADHD/tic disorder were included as covariates (see Table S2, available online). Any maternal and paternal psychiatric diagnosis was associated with TS/CT after controlling for the covariates (odds ratio [OR] 2.3, 95% CI 1.9–2.7 and OR 1.2, 95% CI 1.01–1.5, respectively).

The association between maternal psychiatric disorders and TS/CT was stronger than the association between paternal psychiatric disorders ($p < .001$). Maternal personality disorders (OR 3.1, 95% CI 1.9–5.1), anxiety disorders (OR 2.6, 95% CI 1.9–3.5), affective disorder (OR 2.3, 95% CI 1.8–2.9), schizophrenia and psychosis (OR 2.0, 95% CI 1.2–3.3), alcohol and drug addiction (OR 1.8, 95% CI 1.1–2.8), and other psychiatric disorders (OR 2.0, 95% CI 1.5–2.6) were associated with offspring TS/CT in the final model. The association between maternal OCD and offspring TS/CT could not be assessed. When maternal schizophrenia (*ICD-10*: F20 and *ICD-9*, *ICD-8*: 295) (n = 6 [0.5%] among those with TS/CT and n = 16 [0.4%] among controls) was analyzed separately (i.e., not including other psychotic disorders), no significant association was found with TS/CT in the offspring (OR 1.4; 95% CI 0.6–3.7). However, the power was low due to low number of the cases. When the cases with co-occurring schizophrenia or psychotic disorder (n = 21) were excluded, the adjusted association between maternal schizophrenia and other psychotic disorders and TS/CT remained similar (OR 2.0, 95% CI 1.2–3.3). When the cases with comorbid anxiety disorders (n = 54) and affective disorder (n = 79) were excluded, the associations between the examined disorder and TS/CT remained significant (OR 2.5, 95% CI 1.8–3.4 and OR 2.3, 95% CI 1.8–2.9, respectively).

Of paternal psychiatric diagnoses, only OCD (OR 5.8, 95% CI 1.03–33.2) and anxiety disorders (OR 1.6, 95% CI 1.1–2.3) were associated with TS/CT when adjusted with maternal psychiatric diagnoses. There was no difference between the magnitude of the association between maternal and paternal anxiety disorders and TS/CT ($p = .069$).

Table S3 (available online) shows the results when cases were stratified by sex. The interaction of maternal psychiatric disorders and sex of the offspring was not significant ($p = .87$). The results between specific maternal psychiatric diagnoses and TS/CT remained similar to the results in the original model when mothers with comorbid addiction disorders were excluded (see Table S4, available online). No statistical differences between maternal or paternal psychiatric diagnoses given before versus after the child's birth ($p = .09$ and $p = .50$, respectively) were found. When both parents had a psychiatric disorder, the OR for offspring TS/CT was 2.9 (see Table S5, available online). Due to low frequencies, maternal and paternal childhood-onset disorders are reported jointly: parental tic disorders (OR 20, 95% CI 4.4–91.3), ADHD (OR 3.4, 95% CI 1.3–8.9), and other developmental disorders (OR 1.8, 95% CI 1.1–3.1) were associated with TS/CT (see Table S6, available online).

DISCUSSION

This nationwide case-control study examined parental psychiatric disorders as risk factors for TS/CT in offspring. Three important findings have implications for future research on the etiology of TS/CT. First, maternal psychiatric disorders were strongly and independently associated with TS/CT in offspring, whereas the association between paternal psychiatric disorders and TS/CT was much less

TABLE 1 Associations Among Parental Psychiatric Diagnoses and Tourette Syndrome/Chronic Tic Disorder

	Cases	Controls	Unadjusted Analyses		Adjusted Analyses[a]		Final Model[b]	
Parental Psychiatric Diagnoses	**n (%)**	**n (%)**	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Maternal psychiatric diagnoses								
No	841 (75.1)	3,783 (88.0)	1.0		1.0		1.0	
Yes (any)	279 (24.9)	516 (12.0)	2.4 (2.0–2.8)	<.001	2.3 (1.9–2.7)	<.001	2.3 (1.9-2.7)	<.001
Specific diagnostic groups[d]								
Schizophrenia and other psychosis	32 (2.9)	47 (1.1)	2.6 (1.7–4.1)	<.001	2.2 (1.4–3.6)	.001	2.0 (1.2-3.3)	.005
Affective disorders	145 (13.0)	249 (5.8)	2.4 (1.9–3.0)	<.001	2.3 (1.8–2.9)	<.001	2.3 (1.8-2.9)	<.001
OCD	6 (0.5)	0 (0.0)	NA	NA	NA	NA	NA[c]	NA
Anxiety disorders	83 (7.4)	119 (2.8)	2.7 (2.1–3.6)	<.001	2.6 (2.0–3.5)	<.001	2.6 (1.9-3.5)	<.001
Personality disorders	34 (3.0)	43 (1.0)	3.2 (2.0–5.0)	<.001	3.0 (1.8–4.8)	<.001	3.1 (1.9-5.1)	<.001
Other psychiatric disorders	93 (8.3)	188 (4.4)	2.0 (1.6–2.6)	<.001	2.0 (1.5–2.6)	<.001	2.0 (1.5-2.6)	<.001
Alcohol and drug addiction	38 (3.4)	75 (1.7)	1.9 (1.3–2.9)	.001	1.5 (1.002–2.4)	.0487	1.8 (1.1-2.8)	.010
Paternal psychiatric diagnoses								
No	899 (82.1)	3,708 (87.1)	1.0		1.0		1.0	
Yes (any)	196 (17.9)	550 (12.9)	1.5 (1.2–1.8)	<.001	1.3 (1.1–1.5)	.009	1.2 (1.01-1.5)	.039
Specific diagnostic groups								
Schizophrenia and other psychosis	16 (1.5)	38 (0.9)	1.6 (0.9–2.9)	.106	1.2 (0.7–2.3)	.483	1.2 (0.7-2.3)	.513
Affective disorders	81 (7.4)	216 (5.1)	1.5 (1.1–1.9)	.005	1.3 (0.96–1.7)	.092	1.3 (0.9-1.7)	.119
OCD	4 (0.4)	2 (0.1)	7.2 (1.3–39.8)	.023	5.8 (1.03–33.2)	.047	6.5 (1.1-39.5)[c]	.043
Anxiety disorders	44 (4.0)	101 (2.4)	1.7 (1.2–2.5)	.003	1.6 (1.1–2.3)	.012	1.5 (1.06-2.3)	.024
Personality disorders	29 (2.7)	94 (2.2)	1.2 (0.8–1.8)	.397	1.1 (0.7–1.6)	.767	1.1 (0.7-1.6)	.797
Other psychiatric disorders	47 (4.3)	141 (3.3)	1.3 (0.9–1.9)	.108	1.2 (0.8–1.7)	.353	1.2 (0.8-1.7)	.421
Alcohol and drug addiction	68 (6.2)	221 (5.2)	1.2 (0.9–1.6)	.160	1.1 (0.8–1.4)	.608	1.0 (0.8-1.4)	.875

Note: OCD = obsessive-compulsive disorder; OR = odds ratio.

[a] *Adjusted with maternal/paternal psychiatric disorder.*

[b] *Final model including maternal/paternal psychiatric disorders, maternal age, paternal age, maternal socioeconomic status (SES) and maternal/paternal co-occurring OCD/attention-deficit/hyperactivity disorder/tic disorder and parity.*

[c] *Final model including maternal/paternal psychiatric disorders, maternal age, paternal age, maternal SES, and parity.*

[d] *Diagnoses in the specific group, yes/no.*

prominent. Second, all maternal-specific psychiatric diagnoses showed an approximately two- to three-fold increased risk of TS/CT. Third, only paternal OCD and anxiety disorders were related to increased risk of TS/CT among offspring.

It has not been reported previously that a wide range of maternal psychiatric disorders, but only a few paternal psychiatric disorders, are associated with offspring TS/CT. These findings specific to maternal psychopathology are in line with a study showing that maternal but not paternal self-reported prenatal depression is associated with offspring TS/CT.[17] However, in contrast to this previous study,[17] in our study, paternal anxiety disorders were also associated with TS/CT, which could implicate shared etiological factors between these disorders. A large international study showed that TS had genetic correlations with anxiety disorders. However, these correlations were mediated through the presence of ADHD in these families.[5]

Our findings on the association between several specific maternal psychiatric disorders and TS/CT can be explained by several potential mechanisms. First, maternal-specific, nongenetic effects on the child may arise from direct intrauterine mechanisms, for example, maternal medication use, substance use, other health-related issues (e.g., nutrition, obstetric complications, or stress). Maternal medication (e.g., selective serotonin reuptake inhibitors [SSRI] and valproate during pregnancy) has been suggested to be associated with neurodevelopmental disorders including autism and ADHD, although the findings across studies are inconsistent.[31-33] A recent study based on Finnish register data found an association between prenatal exposure to SSRIs and depression, but not between prenatal SSRI exposure and ADHD or autism.[34] There is a lack of studies on maternal psychotropic medication during pregnancy and risk of TS. Cannabis and alcohol use during pregnancy have been associated with offspring TS.[35] In the present study, lifetime substance use disorders among mothers were associated with TS/CT, but exclusion of the mothers with comorbid substance abuse disorders did not substantially alter the associations between other diagnostic groups and TS/CT. However, substance abuse disorders are likely to be underdiagnosed; thus, the potential effect of substance abuse cannot be excluded based on this study alone. A previous retrospective study has suggested an association between maternal smoking during pregnancy and tic severity.[36] In a previous report based on this sample, maternal smoking was

associated with TS only when comorbid with ADHD.[24] Previous work in this sample did not find an association between prematurity, obstetric complications, or neonatal adversities and TS.[30]

Maternal stress might affect prenatal fetal programming through fetal exposure to glucocorticoids, inflammation, or placental modification.[37] Prenatal maternal stress and neuroendocrine mechanisms have been suggested to be involved in the etiology of TS.[38,39] There is a growing interest in inflammation during pregnancy and neurodevelopmental disorders. Previous studies have shown an association between inflammatory markers during pregnancy and autism and schizophrenia.[40,41] The studies on the association between maternal inflammation during pregnancy and TS are lacking. However, in a large Danish register-based study, maternal autoimmune diseases were associated with an increased risk of TS.[42] Existing studies also suggest that infections may trigger and modulate the course of tic disorders in some individuals.[43] However, the studies are inconsistent, and the possible mechanisms are unclear.[43] In this study, maternal psychiatric diagnoses were stratified to those given before and after birth, to sort out whether the association between maternal psychiatric disorders and TS/CT reflects the prenatal period in particular. No difference was detected between prenatal versus postnatal maternal psychiatric diagnoses and risk of TS/CT; however, the time of diagnosis in a specialized health care setting does not necessarily reflect the time of the onset of the disorder.

Second, TS and OCD are genetically related, and first-degree female relatives of individuals with TS are more likely to have OCD than are first-degree male relatives.[11] Thus, if a mother has OCD and other psychiatric diagnoses, comorbid OCD may represent a sex-influenced genetic risk for TS. Co-occurring parental OCD was added as a covariate to analyses of other maternal psychiatric diagnoses to control for this possibility. However, OCD is not necessarily diagnosed in the specialized health care setting and registered in the FHDR; thus, frequencies of mothers diagnosed with OCD in this sample are low. It therefore was not possible to assess the association between maternal OCD and TS/CT, and a possible effect of comorbid maternal OCD cannot be ruled out.

Third, traditionally maternal but not paternal transmission of a disease may be due to X-linked or mitochondrial transmission. However, psychiatric disorders in general are not commonly considered to be X-linked or transmitted in mitochondria.[44-46] Deletions in an X-linked gene have been associated with TS in one family,[47] but heritability of TS is likely to be polygenic,[48] and large-scale genetic studies of TS have not found significant X-linked loci.[49,50]

Fourth, there is an emerging interest and evidence of gene–environment interactions in the development of psychiatric and neurodevelopmental disorders.[46,51] A genetic susceptibility associated with environmental (e.g., prenatal) risk factors could also explain the association between maternal psychiatric disorders and TS/CT.

Another unexpected finding in this study is that the association between maternal psychiatric diagnoses and offspring TS/CT is nonspecific, that is, all maternal psychiatric diagnostic groups were associated with an approximately two- to threefold increased risk for offspring TS/CT. Genetic correlations have been shown between TS and mood disorders, anxiety disorders, and disruptive behavior disorders, although these correlations were mediated through the presence of OCD and ADHD in these families.[5] Aggregation of several disorders in an individual may explain a part of the nonspecificity. There are also studies suggesting that several common psychiatric and/or neurodevelopmental disorders partly share a genetic origin.[52] Pregnancy-related risk factors may also be nonspecific for several maternal psychiatric disorders.

A register-based nationwide design provides a large sample size, elimination of recall and selection bias, and diagnostic assessments of the health care professionals. However, this study also has several limitations. The recording of severe psychiatric disorders in the FHDR is comprehensive; the accuracy of the register-based diagnoses is good; and the validity of TS diagnoses was shown to be 95%.[22,23] However, mild tic disorders and common psychiatric disorders (e.g., OCD and anxiety disorders) that do not necessarily require treatment in specialized health care services may be underrepresented in the FHDR. The rates of these disorders are relatively low in those with TS/CT, controls, and their parents in these data. Therefore, the associations between these disorders and offspring TS/CT may be underestimated. Undiagnosed OCD may also be a confounder that we are not able to control for in this study. Frequencies of parental childhood-onset disorders were also low. This may be partly due to a lack of outpatient data before 1998. In addition, the awareness and diagnosis of neurodevelopmental disorders has increased during the past decades.[23] Due to low numbers of the parental childhood-onset disorders, particularly tic disorders, in the FHDR, these results must be interpreted with caution. The relatively low numbers of comorbidities among those with TS/CT could be partly due to their young age. Not all children with TS/CT receive diagnoses in specialized health care and thus are not found in the FHDR. Therefore, it was not possible to evaluate the associations between parental psychiatric disorders and nonclinical TS/CT. Furthermore, the FHDR does not record the severity of tic disorders, and it was not possible to assess whether the association between maternal psychiatric disorders and TS/CT is different for differently affected children. It is also possible that children of mothers with psychiatric disorders are more likely to be admitted to specialized health care and to receive diagnoses there. However, because of the universal health care system and regular visits in the child health clinics and school health clinics in Finland, it is likely that at least all severe cases of TS/CT are captured in this study. Further research is required before the results can be generalized to all children with TS/CT. Numbers of the parents in some diagnostic groups were limited to less than 10. This may have limited power to detect stronger associations. Further stratification of the cases based on comorbidities of those with TS/CT or parents would have required a larger sample.

Given that TS/CT arises from a complex interplay between genetic and nongenetic risk factors, identification of each risk factor is important. If future research confirms the association between a wide spectrum of maternal psychiatric disorders and TS/CT, it may lead to earlier detection of this underrecognized and underdiagnosed disorder among the children of mothers with psychiatric disorders. The finding that several maternal psychiatric disorders are associated with increased risk of TS/CT also encourages a future search for maternal-specific factors that are related to these disorders. These may arise from environmental exposures during the prenatal period, shared genetic vulnerability across disorders, or interactions between the two. &

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TABLE S1 Description of Parental Psychiatric Diagnoses Included in Categories

Diagnostic Category	Diagnostic Codes		
	***ICD-10* (1996 Onward)**	***ICD-9* (1987–1995)**	***ICD-8* (1969–1986)**
Schizophrenia and other psychosis	F20 schizophrenia, F21 schizotypal disorder, F22 delusional disorder, F23 acute and transient psychotic disorders, F24 induced delusional disorder, F25 schizoaffective disorder, F28 other nonorganic psychotic disorder, F29 unspecified nonorganic psychosis	295, 297, 2989X, 3012C	295, 297, 298.20, 298.30, 298.99, 299
Affective disorders	F30 hypomania, F31 bipolar affective disorder, F32 depressive episode, F33 recurrent depressive disorder, F34 persistent mood (affective) disorders (including cyclothymia and dysthymia), F38 other single mood (affective) disorder, F39 unspecified mood (affective) disorder	2988A, 296, 3004A	296, 298.00, 298.10, 300.41
OCD	F42 OCD	3003A	300.30
Anxiety disorders	F40 phobic anxiety disorders, F41 other anxiety disorders,	3000A, 3000B, 3000C, 3002B, 3002C, 3002D, 3002X,	300.00, 300.20,
Personality disorders	F60 specific personality disorders, F61 mixed and other personality disorders	3010A, 3012A, 3012C, 3014A, 3015A, 3016A, 3017A, 3018B, 3018C, 3018D, 3018E, 3018X	301.00, 301.10, 301.20, 301.30, 301.40, 301.50, 301.70, 301.80, 301.88, 301.99
Other psychiatric disorders	F43 reaction to severe stress and adjustment disorders, F44 dissociative amnesia, F45 somatoform disorders, F48 other neurotic disorders, F50 eating disorders, F51 nonorganic sleep disorders, F52 lack or loss of sexual desire, F53 mental and behavioral disorders associated with the puerperium, not elsewhere classified, F54 psychological and behavioral factors associated with disorders or diseases classified elsewhere, F55 abuse of substances not producing dependence, F59 unspecified behavioral syndromes associated with psychological disturbances, F62 enduring personality changes, not attributable to brain damage and diseases, F63 habit and impulse disorders, F64 gender identity disorders, F65 fetishism, F66 psychological and behavioral disorders associated with sexual development and orientation, F68 other disorders of adult personality and behavior, F69 unspecified	300–302 (excluding 3010A, 3012AC, 3015–3017A, 3018BCDEX,3014A, 3000A, 3000B, 3000C, 3002B, 3002C, 3002D, 3002X. 3003A, 3004A ja 3012C), 3071A, 3074A, 3074F, 3074H, 3075A, 3075B, 3075C, 3075E, 3078A, 3079X, 309 (excluding 3092A, 3092B, 3093A, 3094A) 312 (excluding 3120A, 3123D)	300–302 (excluding 300.00, 300.20, 300.30, 300.41, 301.00, 301.10, 301.20, 301.30, 301.50, 301.60, 301.7, 301.80, 301.88, 301.99, 301.40), 305, 306.40, 306.50, 306.98, 307.99

TABLE S1 Continued

Diagnostic Category	Diagnostic Codes		
	ICD-10 (1996 Onward)	*ICD-9* (1987–1995)	*ICD-8* (1969–1986)
	disorder of adult personality and behavior, F99 mental disorder not otherwise specified		
Alcohol and drug addiction	Mental and behavioral disorders due to use of F10 alcohol, F11 opioids, F12 cannabinoids, F13 sedatives or hypnotics, F14 cocaine, F15 other stimulants including caffeine, F16 hallucinogens, F17 tobacco, F18 volatile solvents, F19 multiple drug use and use of other psychoactive substances	303, 304, 305, 291, 292	303, 304, 291, 294.30
Tic disorder	F95	3072	306.20
ADHD	F90	314	
ASD	F84	299	
Other childhood-onset disorder	Mental retardation F70–F79, specific developmental disorders of speech and language F80, specific developmental disorders of motor function F82, mixed specific developmental disorders F83, other disorders of psychological development F88, unspecified disorder of psychological development F89, conduct disorders F91, mixed disorders of conduct and emotions F92, emotional disorders with onset specific to childhood F93, other behavioral and emotional disorders with onset usually occurring in childhood and adolescence F98	313, 315, 317–319, 3120A, 3123D, 3070A, 3070B, 3073A, 3074G, 3075D, 3076A, 3076B, 3076C, 3077A, 3092A, 3092B, 3093A, 3094A	310–315, 306.00, 306.10, 306.30, 306.60, 306.70, 308.99

Note: ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ICD = International Classification of Diseases; *OCD = obsessive-compulsive disorder.*

TABLE S2 Unadjusted Associations Among Potential Confounding Factors: Maternal Age, Paternal Age, Parental Immigration Status, Maternal Socioeconomic Status (SES), and Tourette Syndrome/Chronic Tic Disorder

	Cases	Controls	Unadjusted Analyses	
Characteristic	**n (%)**	**n (%)**	**OR (95% CI)**	***p***
Maternal age				
<Median	581 (51.9)	1,985 (46.2)	1.2 (1.1–1.4)	.001
≥Median	539 (48.1)	2,314 (53.8)	1.0	
Paternal age				
<Median	542 (49.5)	1,935 (45.4)	1.2 (1.0–1.3)	.017
≥Median	553 (50.5)	2,323 (54.6)	1.0	
Parental immigration status				
Yes	45 (4.0)	133 (3.1)	1.3 (0.9–1.9)	.122
No	1,075 (96.0)	4,166 (96.9)	1.0	
Maternal SES				
Upper white collar	151 (13.5)	618 (14.4)	1.0	
Lower white collar	454 (40.5)	1,916 (44.6)	1.0 (0.8–1.2)	.776
Blue collar	237 (21.2)	742 (17.3)	1.3 (1.03–1.6)	.028
Others	184 (16.4)	689 (16.0)	1.1 (0.9–1.4)	.478
Missing	94 (8.4)	334 (7.8)	1.1 (0.9–1.5)	.357
Maternal co-occurring OCD/ADHD/tic disorder				
Yes	13 (1.2)	5 (0.1)	10.2 (3.7–28.7)	<.001
No	1,107 (98.8)	4,294 (99.9)	1.0	
Paternal co-occurring OCD/ADHD/tic disorder				
Yes	15 (1.4)	10 (0.2)	5.7 (2.5–12.6)	<.001
No	1,080 (98.6)	4,248 (99.8)	1.0	

Note: ADHD = attention-deficit/hyperactivity disorder; OCD = obsessive-compulsive disorder; OR = odds ratio.

TABLE S3 Associations Among Any Maternal and Any Paternal Psychiatric Disorders When Cases Are Stratified by Sex

	Cases	Controls	Final Model[a]	
	n (%)	**n (%)**	**OR (95% CI)**	***p***
Any maternal psychiatric history				
Females				
Yes	51 (25.3)	98 (12.7)	2.2 (1.5-3.3)	<.001
No	151 (74.8)	677 (87.4)		
Males				
Yes	228 (24.8)	418 (11.9)	2.3 (1.9-2.8)	<.001
No	690 (75.2)	3,106 (88.1)		
Any paternal psychiatric disorder				
Females				
Yes	34 (17.3)	91 (11.9)	1.3 (0.8-2.1)	.253
No	163 (82.7)	673 (88.1)		
Males				
Yes	162 (18.0)	459 (13.1)	1.2 (0.97-1.5)	.089
No	736 (82.0)	3,035 (86.9)		

Note: OR = odds ratio.

[a]*Final model including maternal/paternal psychiatric disorders, maternal age, paternal age, maternal socioeconomic status and maternal/paternal co-occurring obsessive-compulsive disorder/attention-deficit/hyperactivity disorder/tic disorder and parity.*

TABLE S4 Associations Among Maternal Psychiatric Diagnoses and Tourette Syndrome/Chronic Tic Disorder, When Parents With Comorbid Alcohol and Drug Addiction Are Excluded

	Cases (n = 1,077)	Controls (n = 4,065)	Unadjusted Analyses		Final Model[a]	
Maternal Psychiatric History	**n (%)**	**n (%)**	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Schizophrenia and other psychosis	27 (2.5)	37 (0.9)	2.8 (1.7–4.6)	<.001	2.2 (1.3–3.8)	.004
Affective disorders	123 (11.4)	208 (5.1)	2.4 (1.9–3.0)	<.001	2.3 (1.8–2.9)	<.001
OCD	5 (0.5)	0 (0.0)	NA	NA	NA[b]	NA
Anxiety disorders	68 (6.3)	101 (2.5)	2.6 (1.9–3.6)	<.001	2.4 (1.7–3.4)	<.001
Personality disorders	20 (1.9)	30 (0.7)	2.6 (1.5–4.6)	.011	2.5 (1.4–4.6)	.002
Other nonpsychotic disorders	82 (7.6)	169 (4.2)	1.9 (1.5–2.6)	<.001	1.9 (1.4–2.5)	<.001

Note: OCD = obsessive-compulsive disorder; OR = odds ratio.

[a]*Final model including paternal psychiatric disorders, maternal age, paternal age, maternal socioeconomic status (SES) and maternal/paternal co-occurring, OCD/attention-deficit/hyperactivity disorder/tic disorder and parity.*

[b]*Final model including paternal psychiatric disorders, maternal age, paternal age, maternal SES, and parity.*

TABLE S5 Associations Among Any Maternal or Paternal Psychiatric Diagnoses (When Other Parent Has Not Been Diagnosed) and Both Maternal and Paternal Psychiatric Diagnoses and Tourette Syndrome/Chronic Tic Disorder in Unadjusted Analyses

	Cases	Controls	Unadjusted Analyses	
Parental Psychiatric Diagnoses	**n (%)**	**n (%)**	**OR (95% CI)**	***p***
No parental psychiatric diagnoses	711 (64.9)	3,323 (78.0)		
Maternal diagnosis (no paternal diagnosis)	188 (17.2)	385 (9.0)	2.2 (1.8–2.7)	<.001
Paternal diagnosis (no maternal diagnosis)	119 (10.9)	428 (10.1)	1.3 (1.02–1.6)	.032
Both maternal and paternal diagnoses	77 (7.0)	122 (2.9)	2.9 (2.2–3.9)	<.001

Note: OR = odds ratio.

TABLE S6 Associations Between Parental Childhood-Onset Disorders and Tourette Syndrome/Chronic Tic Disorder

	Cases	Controls	Unadjusted Analyses	
	n (%)	**n (%)**	**OR (95% CI)**	***p***
Parental childhood-onset disorder	42 (3.8)	62 (1.5)	2.7 (1.8–4.1)	<.001
Tic disorder	10 (0.9)	2 (0.1)	20 (4.4–91.3)	<.001
ADHD	8 (0.7)	9 (0.2)	3.4 (1.3–8.9)	.011
ASD	3 (0.3)	0 (0.0)	NA	NA
Other developmental/childhood-onset disorder	23 (2.1)	50 (1.2)	1.8 (1.1–3.1)	.017

Note: ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; NA = not available; OR = odds ratio.