

Original Investigation

Familial Clustering of Tic Disorders and Obsessive-Compulsive Disorder

Heidi A. Browne, BSc; Stefan N. Hansen, MSc; Joseph D. Buxbaum, PhD; Shannon L. Gair, BA; Judith B. Nissen, MD, PhD; Kathrine H. Nikolajsen, MD; Diana E. Schendel, PhD; Abraham Reichenberg, PhD; Erik T. Parner, PhD; Dorothy E. Grice, MD

IMPORTANCE Tourette syndrome/chronic tic disorder (TS/CT) and obsessive-compulsive disorder (OCD) overlap in their phenomenological features and often co-occur in affected individuals and families. Understanding how these disorders cluster in families provides important clinical information and is an important step in understanding the causes of these disorders.

OBJECTIVE To determine familial recurrence for TS/CT and OCD using a national epidemiologic sample.

DESIGN, SETTING, AND PARTICIPANTS We performed a population-based study of national health registries in Denmark, including all individuals (n = 1 741 271) born in Denmark from January 1, 1980, through December 31, 2007, and followed up through December 31, 2013. We identified those with TS/CT and/or OCD.

MAIN OUTCOMES AND MEASURES The prevalence of TS/CT and OCD and relative recurrence risk (RRR) for TS/CT or OCD among individuals with an oldest sibling or a parent diagnosed as having TS/CT or OCD compared with individuals without an affected oldest sibling or an affected parent.

RESULTS In this sample, 5596 individuals were diagnosed as having TS/CT; 6191, OCD; and 412, both disorders. The overall cohort prevalence of TS/CT was 0.42% (95% CI, 0.41%-0.43%) and of OCD, 0.84% (95% CI, 0.81%-0.87%). The mean sibling recurrence risk for TS/CT across all birth years was 9.88% (95% CI, 8.02%-12.16%) and for OCD, 4.01% (95% CI, 2.78%-5.76%). The sibling RRR for TS/CT was 18.63 (95% CI, 15.34-22.63). In contrast, the sibling RRR for OCD was 4.89 (95% CI, 3.45-6.93). The parent-offspring RRR for TS/CT was 61.02 (95% CI, 44.43-83.82), whereas the parent-offspring RRR for OCD was 6.25 (95% CI, 4.82-8.11). The sibling and parent-offspring cross-disorder risks were also significant, ranging from 3.20 (95% CI, 2.22-4.62) to 10.27 (95% CI, 5.17-20.39).

CONCLUSIONS AND RELEVANCE Tourette syndrome/CT and OCD cluster in families. The familial aggregation of TS/CT is profound and substantially higher than the familial aggregation for OCD. The recurrence risk estimates provide an important clinical framework for identifying individuals at risk and provide insights into the causes of these disorders.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Dorothy E. Grice, MD, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1230, New York, NY 10029 (dorothy.grice@mssm.edu).

Tourette syndrome (TS) is a childhood-onset, neuropsychiatric disorder defined by multiple waxing and waning motor and phonic tics. A related diagnosis, chronic tic disorder (CT), is characterized by persistent motor or phonic tics.^{1,2} The prevalence of TS and CT is estimated at 0.3% to 1.0% each,^{3,4} with evidence of increasing prevalence in recent years.⁵

Obsessive-compulsive disorder (OCD) is defined by recurrent intrusive thoughts or images (obsessions) that create significant distress and drive individuals to perform repetitive behaviors or mental rituals (compulsions) in an attempt to reduce the distress. Unlike TS/CT, in which symptoms often diminish by young adulthood, OCD is typically more chronic in nature. However, like TS/CT, OCD symptoms may wax and wane over time and are responsive to environmental triggers and modifications.⁶ The prevalence of OCD is estimated at 0.7% to 3.0%.^{7,8}

Tourette syndrome/CT and OCD overlap in their phenomenological features, often cluster in families, and co-occur in affected individuals, the latter observation leading to the tic-related OCD subtype in the *DSM-5*.⁹ Approximately 25% to 50% of those with TS/CT meet criteria for OCD, whereas as many as 80% may exhibit obsessive-compulsive behaviors.¹⁰⁻¹⁵ Similarly, as many as 30% of individuals with OCD have a history of co-occurring TS/CT.¹⁶⁻²⁰ Converging evidence from animal studies and neuroimaging studies suggests that dysfunction in cortical basal ganglia circuitry mediates tics and compulsive behaviors, supporting a role for shared biological vulnerability.²¹⁻²⁴

The clustering of TS/CT and OCD in families supports a significant genetic contribution to these disorders and a shared genetic architecture. Twin studies reveal that both disorders have higher concordance in monozygotic than in dizygotic twins,²⁵⁻³⁰ and twin and family studies estimate a heritability of 30% to 60% for each disorder.^{29,31-34} These reports are supported by a recent study considering inherited common genetic variation³⁵ that estimated heritability at 58% for TS and 37% for OCD. Estimates of recurrence risk in first-degree relatives of probands with TS/CT range from 9% to 44% for TS/CT and from 7% to 31% for OCD.^{33,36-41} For first-degree relatives of probands with OCD, these estimates span 4% to 11% for TS/CT and 10% to 22% for OCD.^{16,42-47} In support of etiological overlap, a recent genome-wide complex trait analysis revealed a significant genetic correlation of 0.41 between TS and OCD.³⁵

To date, most of the studies on recurrence risk use smaller clinic-based and other convenience (non-population-based) samples, rendering them vulnerable to ascertainment bias and lower precision. An approach available in recent years to circumvent these issues is to use national health registries that provide a wealth of data for epidemiologic and etiological analyses. Such registries have been used extensively in epidemiologic analyses of other psychiatric conditions, such as autism.^{5,48-51} Two recent studies^{34,52} used Swedish and Danish registries to study familial risk for OCD and report a similar recurrence risk among first-degree relatives compared with smaller studies. To date, no study has yet examined the familial recurrence risk for TS/CT and OCD using identical methods in a large-scale, population-based sample.

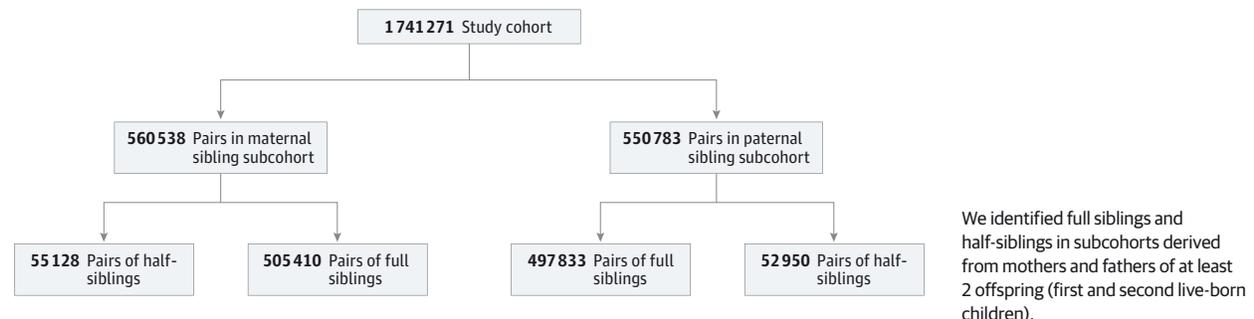
Denmark has more than 200 health and administrative registry systems with individual-level information on all Danish residents collected prospectively for decades, reliably linked with a unique personal identifier. The primary aim of the present study was to use these registries to estimate the recurrence risks for TS/CT and OCD accurately and compare these risks with the prevalence in the population.

Methods

Study Population

This study was approved by the Danish Data Protection Agency, the Danish National Board of Health, and the institutional review board of Icahn School of Medicine at Mount Sinai. Patient data were deidentified. We identified all individuals born from January 1, 1980, through December 31, 2007, in the Danish Medical Birth Registry,⁵³ totaling 1 741 271 individuals, including multiple births. We determined family linkages and information on death from the Danish Civil Registration System.⁵⁴ The resultant population cohort was used to estimate prevalence, recurrence risk, and relative recurrence risk (RRR). Siblings were defined as individuals with the same mother (including full siblings and half-siblings). After excluding multiple births, we identified the following 2 subcohorts for analyses of recurrence risk in full siblings vs half-siblings: (1) a maternal sibling subcohort derived from mothers with at least 2 children consisting of the first and second live-born children in the study period (560 538 sibling pairs) and (2) a paternal sibling subcohort derived in the same man-

Figure 1. Study Cohort



ner from fathers (550 783 sibling pairs) (Figure 1). For subcohort analyses, only first- and second-born children were considered to ensure that half-sibling and full sibling relationships were uniquely defined.

Outcomes

Information on psychiatric diagnoses was obtained by linkage to the Danish Psychiatric Central Register (information on all inpatient admissions to psychiatric hospitals since 1969 and all outpatient admissions since 1995)⁵⁵ and the Danish National Hospital Register (information on all somatic inpatient admissions since 1977 and outpatient and emergency department admissions since 1995).⁵⁶ This approach allows identification of all individuals who had contact with the national health care system and who carried the diagnoses of interest, all made by trained clinicians in the clinical setting.

The *International Classification of Diseases, Eighth Revision (ICD-8)*,⁵⁷ was used in Denmark from 1968 through 1993, and the *International Statistical Classification of Diseases, Tenth Revision (ICD-10)*,⁵⁸ has been used subsequently. From the Danish Psychiatric Central Register and the Danish National Hospital Register, we obtained information on primary and subsidiary diagnoses of TS/CT (ICD-8 code 306.2; ICD-10 codes F95.1 and F95.2) and OCD (ICD-8 code 300.3; ICD-10 codes F42.0, F42.1, and F42.2) for all individuals in the study period. These codes capture individuals diagnosed as having TS or CT (but not transient tic disorder) and/or OCD with predominant obsessions and/or compulsions as per ICD criteria. For parents of these individuals, we collected information on any psychiatric diagnosis at any time (ICD-8 codes 290-315; ICD-10 codes F00-F99). Follow-up began at birth (January 1, 1980, through December 31, 2007) and continued until the diagnosis of TS/CT or OCD, death, or the end of follow-up (December 31, 2013), whichever occurred first. Because most individuals had multiple clinical visits during the study period, fewer than 1% of those diagnosed as having TS/CT or OCD had only an ICD-8 diagnosis.

Statistical Analysis

The population cohort was divided into the following groups by birth year to assess time trends in TS/CT and OCD prevalence: 1980 through 1984, 1985 through 1989, 1990 through 1991, 1992 through 1993, 1994 through 1995, 1996 through 1997, 1998 through 1999, 2000 through 2001, 2002 through 2003, 2004 through 2005, and 2006 through 2007. We estimated the prevalence of and recurrence risk for TS/CT and OCD using Kaplan-Meier methods. In recurrence risk estimation, each younger sibling became at risk for a recurring diagnosis when the oldest sibling was diagnosed as having TS/CT or OCD (ie, the exposure) or at birth, whichever came last (time-dependent covariate). In addition, offspring underwent assessment for a recurring diagnosis if a parent was diagnosed as having TS/CT or OCD.

For RRR, the hazard ratio (HR) associated with a TS/CT or an OCD diagnosis in the oldest sibling was estimated using a Cox proportional hazards regression model with separate diagnostic baseline rates for each birth-year group to adjust for changes in TS/CT and OCD prevalence over time. Given that

TS/CT and OCD are rare disorders (<10% prevalence) and because the group consisting of individuals with a parent or an oldest sibling who did not receive a diagnosis is representative of the background population, we interpreted the estimated adjusted HR as the RRR.⁵⁹ The Cox proportional hazards regression assumption was evaluated for all variables by inspecting estimated log-minus-log survivor curves for the different categories of variables investigated. Control for the lack of independence of individuals within the same family was obtained using a robust (Huber-White sandwich) variance estimator.⁶⁰

Crude and adjusted RRRs were estimated for siblings, with adjustment for parity (grouped as 1, 2, and ≥ 3), sex of the individual, parental age at birth (<35, 35-39, and ≥ 40 years), and parental psychiatric history with the exclusion of TS/CT and OCD (≥ 1 diagnosis before the birth of the child). Parity was calculated from the Danish Civil Registration System, whereas the sex of the individual and the parental age at the individual's birth were derived from the unique identification number. We also estimated the crude and adjusted RRRs for TS/CT and OCD in full siblings and half-siblings in the maternal and paternal subcohorts. In scenarios with less than 5 recurrent cases, the estimation was not performed. For parent-offspring RRRs, covariates included sex, parental age, and parity.

Results

The distribution of variables included in the crude and adjusted analyses for individuals with or without an oldest sibling with TS/CT or OCD are summarized in Table 1. Within the cohort, 5596 individuals were diagnosed as having TS/CT and 6191 individuals were diagnosed as having OCD. A total of 412 individuals were diagnosed as having both disorders.

Table 1 in the Supplement lists the number of births, TS/CT and OCD cases, prevalence, recurrent cases, sibling recurrence risks, and cross-disorder recurrence risks. Overall cohort prevalence of TS/CT was 0.42% (95% CI, 0.41%-0.43%), with 121 recurrent TS/CT cases (ie, cases of TS/CT among individuals whose oldest sibling had TS/CT). Overall cohort prevalence of OCD was 0.84% (95% CI, 0.81%-0.87%), with 34 recurrent OCD cases (ie, cases of OCD among individuals whose oldest sibling had OCD). Mean sibling recurrence risk for TS/CT across all birth years was 9.88% (95% CI, 8.02%-12.16%) and for OCD, 4.01% (95% CI, 2.78%-5.76%).

To adjust for the prevalence of TS/CT and OCD in the study cohort, we calculated the sibling RRR (Table 2). Individuals whose oldest sibling was diagnosed as having TS/CT were more than 18 times more likely to be diagnosed as having TS/CT when compared with individuals without an affected oldest sibling (RRR, 18.63 [95% CI, 15.34-22.63]). In contrast, individuals whose oldest sibling was diagnosed as having OCD were almost 5 times more likely to be diagnosed as having OCD (RRR, 4.89 [95% CI, 3.45-6.93]) (Figure 2). In TS/CT, but not in OCD, we found marginal evidence for decreasing sibling RRR over time ($P = .05$); however, the CIs were large, rendering interpretation of these data difficult (eFigure in the Supplement).

Table 1. Distribution of Variables in Individuals With or Without an Oldest Sibling With TS/CT or OCD^a

Variable	TS/CT in Oldest Sibling, No. (%)		OCD in Oldest Sibling, No. (%)	
	Yes (n = 2642)	No (n = 1 738 629)	Yes (n = 3279)	No (n = 1 737 992)
TS/CT				
Yes	121 (4.58)	5475 (0.31)	37 (1.13)	5559 (0.32)
No	2521 (95.42)	1 733 154 (99.69)	3242 (98.87)	1 732 433 (99.68)
OCD				
Yes	22 (0.83)	6169 (0.35)	34 (1.04)	6157 (0.35)
No	2620 (99.17)	1 732 460 (99.65)	3245 (98.96)	1 731 835 (99.65)
Sex				
Male	1357 (51.36)	892 273 (51.32)	1651 (50.35)	891 979 (51.32)
Female	1285 (48.64)	846 356 (48.68)	1628 (49.65)	846 013 (48.68)
Parity^b				
1	0	777 557 (44.72)	0	777 557 (44.74)
2	1989 (75.28)	647 373 (37.23)	2243 (68.41)	647 119 (37.23)
≥3	653 (24.72)	313 699 (18.04)	1036 (31.59)	313 316 (18.03)
Maternal age at birth, y				
<35	2200 (83.27)	1 530 874 (88.05)	2663 (81.21)	1 530 411 (88.06)
35-39	387 (14.65)	180 156 (10.36)	534 (16.29)	180 009 (10.36)
≥40	55 (2.08)	27 599 (1.59)	82 (2.50)	27 572 (1.59)
Paternal age at birth, y				
<35	1730 (65.48)	1 276 867 (73.44)	2102 (64.10)	1 276 495 (73.45)
35-39	621 (23.50)	303 165 (17.44)	804 (24.52)	302 982 (17.43)
≥40	271 (10.26)	142 749 (8.21)	362 (11.04)	142 658 (8.21)
Missing	20 (0.76)	15 848 (0.91)	11 (0.34)	15 857 (0.91)
Maternal history of TS/CT				
Yes	2 (0.08)	41 (0.002)	0	43 (0.002)
No	2640 (99.92)	1 738 588 (100.00)	3279 (100)	1 737 949 (100.00)
Paternal history of TS/CT				
Yes	3 (0.11)	91 (0.01)	0	94 (0.01)
No	2639 (99.89)	1 738 538 (99.99)	3279 (100)	1 737 898 (99.99)
Maternal history of OCD				
Yes	4 (0.15)	659 (0.04)	5 (0.15)	658 (0.04)
No	2638 (99.85)	1 737 970 (99.96)	3274 (99.85)	1 737 334 (99.96)
Paternal history of OCD				
Yes	1 (0.04)	347 (0.02)	4 (0.12)	344 (0.02)
No	2641 (99.96)	1 738 282 (99.98)	3275 (99.88)	1 737 648 (99.98)
Maternal psychiatric history^c				
Yes	204 (7.72)	54 979 (3.16)	173 (5.28)	55 010 (3.17)
No	2438 (92.28)	1 683 650 (96.84)	3106 (94.72)	1 682 982 (96.83)
Paternal psychiatric history^c				
Yes	126 (4.77)	42 599 (2.45)	105 (3.20)	42 620 (2.45)
No	2516 (95.23)	1 696 030 (97.55)	3174 (96.80)	1 695 372 (97.55)

Abbreviations: CT, chronic tic disorder; OCD, obsessive-compulsive disorder; TS, Tourette syndrome.

^a Tourette syndrome/CT and OCD are diagnosed by trained clinicians (pediatric and adult psychiatrists, pediatric and adult neurologists, and pediatricians) according to *International Classification of Diseases, Eighth Revision* and/or *International Statistical Classification of Diseases, Tenth Revision* criteria. Percentages have been rounded and may not total 100.

^b All case samples are by definition parity 2 or greater; the control group (ie, those not having an oldest sibling with TS/CT or OCD) includes individuals who are born first.

^c Defined as at least 1 psychiatric diagnosis (excluding TS/CT or OCD) before the birth of the child.

We observed significant cross-disorder risk (Table 2 and Figure 2). Tourette syndrome/CT in the oldest sibling was associated with an RRR for OCD of 3.98 (95% CI, 2.58-6.12); OCD in the oldest sibling was associated with an RRR for TS/CT of 4.88 (95% CI, 3.15-7.56). For individuals with TS/CT when the oldest sibling had OCD, 27.0% of these oldest siblings were diagnosed as having TS/CT and OCD. Similarly, for individuals with OCD whose oldest sibling had TS/CT, 18.2% of oldest siblings had both diagnoses. When we excluded oldest siblings with a dual diagnosis, the cross-disorder RRR was only slightly lower and remained significant at 3.67 (95% CI,

2.28-5.91) for OCD when the oldest sibling had TS/CT and 3.35 (95% CI, 1.94-5.78) for TS/CT when the oldest sibling had OCD. Impressively, a diagnosis of both disorders in an oldest sibling was associated with an RRR of 26.37 (95% CI, 13.17-52.81) for TS/CT and 10.90 (95% CI, 4.09-29.08) for OCD (Table 2).

We observed similar RRRs for full siblings from the maternal and paternal cohorts (TS/CT, 21.83 in the maternal subcohort and 21.20 in the paternal subcohort; OCD, 5.62 in the maternal subcohort and 5.75 in the paternal subcohort). For TS/CT, we observed a lower RRR in half-siblings compared with

Table 2. Sibling and Cross-Disorder RRRs for TS/CT and OCD

Variable	TS/CT in Oldest Sibling		OCD in Oldest Sibling		TS/CT and OCD in Oldest Sibling ^a	
	RRR (95% CI)	P Value ^b	RRR (95% CI)	P Value ^b	RRR (95% CI)	P Value ^b
TS/CT						
Study cohort crude	17.59 (14.56-21.24)	<.001	4.61 (3.01-7.06)	<.001	22.95 (11.47-45.92)	<.001
Study cohort adjusted ^c	18.63 (15.34-22.63)	<.001	4.88 (3.15-7.56)	<.001	26.37 (13.17-52.81)	<.001
OCD						
Study cohort crude	3.86 (2.51-5.93)	<.001	4.77 (3.37-6.74)	<.001	10.69 (4.01-28.49)	<.001
Study cohort adjusted ^c	3.98 (2.58-6.12)	<.001	4.89 (3.45-6.93)	<.001	10.90 (4.09-29.08)	<.001

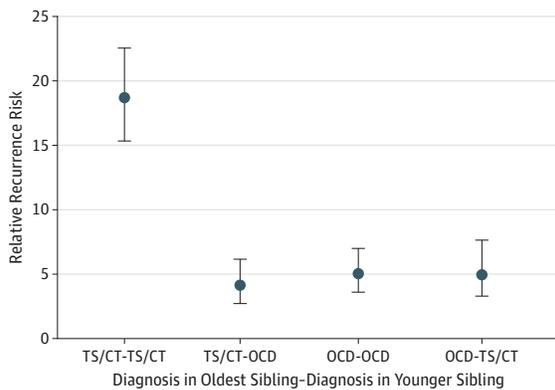
Abbreviations: CT, chronic tic disorder; OCD, obsessive-compulsive disorder; RRR, relative recurrence risk; TS, Tourette syndrome.

^a All oldest siblings in this group were diagnosed as having TS/CT and OCD.

^b Calculated using the test for no RRR.

^c Adjusted for sex, parental age, parental psychiatric history, and parity. Parental psychiatric history was defined as at least 1 psychiatric diagnosis (excluding TS/CT and OCD) before the birth of the child.

Figure 2. Adjusted Sibling Relative Recurrence Risk (RRR) and Cross-Disorder Risk for Tourette Syndrome/Chronic Tic Disorder (TS/CT) and Obsessive-Compulsive Disorder (OCD)

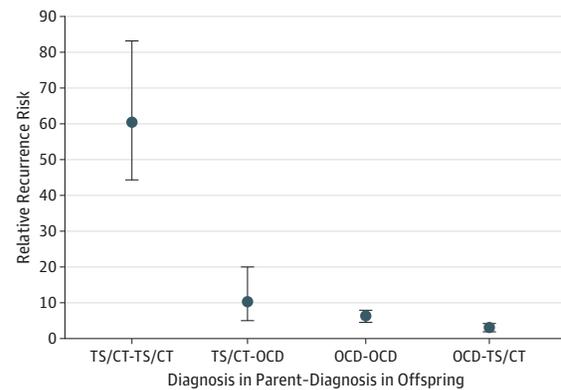


Data points represent mean RRR (whiskers, 95% CIs) for TS/CT in individuals with an oldest sibling with TS/CT (TS/CT-TS/CT); for OCD in individuals with an oldest sibling with TS/CT (TS/CT-OCD); for OCD in individuals with an oldest sibling with OCD (OCD-OCD); and for TS/CT in individuals with an oldest sibling with OCD (OCD-TS/CT).

full siblings, which was similar in the paternal (6.60) and maternal (6.73) cohorts (eTable 2 in the Supplement). The small number of recurrent cases prevented confident estimation of the recurrence risk for OCD in half-siblings.

Parent-offspring recurrence risk for TS/CT was 19.00% (95% CI, 14.09%-25.34%) and parent-offspring recurrence risk for OCD, 4.06% (95% CI, 2.85%-5.78%). In terms of RRR, individuals whose parent had TS/CT were 61 times more likely to be diagnosed as having TS/CT compared with individuals without a parent with TS/CT (adjusted HR, 61.02 [95% CI, 44.43-83.82]), whereas OCD in a parent was associated with an adjusted HR for OCD in the offspring of 6.25 (95% CI, 4.82-8.11). Tourette syndrome/CT diagnosed in a parent (25.0% of whom also had OCD) was associated with an adjusted HR of 10.27 (95% CI, 5.17-20.39) for OCD in offspring. Obsessive-compulsive disorder diagnosed in a parent (54.5% of whom also had TS/CT) was associated with an adjusted HR of 3.20 (95% CI, 2.22-4.62) for TS/CT in offspring (Figure 3 and eTable 3 in the Supplement).

Figure 3. Adjusted Parent-Offspring Relative Recurrence Risk (RRR) and Cross-Disorder Risk for Tourette Syndrome/Chronic Tic Disorder (TS/CT) and Obsessive-Compulsive Disorder (OCD)



Data points represent mean RRR (whiskers, 95% CIs) for TS/CT in the offspring of a parent with TS/CT (TS/CT-TS/CT); for OCD in the offspring of a parent with TS/CT (TS/CT-OCD); for OCD in the offspring of a parent with OCD (OCD-OCD); and for TS/CT in the offspring of a parent with OCD (OCD-TS/CT).

Discussion

In this population-based study of familial risk for TS/CT and OCD, the risks were significantly higher for individuals with an affected oldest sibling than the risks in the general population, and the RRR for TS/CT was substantially higher than that for OCD. In the adjusted analyses, compared with those without a diagnosed oldest sibling, individuals with an oldest sibling with TS/CT were more than 18 times more likely to have a diagnosis of TS/CT. Individuals with an oldest sibling with OCD, by contrast, were about 5 times more likely to have a diagnosis of OCD than individuals without an affected oldest sibling. Cross-disorder RRR was nearly as high as the OCD RRR. Although we found a tendency toward a decreased RRR for TS/CT over time, this result is difficult to interpret because the variance was very high. The RRR for OCD did not change significantly during the study period, which supports a stable contribution of risk architecture (genetic and environmental) for almost 3

decades. Notably, in the case of parent-offspring risk, the RRR for TS/CT was particularly high at 61.02, and the RRR for OCD was also substantial (6.25), as was the cross-disorder RRR.

We found a sibling recurrence risk for TS/CT of 9.88% compared with the overall cohort prevalence of 0.42%. Sibling recurrence risk for OCD was 4.01% compared with the cohort prevalence of 0.84%. The estimates for TS/CT and OCD recurrence in siblings were at the lower end of the range of previously published studies of recurrence risk for first-degree family members. However, the results presented here are not directly comparable to those of previous studies because we defined specific pairs of first-degree relatives, rather than combining all first-degree relatives, as a means of better delimiting exposures. In addition, we ascertained for OCD, although some prior studies included individuals with OCD and/or sub-clinical obsessive-compulsive symptoms. Unlike some previous studies, we grouped TS and CT; however, in exploratory analyses using TS only, our results were similar. A recent report⁶¹ (also using Danish national registries) found a lower recurrence risk for autism spectrum disorders compared with prior smaller-scale studies. One confound to recurrence risk estimates may be improved recognition and the seeking of health care after a family member receives a diagnosis. This bias likely plays a greater role in smaller studies, especially those derived from convenience samples.

Our cohort prevalence for TS/CT and OCD was on the low end of previous estimates. Although this finding may represent increased accuracy in a large study such as ours with minimal ascertainment bias, health-based registries, from which diagnostic status was derived, may not be fully inclusive of all affected individuals if they are not seeking health care. This possibility might affect the interpretation of our recurrence risk estimates. Although the hypothesis that less severely affected cases may not be represented in our cohort is reasonable, thus affecting the absolute prevalence calculations, the Danish national health care system is structured to provide specialized psychiatric care to all citizens at no cost. This system leads to broad inclusion while minimizing other common sources of bias (eg, overascertainment of multiply affected families in convenience samples). Our relative risk calculations adjust for possible incomplete ascertainment. In our cohort, a smaller percentage of individuals with TS/CT had comorbid OCD (and vice versa) compared with prior studies; part of this difference may be accounted for by the fact that many previous studies assessing comorbidity have used specialty clinic-based populations, whereas our population comes from a wide range of clinical settings. An additional limitation to note is that, to date, no studies have validated the TS/CT and OCD registry diagnoses, although the validity for autism has been shown to be 94% in the Danish registries.⁶²

The RRR reflects contributions from genetics and shared environmental factors. A fundamental genetic distinction between full siblings and half-siblings is the proportion of shared

genes, with half-siblings sharing about half as many genes as full siblings. The significantly higher RRR for TS/CT in full siblings compared with maternal and paternal half-siblings thus supports a genetic contribution to TS/CT.

Consideration of parental psychiatric history as a potential confounder in sibling recurrence risk analyses is important. A parental psychiatric diagnosis could precede the birth of the oldest child, could be a consequence of a difficult diagnosis in an older sibling, or could occur independently of these factors. In all of our adjusted analyses, changing the definition of parental psychiatric history from diagnosis at the birth of the child to diagnosis before the birth of the oldest child did not change the risk estimates markedly, nor did exclusion of all multiple births.

Childhood-onset OCD has been suggested to be more familial than adult-onset OCD.⁶³ In exploratory analyses, we found no difference in the sibling RRR for childhood-onset OCD (onset before 15 years of age) compared with adult-onset OCD, although our data may be underpowered to detect such a difference. In addition, families with bilineal inheritance may exhibit a particularly high recurrence risk for TS/CT⁶⁴; unfortunately, in our sample too few individuals had 2 affected parents (with TS/CT and/or OCD) to estimate RRR with bilineal inheritance.

In the present study, we used identical ascertainment methods and thus could compare prevalence, recurrence risk, and RRR for TS/CT and OCD. Absolute risk and RRR were higher for TS/CT than for OCD in this study, whereas cross-disorder recurrence risk was similar in magnitude as the recurrence risk for OCD itself. Similar to analyses of bipolar disorder and schizophrenia,⁶⁵ cross-disorder recurrence risk remained significant when excluding individuals with dual diagnoses.

Conclusions

Using a large, population-based national sample with adjustments for several important confounders, our results indicate that TS/CT and OCD have high recurrence risk in siblings and in children of affected parents. Recurrence risk for TS/CT is particularly profound and substantially higher than that for OCD. Cross-disorder recurrence risk is also significant. Lower recurrence risk among half-siblings compared with full siblings supports a genetic contribution to TS/CT. The 9.88% sibling recurrence risk for TS/CT and the 4.01% sibling recurrence risk for OCD along with the 19.00% parent-offspring recurrence risk for TS/CT and the 4.06% parent-offspring recurrence risk for OCD provide an important clinical framework for identifying individuals at risk and provide insights into the causes of these disorders. In future studies in the Danish national registries, we can examine specific environmental risk factors to further elaborate the risk architecture of TS/CT and OCD.

ARTICLE INFORMATION

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Author Affiliations: Division of Tics, OCD, and Related Disorders, Icahn School of Medicine at

Mount Sinai, New York, New York (Browne, Gair, Grice); Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York (Browne, Buxbaum, Gair, Reichenberg, Grice);

Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York (Browne, Buxbaum, Gair, Grice); Department of Public Health, Section for Biostatistics, Aarhus University, Aarhus, Denmark (Hansen, Parner); Seaver Autism Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum, Reichenberg); Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum); Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum); Mindich Child Health and Development Institute, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum, Reichenberg, Grice); Children and Adolescent Psychiatric Center, Aarhus University Hospital, Aarhus, Denmark (Nissen, Nikolajsen); Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark (Schendel); Department of Economics and Business and National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark (Schendel); Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark (Schendel); Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, New York (Reichenberg); Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York, New York (Reichenberg).

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Study concept and design: Hansen, Schendel, Reichenberg, Parner, Grice.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Browne, Buxbaum, Reichenberg, Parner, Grice.

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