ABSTRACT: Background: Insomnia is common in Tourette syndrome (TS) and chronic tic disorder (CTD), but precise prevalence estimates are lacking.

Objective: In this Swedish register-based cohort study, we estimated the prevalence of insomnia in TS/CTD and quantified the magnitude of this association, accounting for familial confounders and relevant somatic and psychiatric comorbidities.

Methods: Of 10,444,702 individuals living in Sweden during the period from 1997 to 2013, 5877 had a diagnosis of TS/CTD and were compared to unexposed individuals from the general population on the presence of insomnia using logistic regression models.

Results: Individuals with TS/CTD had a period prevalence of insomnia of 32.16%, compared to 13.70% of the unexposed population. This translated into a 6.7-fold increased likelihood of insomnia in TS/CTD (odds ratio adjusted [aOR] for sex, birth year, birth country, and somatic disorders = 6.74; 95% confidence interval [CI], 6.37–7.15). A full sibling comparison, designed to adjust for shared familial factors, attenuated the estimates (aOR = 5.41; 95% CI, 4.65–6.30). When individuals with attention-deficit/hyperactivity disorder (ADHD) and pervasive developmental disorders were excluded, the association was also attenuated, whereas exclusion of other psychiatric comorbidities had minimal impact. Having persistent TS/CTD, comorbid ADHD, and taking ADHD medication greatly increased the likelihood of insomnia.

Conclusions: Insomnia is significantly associated with TS/CTD, independently from somatic disorders, familial factors or psychiatric comorbidities, although familial factors, neurodevelopmental comorbidities, and ADHD/ADHD medication may explain part of the association. Insomnia should be routinely assessed and managed in TS/CTD, particularly in chronic patients and in those with comorbid ADHD. Other sleep disorders require further study. © 2021 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: Tourette syndrome; chronic tic disorder; attention-deficit/hyperactivity disorder; insomnia; sleep problems

Sleep difficulties are common in individuals with Tourette syndrome (TS) or chronic tic disorder (CTD), with studies reporting an extremely wide prevalence range (from 7% to 80%) of a broad variety of sleep-related problems. Overall, the most common sleep difficulties in this population are insomnia, excessive daytime sleepiness, disorders of arousal (eg, sleep walking, sleep talking, sleep terrors, and enuresis), persistence of tics during sleep, and presence of periodic limb movements during sleep. Nonetheless, previously published studies have generally been small and control groups have often not been available for comparison. Additionally, the
majority of studies reporting on subjective sleep-related symptoms have used self-reported or parent-reported questionnaires rather than clinician-reported diagnoses. Moreover, many of these questionnaires merge together a wide range of sleep problems. Given that different sleep disorders may have different treatment indications, studying these disorders separately is clinically relevant.

Studies focusing specifically on TS/CTD and insomnia—as a clinical or self-reported diagnosis—have been generally small and generated imprecise prevalence estimates, ranging widely from 0.3% to 77%. The handful of studies that included a control group also reported a higher prevalence of insomnia in those with TS/CTD than in controls. The only exception to this is a Taiwanese population-based study including 1124 children and adolescents newly diagnosed with TS and 3372 matched unexposed controls from the general population, which found no significant differences in the prevalence of insomnia between the groups. However, the analysis was severely underpowered and based on three cases of insomnia in the TS group (0.3%) and seven cases of insomnia in the control group (0.2%). Hence, more precise estimates of the prevalence of insomnia in individuals with TS/CTD are needed. Additionally, whether insomnia is more prevalent in individuals with TS/CTD than in the general population and whether individuals whose tics persist or require clinical attention in adulthood have higher prevalence of insomnia requires further study.

Similarly, the knowledge about the role that psychiatric comorbidities play in the potential association between TS/CTD and insomnia is rather limited. A previous study reported a higher prevalence of primary insomnia in young individuals (age ≤21 years) with TS and comorbid attention-deficit/hyperactivity disorder (ADHD) (n = 48, 42%) than in those with TS only (n = 31, 32%). Moreover, 33% of individuals in the TS +ADHD group presented with insomnia that the authors considered to be secondary to ADHD medication. ADHD has previously been associated to insomnia in its own right, and specifically linked to the side effects of stimulant drugs, which are the first line treatment for ADHD. Similarly, other psychiatric comorbidities, such as depression, anxiety or obsessive-compulsive disorder are known to be associated with both TS/CTD and insomnia. Therefore, the specific contribution of psychiatric comorbidities to the association between TS/CTD and insomnia should be systematically evaluated.

This study aimed to provide more precise estimates of the prevalence of clinically diagnosed insomnia in a large population cohort of individuals with TS/CTD (n = 5877) and to estimate the magnitude of the association between TS/CTD and insomnia in the population. Additional discordant sibling models were used to control for a host of unmeasured familial confounders. We also explored whether TS/CTD chronicity was associated with a higher likelihood of insomnia. The role of psychiatric comorbidities was systematically assessed, with particular emphasis on ADHD and ADHD medication.

### Methods

The study received ethical approval from the Stockholm Regional Ethical Review Board (registration number 2013/862-31/5). Because of the register-based nature of the study and the fact that participants are not identifiable at any time, informed consent was waived.

### Data Sources

In this total population cohort study, a number of nationwide administrative and health registers were linked by means of the personal identification number assigned to all Swedish residents. Included registers were: (1) the Total Population Register, which contains information on all Swedish inhabitants since 1968 and provides demographic data for the cohort members; (2) the Migration Register, which contains records on every immigration into and emigration out of Sweden; (3) the Cause of Death Register, which covers records of all deaths in Sweden since 1952, including date and causes of death, based on International Statistical Classification of Diseases (ICD) codes; (4) the Multi-Generation Register, which connects every person born in Sweden since 1932 or ever registered as living in the country after 1960 to their parents; (5) the National Patient Register (NPR), which contains information on inpatient care (since 1969 for somatic disorders and since 1973 for psychiatric disorders) and outpatient specialist services (since 2001), with diagnoses based on ICD codes (ICD-8: 1969–1986, ICD-9: 1987–1996, and ICD-10: 1997 and onward); and (6) the Prescribed Drug Register, which records all prescribed medications dispensed across pharmacies in Sweden since July 2005, using Anatomical Therapeutic Chemical (ATC) Classification System codes.

### Study Cohort

We identified all individuals aged 3 or older living in Sweden anytime during the period ranging from January 1, 1997 (implementation of the ICD-10 codes in Sweden) to December 31, 2013 (end of the study period). Those that emigrated from the country during the study period and did not return were excluded from the cohort. Those with a diagnosis of organic brain disorder (ICD-8: 290, 292, 293, and 294, except 294.3; ICD-9: 290, 293, 294; ICD-10: F00-09) and/or epilepsy (ICD-8: 345; ICD-9: 345; ICD-10: G40, G41) registered in the NPR during the study period were also excluded. Individuals in the cohort were divided into TS/CTD-exposed and non-exposed. Further, the full siblings (ie, those sharing the same mother and father) of TS/CTD-exposed individuals were identified from

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the Multi-Generation Register to control for shared familial confounders.

**Exposure**

We defined the exposure as having a diagnosis of TS or CTD recorded at any time from January 1, 1973 (beginning of the registration of psychiatric disorders in the NPR) until the end of the study period, if diagnosed at the age of 3 years or older, as per prior research on these disorders.23-25 TS/CTD cases were selected on the basis of an algorithm26 that includes all cases with at least one diagnosis of tic disorder in ICD-8 (306.2) or ICD-9 (307C), and all cases in ICD-10 with at least one diagnosis of CTD (F95.1) or TS (F95.2), unless a diagnosis of transient tic disorder (F95.0) was recorded within the same year as the initial diagnosis. The diagnoses of “other tic disorders” (F95.8) and “tic disorders, unspecified” (F95.9) were included if at least one additional tic disorder diagnosis (F95.1, F95.2, F95.8 or F95.9) was also present, unless a final diagnosis of transient tic disorder within the same year had been recorded. This algorithm has been widely used in previous population-based studies using the Swedish registers23-25 and the included Swedish codes for TS/CTD have shown excellent validity, with positive predictive values of 0.86–0.97.26

**Outcomes**

Outcome variables included all registered diagnoses of insomnia (ICD-10 codes: F51.0 or G47.0) in the NPR (from 1997 to 2013). To improve the coverage of insomnia cases, individuals who were dispensed medications that have a specific indication for insomnia in Sweden (ie, zopiclone [ATC code N05CF01], zolpidem [N05CF02], zaleplon [N05CF03], melatonin [N05CH01], nitrazepam [N05CD02], and triazolam [N05CD05]), as registered in the Prescribed Drug Register, from July 1, 2005 (when the register became available) to December 31, 2013 were also identified as having the outcome. This combined method to ascertain insomnia outcomes (ie, ICD codes plus medication with specific insomnia indication) results in better coverage of the outcome because insomnia is often managed in primary care by general practitioners and, therefore, not always captured in the NPR, which only includes specialist physician diagnoses.

**Covariates and Additional Variables**

Covariates included sex, birth year, birth country (Sweden or other), and somatic disorders diagnosed during the study period with a known association with insomnia and known for their immune dysregulation and inflammatory mechanisms,27-30 which in turn are suggested to underlie the neurobiology of TS.31,32 These included asthma, arthropathies, inflammatory bowel disease (including Crohn’s disease and ulcerative colitis), and other inflammatory liver diseases (see Supplementary Table S1 for ICD codes).

Persistence of the TS/CTD diagnosis was defined as those individuals who had at least two recorded diagnoses of TS/CTD after the age of 18 years (as a proxy for tic severity and chronicity of the tic disorder into adulthood); otherwise, TS/CTD were considered as non-persistent.

Psychiatric comorbidities were grouped as follows: (1) pervasive developmental disorders and learning disabilities; (2) ADHD; (3) conduct disorders; (4) phobic, anxiety, and reaction to severe stress and adjustment disorders; (5) obsessive–compulsive disorder; (6) major depressive disorder; (7) persistent mood disorder and unspecified mood disorder; (8) manic episode or bipolar disorder; (9) schizophrenia and other psychotic disorders; (10) substance use disorders; and (11) personality disorders (see Supplementary Table S2 for ICD-10 codes). ICD diagnoses of ADHD were complemented with the identification in the Prescribed Drug Register of all dispensed medications approved in Sweden for the management of ADHD during the study period, including amphetamine (ATC code N06BA01), dexamphetamine (N06BA02), methylphenidate (N06BA04), atomoxetine (N06BA09), and lisdexamphetamine (N06BA12).

**Data Analysis**

The main analysis consisted of a logistic regression model used to compare TS/CTD-exposed individuals with their unexposed counterparts from the general population on the composite insomnia outcome. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). The initial model was adjusted for sex, birth year, and birth country (model 1). In a subsequent step, we additionally adjusted for the above-listed somatic disorders (model 2). These analyses were stratified by sex.

From the full cohort, a sub-cohort of all clusters of full siblings where at least one sibling had a diagnosis of TS/CTD was identified. Fixed-effects logistic regression models were implemented comparing individuals with TS/CTD to their unaffected siblings within families, where each family was considered a stratum. The models followed the same adjustment strategy as the main analysis. Sibling comparisons control for unmeasured familial environmental confounders shared by siblings (eg, parental socioeconomic status, parental education, parental history of somatic and psychiatric disorders, and rearing style) and partially for genetic factors, because full siblings share ~50% of their genes.33

To examine whether tic disorder persistence had an effect on the association with insomnia, the main analysis was repeated in the sub-cohort of those aged 18 or
older where individuals with persistent tics and non-persistent tics were compared with those without a TS/CTD diagnosis.

To explore the role of psychiatric comorbidities on the association between TS/CTD and insomnia, a number of analyses were performed. First, the fully adjusted analysis was repeated excluding different groups of comorbidities from the whole cohort (exposed and unexposed), one disorder group at a time. Second, to specifically investigate the role of ADHD comorbidity, we subdivided the individuals exposed to TS/CTD by their ADHD comorbidity status into two groups ("TS/CTD with ADHD" and "TS/CTD without ADHD") and compared each of them to the general unexposed population by fitting logistic regression models fully-adjusted as in the main analysis. Additionally, we focused on the role of ADHD medication by using the sub-cohort of individuals living in Sweden during the period from July 2005 (start of the Prescribed Drug Register) to December 2013 (end of the study period) and who did not receive a record of insomnia before July 2005. In this sub-cohort, we ran the same fully adjusted models for individuals exposed to TS/CTD with ADHD who were on ADHD medication and individuals exposed to TS/CTD with ADHD who were not on ADHD medication, compared to TS/CTD-unexposed individuals from the general population.

Data management was performed using SAS, version 9.4 (SAS Institute, Cary, NC) and analyses were performed using Stata version 16.0 (StataCorp LLC, College Station, TX). All tests used 2-tailed significance set at P < 0.05 and robust standard errors.

Results

Prevalence of Insomnia and Association between TS/CTD and Insomnia

The study cohort included 10,444,702 individuals, of which 5877 were TS/CTD-exposed. A total of 1890 individuals in the exposed cohort had at least one insomnia diagnosis or had been dispensed a medication to treat insomnia at least once during the study period, corresponding to a period prevalence of 32.16%, compared to 1,429,774 individuals with insomnia in the general population cohort, corresponding to a period prevalence of 13.70%. See Table 1 for further characteristics of the study cohort.

After adjusting for all relevant covariates, this corresponded to 6.7-times higher odds of insomnia in individuals with TS/CTD than in individuals from the general population (fully-adjusted OR [aOR] = 6.74 [95% CI, 6.37–7.15]) (Table 2). In the analyses

| TABLE 1 Demographic characteristics and psychiatric comorbidities in individuals with TS/CTD and in unaffected individuals from the general population |
|-----------------------------------------------|
| **Individuals with TS/CTD (n = 5877)** | **Individuals without TS/CTD (n = 10,438,825)** |
|----------------|----------------|
| **Men** | **Men** |
| 4583 (77.98) | 5,216,814 (49.95) |
| **Year of birth**<sup>a</sup> | | |
| 1949 or earlier | 181 (3.08) | 3,133,142 (30.01) |
| 1950–1959 | 172 (2.93) | 1,175,846 (11.26) |
| 1960–1969 | 342 (5.82) | 1,292,442 (12.38) |
| 1970–1979 | 519 (8.83) | 1,238,878 (11.87) |
| 1980–1989 | 1192 (20.28) | 1,238,165 (11.86) |
| 1990–1999 | 2463 (41.91) | 1,165,107 (11.16) |
| 2000–2010 | 1008 (17.15) | 1,195,245 (11.45) |
| **Country of birth** | | |
| Sweden | 5504 (93.65) | 8,777,535 (84.09) |
| Other countries | 373 (6.35) | 1,661,290 (15.91) |
| **Any psychiatric comorbidity (at least one)**<sup>b</sup> | 4522 (76.94) | 1,010,648 (9.68) |
| Pervasive developmental disorders and learning disabilities | 1595 (27.14) | 45,764 (0.44) |
| Attention-deficit/hyperactivity disorder | 3130 (53.26) | 125,522 (1.20) |
| Conduct disorder | 418 (7.11) | 9914 (0.09) |
| Phobic, anxiety, and reaction to severe stress and adjustment disorders | 1510 (25.69) | 465,671 (4.46) |
| Obsessive–compulsive disorder | 1106 (18.82) | 30,544 (0.29) |
| Major depressive disorder | 1128 (19.19) | 401,148 (3.84) |
| Persistent mood disorder and unspecified mood disorder | 165 (2.81) | 42,745 (0.41) |
| Manic episode or bipolar disorder | 278 (4.73) | 60,099 (0.58) |

(Continues)
stratified by sex, the corresponding ORs for men were higher than the ORs for women (Table 2).

The sibling cohort consisted of all families \( n = 2,656,561 \) with at least two singleton children, of which 3919 included clusters of full siblings discordant for TS/CTD. When comparing individuals with TS/CTD \( n = 3959 \) to their unaffected full siblings \( n = 5859 \), the association between TS/CTD and insomnia remained statistically significant (aOR = 5.41 [95% CI, 4.65–6.30]), but the magnitude of the association was significantly reduced compared to the main analysis (non-overlapping CIs), suggesting that familial factors shared by siblings may explain a small part of the association between TS/CTD and insomnia (Table 2).

### Tic Persistence

In a sub-cohort of 8,847,343 individuals aged 18 and older, a total of 1650 individuals were classed as having persistent TS/CTD and 2264 as having non-persistent TS/CTD. In these groups, 757 (45.88%) and 599 (26.46%), respectively, met our insomnia definition. Individuals with persistent TS/CTD had an aOR of 7.95 (95% CI, 7.19–8.80), which was significantly higher than the corresponding estimates for non-persistent TS/CTD (aOR = 3.63 [95% CI, 3.29–4.00]).

### Role of Psychiatric Comorbidities and ADHD/ADHD Medication

Table 1 shows the distribution of psychiatric comorbidities in the study cohort. When we repeated the main analysis systematically excluding these groups of comorbidities one at a time (Table 3), we observed a slight attenuation in the ORs, compared to the main analysis. The only exceptions to this were the pervasive developmental disorders and learning disabilities group and ADHD. When excluding these groups of comorbidities from the whole cohort, the association between TS/CTD and insomnia remained statistically significant, but the magnitude of the association significantly decreased from an aOR = 6.74 (95% CI, 6.37–7.15) in the main analysis to 5.37 (95% CI, 5.00–5.76), and 3.60 (95% CI, 3.27–3.96), respectively (Table 3).

To focus specifically on the comorbidity with ADHD, we calculated the odds of insomnia in the “TS/CTD with comorbid ADHD” group \( n = 3130 \), of which 1302 [41.60%] had insomnia, compared to the odds

### Table 2

OR and corresponding 95% CIs for insomnia among individuals with TS/CTD, compared to unaffected individuals from the general population and to their unaffected full siblings

| General population comparison | Individuals with TS/CTD \( n = 5877 \) | Individuals without TS/CTD \( n = 10,438,825 \) | OR (95% CI) Model 1* | OR (95% CI) Model 2b |
|------------------------------|--------------------------------|--------------------------------|-------------------|-------------------|
| In insomnia outcomes | | | | |
| All | 1890 (32.16) | 1,429,774 (13.70) | 6.82 (6.44–7.22) | 6.74 (6.37–7.15) |
| Men | 1410 (30.77) | 552,630 (10.60) | 7.23 (6.78–7.71) | 7.23 (6.78–7.72) |
| Women | 480 (37.09) | 877,144 (16.78) | 5.33 (4.74–5.99) | 5.23 (4.65–5.89) |

| Full sibling comparison | Individuals with TS/CTD with unaffected full siblings \( n = 3959 \) | Unaffected full siblings of individuals with TS/CTD \( n = 5859 \) | OR (95% CI) Model 1* | OR (95% CI) Model 2b |
|-------------------------|--------------------------------|--------------------------------|-------------------|-------------------|
| In insomnia outcomes | | | | |
| All | 1218 (30.77) | 665 (11.35) | 5.43 (4.67–6.33) | 5.41 (4.65–6.30) |

*Model 1: adjusted for sex, birth year, and birth country (Sweden or other).

*Model 2: adjusted for sex, birth year, birth country, and somatic disorders, including asthma, arthropathies, inflammatory bowel disease, and other inflammatory liver diseases.

Abbreviations: OR, odds ratio; CI, confidence interval; TS/CTD, Tourette syndrome/chronic tic disorder.
in the general population unexposed to TS/CTD. This translated into an aOR of 11.49 (95% CI, 10.68–12.37). The corresponding calculations for the "TS/CTD without ADHD" group (n = 2747, of which 588 [21.41%] had insomnia), compared to the general population unexposed to TS/CTD, resulted in an aOR of 3.30 (95% CI, 3.00–3.62) (Fig. 1, panel A).

Next, we explored the contribution of ADHD medication to the observed associations in the sub-cohort restricted to individuals living in Sweden between July 2005 and the end of 2013 and who did not have an insomnia outcome before July 2005. Specifically, we estimated the likelihood of having insomnia among individuals with TS/CTD and ADHD who were on ADHD medication (n = 2568, of which 1170 [45.56%] had insomnia) and among those with TS/CTD and ADHD who were not on ADHD medication (n = 545, of which 119 [21.83%] had insomnia), compared to the general population unexposed to TS/CTD (n = 9,721,898, of which 1,421,752 [14.62%] had insomnia). Results showed a significant increase of the likelihood of having insomnia in both subgroups; however, the association was considerably stronger in individuals who were medicated for their ADHD (aOR = 17.33 [95% CI, 15.98–18.80]) than in individuals who were not on ADHD medication (aOR = 5.22 [95% CI, 4.26–6.40]) (Fig. 1, panel B).

**Discussion**

This population cohort study including 5877 individuals with TS/CTD is the largest to date to explore the association between tic disorders and insomnia. Results showed that 32.16% of individuals with TS/CTD had a record of insomnia during the study period. The corresponding period prevalence of insomnia among the individuals unexposed to TS/CTD was 13.70%, which is in line with the prevalence reported for the general population both in Sweden and elsewhere. The latter confirms that our combined outcome definition, including ICD diagnoses and dispensation of

**TABLE 3**  **OR and corresponding 95% CIs for insomnia among individuals with TS/CTD, compared to unaffected individuals from the general population, excluding from the whole cohort one group of psychiatric comorbidities at a time**

| Description                                                                 | OR (95%), adjusted by sex, birth year, birth country, and somatic comorbiditiesa |
|----------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Pervasive developmental disorders and learning disabilities                | 5.37 (5.00–5.76)                                                                |
| Attention–deficit/hyperactivity disorder                                    | 3.60 (3.27–3.96)                                                                |
| Conduct disorder                                                            | 6.32 (5.96–6.71)                                                                |
| Phobic, anxiety, and reaction to severe stress and adjustment disorders     | 6.37 (5.92–6.86)                                                                |
| Obsessive–compulsive disorder                                               | 6.16 (5.76–6.57)                                                                |
| Major depressive disorder                                                   | 6.63 (6.19–7.10)                                                                |
| Persistent mood disorder and unspecified mood disorder                      | 6.71 (6.33–7.12)                                                                |
| Manic episode or bipolar disorder                                           | 6.50 (6.12–6.90)                                                                |
| Schizophrenia and other psychotic disorders                                 | 6.60 (6.21–7.01)                                                                |
| Substance use disorders                                                    | 6.60 (6.19–7.03)                                                                |
| Personality disorders                                                       | 6.67 (6.27–7.08)                                                                |

aSomatic disorders include asthma, arthropathies, inflammatory bowel disease, and other inflammatory liver diseases.

Abbreviations: OR, odds ratio; CI, confidence interval; TS/CTD, Tourette syndrome/chronic tic disorder.

**FIG. 1.** Adjusted odds ratios and corresponding 95% confidence intervals for insomnia among individuals with TS/CTD only and TS/CTD + ADHD (A) and among individuals with TS/CTD only and TS/CTD + ADHD with and without ADHD medication (B). The cohort in panel A corresponds to individuals living in Sweden during the period January 1, 1997 to December 31, 2013, whereas the cohort in panel B corresponds to the period July 1, 2005 (start of the Prescribed Drug Register) to December 31, 2013. ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; TS/CTD, Tourette syndrome/chronic tic disorder.
drugs with specific indication for insomnia, resulted in adequate coverage of the outcome of interest.

Individuals with TS/CTD had 6.7-fold increased odds of insomnia, compared to the unexposed population, which is in line with reports from previous clinical case–control studies. Nonetheless, those studies were much smaller, mostly based on self-reported symptoms, and unable to control for other relevant variables. Our analyses adjusted for a number of somatic conditions with known association with insomnia and TS/CTD, which had not been done before. Our full sibling models produced attenuated estimates, compared to those in the main analysis, indicating that genetic and environmental factors shared by siblings may explain a small part of the association between tic disorders and insomnia. Nonetheless, even after adjusting for familial confounders, the likelihood of insomnia was still over 5-fold higher in the TS/CTD group than in the general population.

Individuals with chronic tics persisting and requiring medical attention beyond childhood (ie, multiple diagnoses of TS/CTD beyond age 18) had a particularly high likelihood of having insomnia. Therefore, clinicians should expect a relatively high prevalence of insomnia in adult patients with TS/CTD and should attempt to manage it to minimize its known negative impact on health.

Analyses exploring the role of major groups of psychiatric disorders suggest that TS/CTD are associated with insomnia in their own right, because the systematic exclusion of different groups of psychiatric disorders did not substantially alter the estimates. This was true for all groups of psychiatric disorders under study except for ADHD and, to a lesser extent, pervasive developmental disorders. Our results indicate that these neurodevelopmental comorbidities contribute to the observed association between tics and insomnia. However, their exclusion did not completely eliminate the association, which still showed an over 3-fold (after exclusion of ADHD cases) and over 5-fold (after exclusion of pervasive developmental disorders) increased likelihood of insomnia among the individuals with TS/CTD, compared to their unexposed counterparts. From a clinical perspective, our results highlight the need to systematically evaluate and manage insomnia in individuals with TS/CTD, particularly if they present with comorbid neurodevelopmental disorders.

Because ADHD and drugs commonly prescribed to manage it have been previously associated with sleep-related problems, we explored these variables more in depth. Ghosh et al reported a higher prevalence of primary insomnia in TS patients with than in those without comorbid ADHD. Moreover, they considered that one third of the TS and ADHD sample had insomnia attributable to the medication for ADHD taken by these patients. In our study, prevalence figures followed the same pattern that those reported in Ghosh et al. Further, we found a much higher likelihood of having insomnia in individuals with TS/CTD and comorbid ADHD (aOR = 11.89) than in individuals without this comorbidity (aOR = 3.38). Similarly, the likelihood of insomnia in individuals with TS/CTD and medicated ADHD was higher than that for those with TS/CTD with non-medicated ADHD (aOR = 17.83 and aOR = 5.26, respectively). These results suggest that the impact of TS/CTD and ADHD on sleep problems could be additive. Previous studies using objective sleep measures show that tic disorders and ADHD have specific polysomnographic alterations that affect sleep patterns in different ways. Further, because the prevalence of ADHD (and hence the likelihood of being on ADHD medication) is higher in men, the fact that ADHD and ADHD medication are associated to higher likelihood of insomnia could explain that, in the main analysis, TS/CTD was more strongly associated with insomnia among men (over 7-fold increase) than among women (over 5-fold increase), compared to their same-sex unexposed counterparts. This contrasts with the expected sex distribution of insomnia in the general population, which is higher in women than in men.

This study has several limitations. First, register-based studies have intrinsic coverage issues. The NPR only includes individuals who sought help and that were seen on specialist settings by specialist physicians. Further, outpatient care was only introduced in 2001. These limitations might affect the generalizability of the results to milder forms of tic disorders. Second, the results should be interpreted in the context of potential surveillance bias, whereby the outcomes might be more likely to be detected in individuals who are already in the health system because of TS/CTD. Third, we used a combined method to ascertain insomnia cases, one based on individuals being diagnosed with insomnia and another one based on individuals using specific medications for insomnia as a proxy for the diagnosis. However, it was reassuring that the combined use of these methods led to similar prevalence rates of insomnia than those previously reported in Sweden and elsewhere. Fourth, although our adjusted models accounted for a number of relevant somatic conditions with known association with TS/CTD and insomnia, we could not adjust for all possible confounding variables (eg, restless legs syndrome does not have its own ICD code). Finally, for the comparison of TS/CTD and ADHD-exposed individuals with and without ADHD medication, it is important to consider that medication prescription does not occur at random and that the most severe or complex patients are more likely to be medicated. Hence, these results should be interpreted with caution.
Conclusions

Approximately one-third of individuals with TS/CTD suffer from insomnia. This period prevalence translates into a 6.7-fold increased likelihood of having insomnia in this patient group, compared to the general population. Therefore, insomnia should be systematically evaluated in individuals with tic disorders and managed according to the available evidence to minimize its potential negative impact. This is particularly important for those patients with chronic tics that persist into adulthood and for those with comorbid neurodevelopmental disorders, especially ADHD. In these cases, clinicians should carefully balance the benefits and side effects of ADHD medication because it is likely to impact sleep in this patient group. Other kinds of sleep disorders require further study in TS/CTD.

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Data Availability Statement

No data are available.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.