

RESEARCH ARTICLE

Early-Life and Family Risk Factors for Tic Disorder Persistence into Adulthood

David Mataix-Cols, PhD,^{1,2*} Kayoko Isomura, MD, PhD,^{1,2} Gustaf Brander, PhD,^{3,4} Isabell Brikell, PhD,⁵ Paul Lichtenstein, PhD,⁵ Zheng Chang, PhD,⁵ Henrik Larsson, PhD,^{5,6} Ralf Kuja-Halkola, PhD,⁵ Kevin J. Black, MD,⁷ Anna Sidorchuk, MD, PhD,^{1,2} and Lorena Fernández de la Cruz, PhD^{1,2}

¹Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

²Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden

³Science for Life Laboratory, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden

⁴Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA

⁵Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

⁶School of Medical Sciences, Örebro University, Örebro, Sweden

⁷Departments of Psychiatry, Neurology, Radiology, and Neuroscience, Washington University in St. Louis, St. Louis, Missouri, USA

ABSTRACT: Background: Many children with tic disorders outgrow their tics, but little is known about the proportion of individuals who will continue to require specialist services in adulthood and which variables are associated with tic persistence.

Objectives: The aims were to estimate the proportion of individuals first diagnosed with tic disorders in childhood who continued to receive tic disorder diagnoses after age 18 years and to identify risk factors for persistence.

Methods: In this Swedish nationwide cohort study including 3761 individuals diagnosed with tic disorders in childhood, we calculated the proportion of individuals whose diagnoses persisted into adulthood. Minimally adjusted logistic regression models examined the associations between sociodemographic, clinical, and family variables and tic disorder persistence. A multivariable model was then fitted, including only variables that were statistically significant in the minimally adjusted models.

Results: Seven hundred and fifty-four (20%) children with tic disorders received a diagnosis of a chronic tic disorder in adulthood. Psychiatric comorbidity in childhood (particularly

attention-deficit hyperactivity disorder, obsessive-compulsive disorder, pervasive developmental disorders, and anxiety disorders) and psychiatric disorders in first-degree relatives (particularly tic and anxiety disorders) were the strongest risk factors for persistence. We did not observe statistically significant associations with socioeconomic variables, perinatal complications, comorbid autoimmune diseases, or family history of autoimmune diseases. All statistically significant variables combined explained approximately 10% of the variance in tic disorder persistence ($P < 0.0001$).

Conclusions: Childhood psychiatric comorbidities and family history of psychiatric disorders were the strongest risk factors associated with tic disorder persistence into adulthood. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: tic disorders; Tourette syndrome; children; adults; risk factors

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***Correspondence to:** Dr. David Mataix-Cols, Department of Clinical Neuroscience, Child and Adolescent Psychiatry Research Center, Karolinska Institutet, Gävlegatan 22 (Entré B), Floor 8, SE-11330 Stockholm, Sweden; E-mail: david.mataix.cols@ki.se

Relevant conflicts of interest/financial disclosures: David Mataix-Cols receives royalties for contributing articles to UpToDate, Wolters

Kluwer Health, outside the submitted work. Lorena Fernández de la Cruz receives royalties for contributing articles to UpToDate, Wolters Kluwer Health, outside the submitted work. All other authors report no potential conflicts of interest.

Received: 7 March 2023; **Revised:** 18 April 2023; **Accepted:** 1 May 2023

Published online 29 May 2023 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29454

Introduction

Tic disorders, including Tourette syndrome (TS) and chronic tic disorder (CTD), are childhood-onset neuropsychiatric disorders characterized by motor and/or vocal tics with a duration of at least 1 year.¹ CTD is considered to represent a milder form of TS.² TS/CTD affect approximately 1% to 3% of all children and are more common in boys (3:1 ratio).^{3,4}

TS/CTD are highly familial conditions with a genetic basis. First-degree relatives of affected individuals have nearly 20-fold increased odds of having TS/CTD compared to relatives of unaffected individuals.^{5,6} Despite being among the most heritable neuropsychiatric disorders,⁶ adverse environmental factors, such as perinatal complications, are considered to further contribute to the risk.⁷ A majority of individuals with TS/CTD present with psychiatric comorbidities, such as attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), or pervasive developmental disorders (PDD), which are often more impairing than the tics themselves.⁸⁻¹⁰ Multiple somatic comorbidities, such as autoimmune diseases, have also been described.^{11,12}

Tics typically appear between ages 4 and 6 years and are at their worst around ages 10 to 12 years.⁹ Thereafter, tics tend to gradually improve. Although most children with TS/CTD still have tics as adults if examined directly, they are often unaware of the tics or not bothered by them.^{9,13-15} However, some individuals will continue to have impairing symptoms well into their adult life and will require specialist care for their tics and associated comorbidities. The precise proportion of individuals requiring long-term specialist care in adulthood is unclear, but approximately 20% of pediatric patients present moderate to severe symptoms in adulthood.^{9,14} The question is important not only for the affected individuals, who may have increased risks of long-term adverse outcomes, such as somatic diseases or suicide,^{12,16-18} but also for service planning and allocation of resources. Furthermore, families of children with TS/CTD often want to know whether their child will require long-term support, a question for which no reassuring answers can be currently offered.

A limited number of studies have attempted to identify clinical and biological variables that may predict the persistence of tics and other comorbidities into adulthood, with limited success. Higher tic severity and psychiatric comorbidity at baseline have been associated with worse prognosis in some studies.¹⁹⁻²² Cavanna and colleagues²¹ found that childhood tic severity, premonitory urges, and a family history of tic disorders predicted poorer quality of life in adulthood (n = 46). Groth and colleagues²² also found that tic severity at baseline was predictive of tic severity at

follow-up and that female sex and childhood ADHD severity were predictive of emotional disorders later in life (n = 227). In another study, smaller caudate nucleus volumes²³ and poorer fine-motor skills²⁴ in childhood were associated with tic severity and psychosocial functioning in adulthood (n = 43). Many of these findings are based on small specialist clinic samples and, to our knowledge, have generally not been replicated, with the possible exception of baseline tic severity. In sum, the evidence is currently weak and insufficient to guide clinical practice and confidently inform families about the prognosis of the disorder.

In this Swedish nationwide cohort study including 3761 individuals diagnosed with tic disorders in childhood, we first aimed to estimate the proportion of individuals who continued to receive diagnoses of tic disorders in specialist services after age 18 years. We next aimed to explore a range of early-life and family variables that were associated with tic disorder persistence in adulthood. In particular, we focused on sociodemographic variables, psychiatric comorbidities in childhood, and family history of psychiatric disorders, including tic disorders (as a measure of familial risk), perinatal complications (as a known environmental risk factor for TS/CTD), and autoimmune diseases (as a frequent somatic comorbidity in TS/CTD).

Patients and Methods

The study was approved by the Swedish Ethical Review Authority (reference number: 2020-06540). Because the study was register based and individuals were not identifiable at any time, informed consent was waived.

Data Sources

Data were obtained by linking various Swedish nationwide health and administrative registers. Linkage is possible through the unique personal identification number assigned at birth or immigration to all Swedish residents.²⁵ Registers included the National Patient Register (NPR), which comprises information on inpatient (from 1973) and outpatient (from 2001) care for somatic and psychiatric disorders, based on the International Classification of Diseases system (ICD-8: 1973–1986; ICD-9: 1987–1996; ICD-10: 1997 onward)²⁶; the Prescribed Drug Register, containing data on all dispensed medications from July 2005, according to the Anatomical Therapeutic Chemical system²⁷; the Swedish Medical Birth Register, which contains information (from 1973) on antenatal, obstetric, and neonatal care on more than 98% of all births in Sweden^{28,29}; and the Multi-Generation Register that connects every person born in Sweden since 1932, and ever registered as living

in the country from 1961, with their biological or adoptive parents.³⁰ The Total Population Register,³¹ the Cause of Death Register,³² and the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA, in its Swedish acronym)³³ were used to extract additional sociodemographic information, including births, deaths, education, and migration.

Study Cohort

The cohort included all individuals with at least one diagnosis of a tic disorder, registered between ages 3 and 17 years, who were born in Sweden between January 1, 1973, and December 31, 1999. Because study data were available up to December 31, 2020, this ensured that all cohort members had at least 3 years' follow-up after their 18th birthday.

Diagnoses of tic disorders were based on the Swedish versions of the ICD-8 (306.2), ICD-9 (307C), and ICD-10 (transient tic disorder: F95.0, chronic motor or vocal tic disorder: F95.1, TS: F95.2, other tic disorders: F95.8, or unspecified tic disorder: F95.9), if diagnosed from age 3 years to avoid potential misclassification, in line with previous research.^{16,34,35} These ICD codes have excellent validity and reliability.³⁶

Individuals who had died or emigrated before age 21 years, those with missing information on maternal or paternal identification number, and those with a diagnosis of organic brain disorder (ICD-8: 290, 292, 293, 294, -294.3; ICD-9: 290, 293, 294; and ICD-10: F00–F09) or epilepsy (ICD-8: 345; ICD-9: 345; ICD-10: G40, G41) were excluded, as were those with a tic disorder first diagnosed only after age 17 years.

Individuals in the final cohort were linked to their parents and full siblings (those sharing the same mother and the same father) to explore family history as a risk factor.

Definition of Persisting Tic Disorders

Individuals in the study cohort were divided into those with tic disorders persisting into adulthood and those with tic disorders not persisting into adulthood. The group with persisting tic disorders included individuals with a childhood (from ages 3 to 17 years) diagnosis of a tic disorder and at least one additional diagnosis of a tic disorder after their 18th birthday. The remaining individuals (ie, those with a childhood diagnosis of a tic disorder who had no additional diagnoses of tic disorders after their 18th birthday) were classified as having nonpersisting tic disorders.

Potential Risk Factors

A series of variables were selected to investigate their association with tic disorder persistence. These variables included sex, socioeconomic status (highest parental level of education as a proxy), psychiatric

comorbidities diagnosed in childhood (before age 18 years), family history of psychiatric disorders (lifetime), number of perinatal complications, diagnoses of autoimmune diseases (lifetime), and family history of autoimmune diseases (lifetime). Table 1 presents a full description of the potential risk factor variables, and Table S1 presents the corresponding ICD codes.

Statistical Analyses

For descriptive purposes, we reported the distribution of the potential risk factor variables among the participants with and without persisting tic disorders. The association between each variable and tic disorder persistence was first assessed in separate logistic regression models adjusted for birth year to control for potential cohort effects (hereafter, minimally adjusted models). Next, using variables that were statistically significant in the minimally adjusted models, we identified the best-fitting variables by means of a backward stepwise selection procedure with likelihood ratio tests (a P -value of <0.05 served as a selection cutoff). The best-fitting variables were then entered into a final multivariable logistic regression model. This allowed the identification of risk factors that were significantly and independently associated with tic disorder persistence in adulthood.

The results were reported as adjusted odds ratios (aOR) and 95% confidence intervals (CI). All statistical tests were 2-tailed, and a P -value <0.05 was used to denote statistical significance. Data management and analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA), and STATA, version 17.1 (StataCorp LLC, College Station, TX, USA), respectively.

Results

Proportion of Persisting Tic Disorders

Figure 1 shows a flowchart of the study participants. Of the 7684 individuals with a diagnosis of a tic disorder born in Sweden between January 1, 1973, and December 31, 1999, 3761 met all our inclusion and exclusion criteria. Of those, 754 (20.05%) were classified as being in the persisting tic disorder group and 3007 (79.95%) in the nonpersisting tic disorder group.

Risk Factors for Tic Disorder Persistence Minimally Adjusted Logistic Regression Models

Table 2 presents the distribution of the potential risk factor variables in each of the groups. The minimally adjusted logistic regression models, which adjusted for birth year, showed that neither sex nor parental education were associated with tic disorder persistence in adulthood. By contrast, all childhood psychiatric

TABLE 1 Potential risk factors and their definitions

Potential risk factor	Description
Sex	Male/female.
Socioeconomic status	Highest registered level of education of parents, categorized as elementary school, high school, and higher education.
Psychiatric comorbidities diagnosed in childhood	Psychiatric comorbidities diagnosed before age 18 years, including the following groups of disorders (separately): (1) pervasive developmental disorders; (2) attention-deficit hyperactivity disorder; (3) conduct disorder; (4) phobic, anxiety, reaction to severe stress disorders, and adjustment disorders (abbreviated as anxiety disorders); (5) obsessive-compulsive disorder; (6) major depressive disorder, persistent mood disorder, or unspecified mood disorder (abbreviated as depressive disorders); and (7) bipolar disorder, schizophrenia, and other psychotic disorders (abbreviated as bipolar and psychotic disorders).
Family history of lifetime psychiatric comorbidities	Psychiatric comorbidities (as above, minus conduct disorder) diagnosed at any time during the study period (1973–2020) in first-degree relatives (ie, parents and full siblings), collapsed into a single binary variable.
Perinatal complications	Number of complications (categorized as 0, 1, and 2 or more), including daily maternal smoking during pregnancy, breech presentation, delivery by cesarean section, gestational age <37 weeks, birth weight ≤2500 g, being small for gestational age, and small head circumference. ⁷
Lifetime autoimmune diseases	Any autoimmune diseases diagnosed at any time during the study period (1973–2020).
Family history of lifetime autoimmune diseases	Autoimmune diseases diagnosed at any time during the study period (1973–2000) in first-degree relatives (ie, parents and full siblings).

comorbidities were statistically significantly associated with tic disorder persistence. The strongest associations were with ADHD (OR, 3.35; 95% CI, 2.82–3.99), PDD (OR, 2.80; 95% CI, 2.31–3.40), and OCD (OR, 2.71; 95% CI, 2.18–3.36) (Table 2).

We next examined whether the number of psychiatric comorbidities in childhood (coded as 0, 1, 2, and 3 or more disorders) was associated with increased odds of tic disorder persistence in adulthood. A total of 161 (21.35%) individuals in the persisting tic disorder group and 1578 (52.48%) in the nonpersisting tic disorder group had no childhood comorbidities. A total of 258 (34.22%) and 733 (24.38%) in the persisting tic disorder group and nonpersisting tic disorder group, respectively, had one childhood comorbidity; 187 (24.80%) and 423 (14.07%), respectively, had two comorbidities; and 148 (19.63%) and 273 (9.08%), respectively, had three or more comorbidities. We found that the higher the number of childhood psychiatric comorbidities, the higher the odds of tic disorder persistence in adulthood (Fig. 2). For example, for individuals with three or more childhood comorbidities, the OR increased substantially to 7.29 (95% CI, 5.56–9.54), compared to individuals with no childhood psychiatric comorbidities.

Regarding family history of psychiatric disorders, all were statistically significantly associated with increased odds of tic disorder persistence (Table 2). The strongest associations were with family history of tic disorders (OR, 2.04; 95% CI, 1.39–3.00) and of OCD (OR,

2.02; 95% CI, 1.48–2.75). We did not observe any statistically significant associations with the number of perinatal complications, comorbid autoimmune diseases, or family history of autoimmune diseases (Table 2).

Multivariable models

In the multivariable analyses, all statistically significant variables in the minimally adjusted models (ie, including childhood psychiatric comorbidities and family history of lifetime psychiatric comorbidities) were entered in the model simultaneously to undergo a backward stepwise selection procedure. Six variables remained statistically significant (Table S2) and were included in the final multivariable logistic regression model. Variables that were independently associated with tic disorder persistence in adulthood included childhood ADHD (aOR, 2.67; 95% CI, 2.22–3.20), childhood OCD (aOR, 2.16; 95% CI, 1.71–2.71), childhood PDD (aOR, 1.95; 95% CI, 1.59–2.39), anxiety disorder comorbidity in childhood (aOR, 1.31; 95% CI, 1.02–1.68), family history of tic disorders (aOR, 1.63; 95% CI, 1.09–2.43), and family history of anxiety disorders (aOR, 1.48; 95% CI, 1.25–1.76) (Table 3). The final model with all the significant associations explained approximately 10% of the variance in tic disorder persistence (pseudo- $R^2 = 0.1029$, $P < 0.0001$).

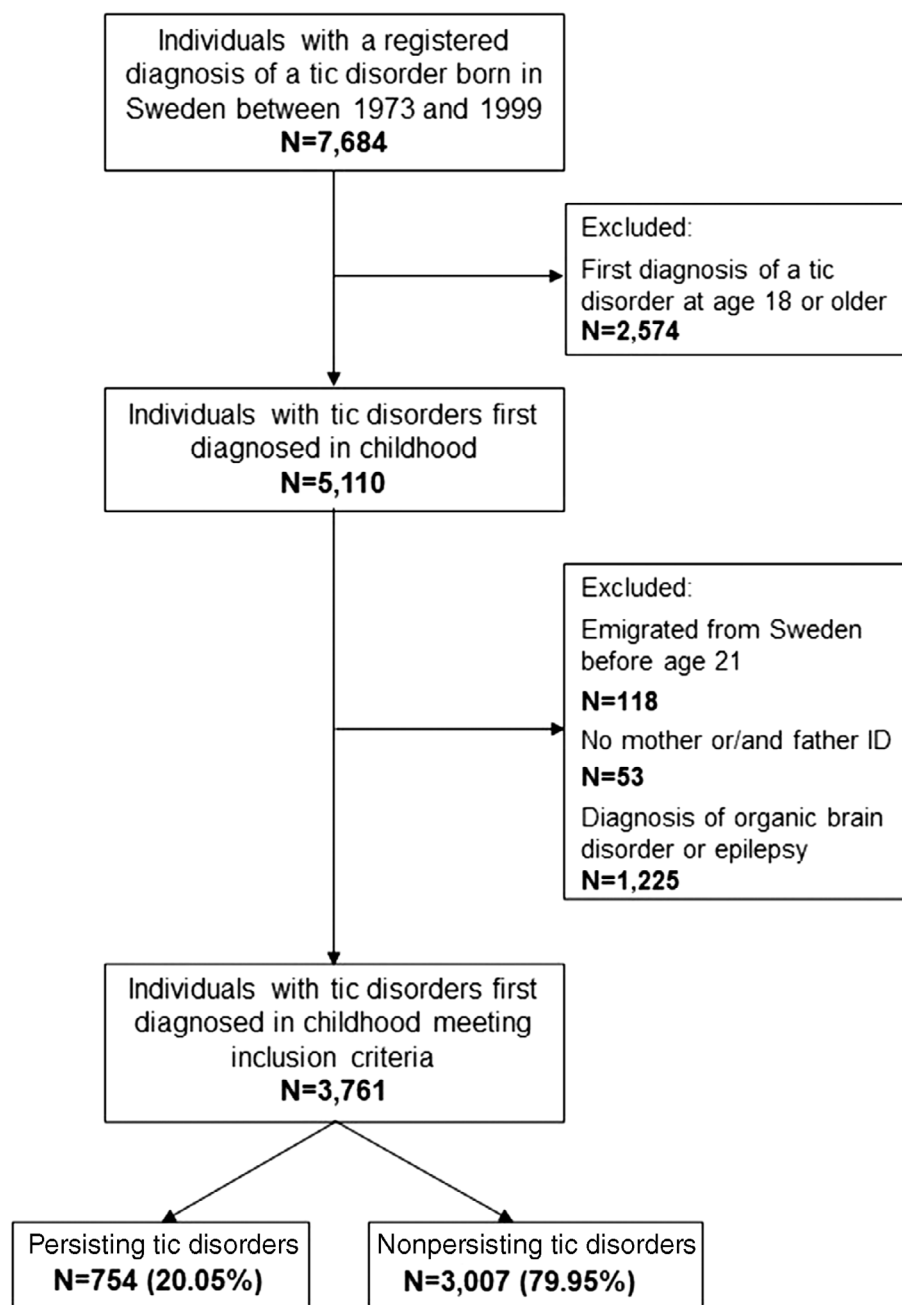


FIG. 1. Flowchart of study participants.

Discussion

This nationwide cohort study aimed to estimate the proportion of individuals whose diagnoses of tic disorder persisted into adulthood and to explore potential variables associated with such persistence. Several main findings emerged.

First, the proportion of individuals initially diagnosed with tic disorders in childhood who continued to receive diagnoses of tic disorders in specialist services after age 18 years was about 20%. This proportion is remarkably similar to the proportion of individuals

reportedly having “moderate or severe” tics in adulthood in other longitudinal clinic-based studies, which had reported estimates ranging from 19%⁹ to 23%.¹⁴ The current study adds to the previous literature by contributing nationwide data from across a range of clinical services (eg, psychiatry, neurology, and pediatrics) that are not necessarily specialized in tic disorders. Overall, the results confirm a widely accepted view that most individuals with tic disorders will not require specialist services for tics when they reach adulthood. This does not mean that these individuals will have no tics at all. Indeed, we know from the literature that many

TABLE 2 Distribution of study variables by tic persistence status and results of the minimally adjusted logistic regression models

Variable	Persistent tics (n = 754)		Nonpersistent tics (n = 3007)		Odds ratio, adjusted for birth year (95% CI)
	n	%	n	%	
Sex					
Men	597	79.18	2356	78.35	Ref
Women	157	20.82	651	21.65	0.99 (0.82–1.22)
Parental education					
Elementary	36	4.77	109	3.62	Ref
High school	378	50.13	1429	47.52	0.93 (0.62–1.39)
Higher education	340	45.09	1469	48.85	0.85 (0.57–1.28)
Comorbidities in childhood					
Pervasive developmental disorders	213	28.25	396	13.17	2.80 (2.31–3.40)
Attention-deficit hyperactivity disorder	446	59.15	1036	34.45	3.35 (2.82–3.99)
Conduct disorder	72	9.55	167	5.55	1.95 (1.46–2.61)
Anxiety disorders	121	16.05	311	10.34	1.88 (1.49–2.37)
Obsessive-compulsive disorder	162	21.49	291	9.68	2.71 (2.18–3.36)
Depressive disorders	91	12.07	242	8.05	1.68 (1.30–2.18)
Bipolar and psychotic disorders	30	3.98	51	1.70	2.55 (1.61–4.06)
Family history					
Tic disorders	42	5.57	82	2.73	2.04 (1.39–3.00)
Obsessive-compulsive disorder	67	8.89	134	4.46	2.02 (1.48–2.75)
Attention-deficit hyperactivity disorder	212	28.12	533	17.73	1.87 (1.55–2.25)
Pervasive developmental disorders	65	8.62	163	5.42	1.60 (1.18–2.16)
Anxiety disorders	377	50.00	1041	34.62	1.86 (1.58–2.19)
Depressive disorders	277	36.74	770	25.61	1.65 (1.39–1.96)
Bipolar and psychotic disorders	96	12.73	259	8.61	1.50 (1.17–1.93)
Autoimmune diseases	58	7.69	202	6.72	1.16 (0.85–1.57)
Family history of autoimmune diseases	223	29.58	842	28.00	1.02 (0.85–1.21)
Number of perinatal complications					
0	415	55.04	1697	56.43	Ref
1	234	31.03	876	28.13	1.07 (0.90–1.29)
2 or more	97	12.86	361	12.01	1.12 (0.87–1.44)
Missing	8	1.06	73	2.43	0.51 (0.24–1.07)

Note: Significant odds ratios are highlighted in bold font.

Abbreviations: CI, confidence interval; Ref, Reference.

individuals will continue to have mild tics in adulthood but are simply not impaired by them.^{9,13–15} Similarly, our results do not imply that these individuals will not have other clinical needs that may require attention and medical surveillance. A growing body of literature is uncovering a wide range of long-term health adversities in individuals with TS/CTD, including but not limited

to substance misuse, autoimmune diseases, or cardiometabolic disorders.^{12,16,18,37}

Second, we found that psychiatric comorbidities in childhood were significantly associated with tic disorder persistence in adulthood. Additional analyses revealed a gradient of association, whereby the higher the number of childhood psychiatric comorbidities, the higher the

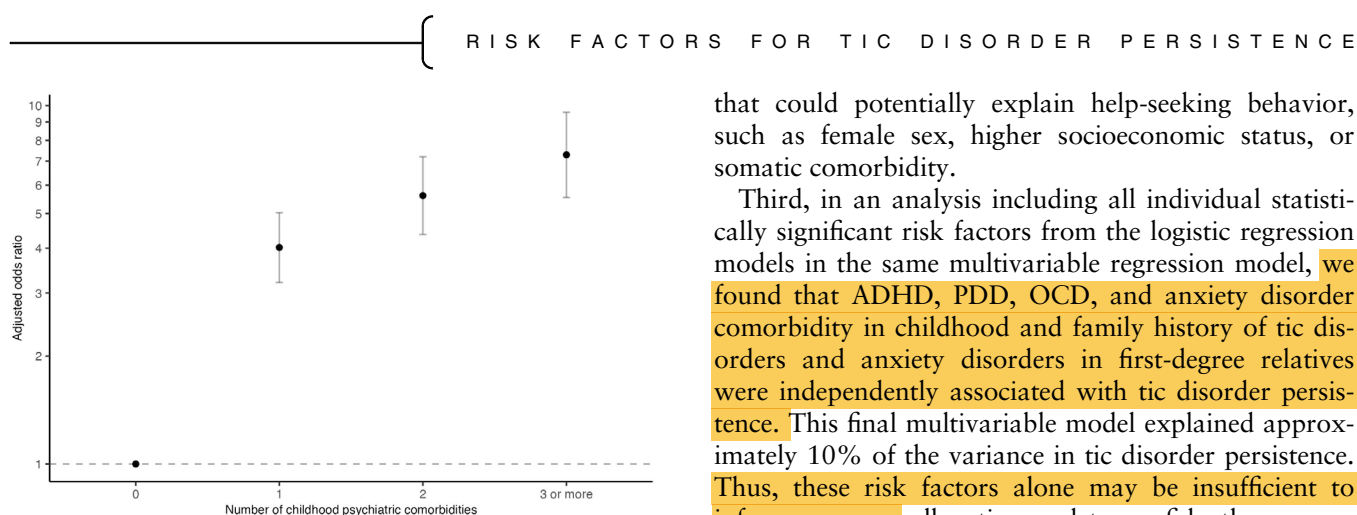


FIG. 2. Odds ratios and 95% confidence intervals for the association between the number of childhood psychiatric comorbidities and tic disorder persistence (models minimally adjusted for birth year).

TABLE 3 Results of the final multivariable risk factor model

Risk factors for tic persistence	Odds ratio, adjusted for birth year (95% CI)
Comorbidities in childhood	
Pervasive developmental disorders	1.95 (1.59–2.39)
Attention-deficit hyperactivity disorder	2.67 (2.22–3.20)
Anxiety disorders	1.31 (1.02–1.68)
Obsessive-compulsive disorder	2.16 (1.71–2.71)
Family history	
Tic disorders	1.63 (1.09–2.43)
Anxiety disorders	1.48 (1.25–1.76)
Pseudo- R^2 for the model	0.1029 ($P < 0.0001$)

Note: Statistically significant odds ratios are highlighted in bold font.
Abbreviation: CI, confidence interval.

odds of tic disorder persistence in adulthood. For example, individuals with three or more childhood comorbidities had seven times the odds to have persisting tic disorders in adulthood. These results extend the results of previous, much smaller studies^{19–22} by suggesting that clinical complexity in childhood may be associated with tic disorder persistence. We also found that tic disorder persistence was associated with family history of psychiatric disorders, suggesting that familial or genetic factors may play a role. By contrast, sociodemographic variables such as sex or parental education (a proxy for socioeconomic status), perinatal complications, comorbid autoimmune diseases, and family history of autoimmune diseases were not associated with tic disorder persistence. Thus, in this study, tic disorder persistence was unrelated to some variables

that could potentially explain help-seeking behavior, such as female sex, higher socioeconomic status, or somatic comorbidity.

Third, in an analysis including all individual statistically significant risk factors from the logistic regression models in the same multivariable regression model, we found that ADHD, PDD, OCD, and anxiety disorder comorbidity in childhood and family history of tic disorders and anxiety disorders in first-degree relatives were independently associated with tic disorder persistence. This final multivariable model explained approximately 10% of the variance in tic disorder persistence. Thus, these risk factors alone may be insufficient to inform resource allocation and to confidently reassure families about their child's prognosis. Future studies should ideally include additional variables, such as tic severity and cognitive or biological variables, none of which were available in our data set. Independent replication of the current results in other studies will be necessary to evaluate the accuracy and generalizability of the models.

Strengths and Limitations

Some strengths include the use of population-based registers, which minimize the risk of sampling error and recall bias and ensure generalizability of the results at the national level. The Swedish ICD codes for tic disorders have excellent validity and reliability.³⁶ Unlike research-active tic disorder clinics, our naturalistic design means that no active efforts were made to retain and follow up participants, thus theoretically providing less biased estimates. Our sample was several orders of magnitude larger than that of previous studies. Furthermore, we had access to a range of potential risk factors, collected from individuals and their relatives from birth to adulthood, which are difficult to gather in clinical studies with active data collection.

The study also has some limitations. First, we did not have a measure of tic severity, which was consistently identified in previous studies as a predictor of tic persistence.^{21,22} Second, we cannot be sure that tic disorders were the main reason for consultation in adulthood, resulting in potential surveillance bias. For example, individuals may have sought specialist care for psychiatric symptoms other than tics despite receiving a TS/CTD diagnosis in the same visit. This scenario would exaggerate the apparent persistence of diagnosable tics in those with, for example, ADHD. However, this bias would less obviously explain the monotonic increase in the proportion of individuals with tic disorder diagnoses by number of childhood comorbidities, because patients with one versus three non-tic diagnoses recorded by a physician are equally at the specialist's office. More important, because pure TS/CTD without other psychiatric comorbidities is uncommon,

focusing on this subgroup would ignore the great majority of adults with clinically apparent tics. Third, register-based studies have some intrinsic coverage issues. Data from outpatient care were introduced only in 2001. Furthermore, the NPR includes only individuals who sought help and who were seen in specialist settings by specialist physicians. Thus, the results may not generalize to primary care settings, to less severe cases, or to individuals who never sought help for their tics.

Conclusions

Approximately 20% of children with tic disorders received a diagnosis of a TS/CTD in adulthood. Psychiatric comorbidity in childhood (particularly ADHD, PDD, OCD, and anxiety disorders) and psychiatric disorders in first-degree relatives (particularly tic disorders and anxiety disorders) were the strongest risk factors associated with tic disorder persistence. All statistically significant risk factors together explained approximately 10% of the variance in tic persistence. Future studies would benefit from exploring additional variables to improve our understanding of tic disorder persistence. ■

Acknowledgments: No funding. K.I. and A.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability Statement

The administrative register data analysed in this study cannot be made publicly available, according to European and Swedish law.

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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.