

# Association of Streptococcal Throat Infection With Mental Disorders

## Testing Key Aspects of the PANDAS Hypothesis in a Nationwide Study

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**IMPORTANCE** Streptococcal infection has been linked with the development of obsessive-compulsive disorder (OCD) and tic disorders, a concept termed *pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection* (PANDAS). However, previous studies of this association have been small, and the results have been conflicting.

**OBJECTIVE** To investigate the risk of mental disorders, specifically OCD and tic disorders, after a streptococcal throat infection.

**DESIGN, SETTING, AND PARTICIPANTS** A population-based cohort study was conducted using data from the nationwide Danish registers from January 1, 1996, to December 31, 2013, with up to 17 years of follow-up. The Danish National Health Service Register provided information on individuals with the registration of a streptococcal test. Data analysis was conducted from January 1, 2016, to February 28, 2017.

**MAIN OUTCOMES AND MEASURES** Individuals were followed up in the nationwide Psychiatric Central Register for a diagnosis of any mental disorder, OCD, or tic disorders. Incidence rate ratios (IRRs) were calculated by Poisson regression analysis.

**RESULTS** Of the 1 067 743 children (<18 years of age) included in the study (519 821 girls and 547 922 boys), 638 265 received a streptococcal test, 349 982 of whom had positive test results at least once. Individuals with a positive streptococcal test result had an increased risk of any mental disorder (n = 15 408; IRR, 1.18; 95% CI, 1.15-1.21;  $P < .001$ ), particularly of OCD (n = 556; IRR, 1.51; 95% CI, 1.28-1.77;  $P < .001$ ) and tic disorders (n = 993; IRR, 1.35; 95% CI, 1.21-1.50;  $P < .001$ ), compared with individuals without a streptococcal test. Furthermore, the risk of any mental disorder and OCD was more elevated after a streptococcal throat infection than after a nonstreptococcal infection. Nonetheless, individuals with a nonstreptococcal throat infection also had an increased risk of any mental disorder (n = 11 315; IRR, 1.08; 95% CI, 1.06-1.11;  $P < .001$ ), OCD (n = 316; IRR, 1.28; 95% CI, 1.07-1.53;  $P = .006$ ), and tic disorders (n = 662; IRR, 1.25; 95% CI, 1.12-1.41;  $P < .001$ ).

**CONCLUSIONS AND RELEVANCE** This large-scale study investigating key aspects of the PANDAS hypothesis found that individuals with a streptococcal throat infection had elevated risks of mental disorders, particularly OCD and tic disorders. However, nonstreptococcal throat infection was also associated with increased risks, although less than streptococcal infections for OCD and any mental disorder, which could also support important elements of the diagnostic concept of pediatric acute-onset neuropsychiatric syndrome.

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In recent years, an increasing body of evidence has pointed toward a critical role of the immune system and infections in the development of mental disorders.<sup>1-3</sup> Childhood obsessive-compulsive disorder (OCD) and tic disorders have been suggested to be associated with infections caused by group A  $\beta$ -hemolytic streptococcus, a hypothesis termed *pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection* (PANDAS),<sup>4</sup> which are suggested to be caused by molecular mimicry in which antibodies directed toward the streptococcal bacteria cross-react with the basal ganglia of the brain, possibly owing to structural similarities between the streptococcal cell surface and proteins of the basal ganglia.<sup>5</sup> This hypothesis is supported by findings of autoantibodies directed toward the basal ganglia in the serum of children with PANDAS compared with that of controls<sup>6,7</sup> and by the results of imaging studies suggesting inflammation in these parts of the brain in individuals with PANDAS compared with controls.<sup>8</sup> Moreover, a study observing 12 children with PANDAS for 3 years found that exacerbations of OCD and tic disorders were associated with preceding streptococcal infections.<sup>9</sup> Furthermore, studies have found that immunotherapy has a positive effect on symptoms of OCD and tic disorders in children with PANDAS,<sup>10,11</sup> indicating that autoimmune-based mechanisms may play a causal role.

However, the PANDAS hypothesis remains controversial, and most prior studies are small and have methodological shortcomings. Furthermore, not all studies confirmed the findings of autoantibodies against the basal ganglia in children with PANDAS,<sup>12-14</sup> and several other studies also did not support the PANDAS hypothesis,<sup>15-18</sup> including recent investigations of the effect of immunotherapy.<sup>19</sup> Studies with the most intensive clinical observation and testing either did not find recent streptococcal infections to worsen neuropsychiatric symptoms in individuals with PANDAS<sup>17</sup> or found that most of the neuropsychiatric worsening occurred in individuals with no association with a preceding streptococcal infection,<sup>18</sup> thereby questioning the core criterion of PANDAS. Furthermore, many studies are limited by short-term follow-up, recall bias, and cross-sectional design.

We investigated the risk of any mental disorders, with particular focus on OCD and tic disorders, in children exposed to streptococcal throat infection in the largest population-based cohort study to date, to our knowledge, using the nationwide Danish registers. We observed the cohort for up to 17 years without loss to follow-up with an investigation of age at the time of streptococcal throat infection, the timing and number of streptococcal infections, and stratified by sex and personal or parental history of autoimmune disease.

## Methods

### The Registers

All Danish residents are assigned a unique identification number by the Danish Civil Registration System, permitting linkage between the national registers and including information on parents and siblings.<sup>20</sup> Psychiatric inpatient contacts since 1969 are available in the Danish Psychiatric Central Research

### Key Points

**Question** Is streptococcal throat infection associated with obsessive-compulsive disorder (OCD) and tic disorders, as suggested by the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) hypothesis?

**Findings** In this population-based cohort study, streptococcal throat infections increased the risk of any mental disorder, OCD, and tic disorders; however, compared with nonstreptococcal throat infections, only the risk of any mental disorder and OCD was significantly higher after a streptococcal infection.

**Meaning** The PANDAS hypothesis was supported to some extent, but because other infections also increased the risk of mental disorders, our results could also support aspects of the wider diagnostic concept of pediatric acute-onset neuropsychiatric syndrome.

Register,<sup>21</sup> and somatic inpatient contacts since 1977 are available in the National Hospital Register<sup>22</sup>; since 1995, both registers also include outpatient contacts.<sup>21,22</sup> The Danish National Health Service Register documents activities of general practitioners since 1990.<sup>23</sup> Data on filled prescriptions since 1994 are accessible in the Danish National Prescription Registry.<sup>24</sup> Registered diagnoses are defined according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, codes. The study was approved by the Danish Data Protection Agency, who waived the need for patient consent.

### Study Population

Individuals born in Denmark between January 1, 1996, and December 31, 2013, were identified by their identification number and followed up until death, emigration, or December 31, 2013. Individuals were followed up in the Danish National Health Service Register for a record of a rapid antigen diagnostic test for group A  $\beta$ -hemolytic streptococcal throat infection (streptococcal test) performed by the general practitioner and in the Danish National Prescription Registry for a history of subsequently filled antibiotics. Individuals with a record of a streptococcal test were followed up in the Danish Psychiatric Central Register using the first-time psychiatric diagnoses during the period from 1996 to 2013. Because hospital contact, including emergency department contact, for infections is a known risk factor for mental disorders,<sup>1,2</sup> individuals with a record of hospital treatment for infections were censored, as were individuals with a psychiatric diagnosis.

### Assessment of Mental Disorders

The Danish Psychiatric Central Register provided information on the outcome diagnoses of OCD, tic disorders including Tourette syndrome, and an outcome category of all mental disorders (eTable 1 in the Supplement). In the rare case of the registration of first-time psychiatric diagnoses of both OCD and a tic disorder on the same day, these individuals were counted in both groups. Because some of the cases might have

Table 1. Risk of Mental Disorders in Individuals With Positive or Negative Streptococcal Test Results<sup>a</sup>

Result of Streptococcal Test	Any Mental Disorder			OCD			Tic Disorders		
	No.	IRR <sup>b</sup> (95% CI)	IRR <sup>c</sup> (95% CI)	No.	IRR <sup>b</sup> (95% CI)	IRR <sup>c</sup> (95% CI)	No.	IRR <sup>b</sup> (95% CI)	IRR <sup>c</sup> (95% CI)
No test performed	13 712	1 [Reference]	1 [Reference]	206	1 [Reference]	1 [Reference]	522	1 [Reference]	1 [Reference]
Positive	15 408	1.18 (1.15-1.21) <sup>d</sup>	1.16 (1.14-1.20) <sup>d</sup>	556	1.51 (1.28-1.77) <sup>d</sup>	1.49 (1.27-1.76) <sup>d</sup>	993	1.35 (1.21-1.50) <sup>d</sup>	1.34 (1.20-1.49) <sup>d</sup>
Negative	11 315	1.08 (1.06-1.11) <sup>d</sup>	1.07 (1.04-1.09) <sup>d</sup>	316	1.28 (1.07-1.53) <sup>d</sup>	1.27 (1.07-1.52) <sup>d</sup>	662	1.25 (1.12-1.41) <sup>d</sup>	1.24 (1.10-1.39) <sup>d</sup>

Abbreviations: IRR, incidence rate ratio; OCD, obsessive-compulsive disorder.

<sup>a</sup> The streptococcal test was the rapid antigen diagnostic test for group A

$\beta$ -hemolytic streptococcal throat infections.

<sup>b</sup> Adjusted for sex, age, and calendar year.

<sup>c</sup> Further adjusted for parental educational level, income, marital status, family history of psychiatric disorders, and personal or parental history of autoimmune diseases.

<sup>d</sup> The reference interval did not include 1 [Reference].

been diagnosed by pediatricians instead of psychiatrists, psychiatric diagnoses were also obtained from the National Hospital Register.

### Assessment of Streptococcal Throat Infection

The Danish National Health Service Register provided information on individuals registered with a streptococcal test (register code 7109) but without information on the test result. Hence, the combination of a streptococcal test and an antibiotic prescription filled within 8 days of the test (eTable 1 in the Supplement) was used as a proxy for positive test results, and tests without an antibiotic were counted as negative test results. Because we had information only on the week in which the test was conducted, we determined the day of testing to be Monday. Individuals with negative test results probably had a nonstreptococcal throat infection and were included in the study to explore whether the risk of mental disorders was specific for streptococcal infections. Individuals with at least 1 positive test result remained in the cohort of individuals with positive test results regardless of any exposure to negative test results. Hence, individuals with negative test results had only negative results and no positive test results. If an individual had 2 or more positive streptococcal test results within 4 weeks, it was counted as 1 infection.

### Statistical Analyses

Statistical analysis was conducted from January 1, 2016, to February 28, 2017. Survival analysis was performed in Stata, version 13.1 (StataCorp), and incidence rate ratios (IRRs) were estimated by Poisson regression. The basic model adjusted for age, sex, and calendar year, and the fully adjusted model further adjusted for socioeconomic factors (parental marital status, educational level, and income), family history of mental disorders, and personal or parental history of autoimmune diseases. Variables were available from the Danish Civil Registration System, the Danish Psychiatric Central Research Register, the National Hospital Register, and Statistics Denmark. All variables except sex were treated as time dependent. In addition, we conducted a case-control study by matching patients with full siblings who had not received a diagnosis of mental disorder at the age when the patient became considered a case. We controlled for sex and calendar year by conditional logistic regression. Each case with sibling(s) made a stratum in which the streptococcal test preceded the mental disorder of the patient (in age) as an analog to a time-

dependent variable.  $P < .05$  was considered significant. Further information regarding statistical analyses is available in the eAppendix in the Supplement.

### Results

The study population consisted of all 1 067 743 individuals born in Denmark between January 1, 1996, and December 31, 2013, and followed up for up to 17 years, corresponding to 7.9 million person-years at risk. A total of 638 265 children (<18 years of age) were registered with at least 1 streptococcal test, of whom 349 982 individuals (54.8%) had at least 1 positive test result. During the study period, 40 435 children received a diagnosis of a mental disorder, of whom 15 408 individuals (38.1%) had a previous positive streptococcal test result. A total of 1078 individuals received a diagnosis of OCD, of whom 556 children (51.6%) had a previous positive streptococcal test result. A tic disorder was diagnosed in 2177 individuals, of whom 993 children (45.6%) had a previous positive streptococcal test result. Demographic variables are shown in eTable 2 in the Supplement, displaying only small differences between the group of individuals who did not undergo a streptococcal test and those with negative or positive test results.

Persons with a positive streptococcal test result had an 18% higher risk of any mental disorder (IRR, 1.18; 95% CI, 1.15-1.21;  $P < .001$ ), a 51% higher risk of OCD (IRR, 1.51; 95% CI, 1.28-1.77;  $P < .001$ ), and a 35% higher risk of tic disorders (IRR, 1.35; 95% CI, 1.21-1.50;  $P < .001$ ) compared with individuals who did not undergo a streptococcal test (Table 1 and Figure). Full adjustment did not change the associations. The relative risk of OCD and tic disorders was higher than the risk of any mental disorder. Stratified analyses for the remaining diagnostic codes included in the category of any mental disorder showed that after a positive streptococcal test result, the risk was most elevated for disorders of adult personality and behavior (IRR, 1.85; 95% CI, 1.23-2.80) and mood disorders (IRR, 1.64; 95% CI, 1.36-1.98) (eTable 3 in the Supplement). Individuals with a negative streptococcal test result also had an 8% higher risk of any mental disorder (IRR, 1.08; 95% CI, 1.06-1.11;  $P < .001$ ), a 28% higher risk of OCD (IRR, 1.28; 95% CI, 1.07-1.53;  $P = .006$ ), and a 25% higher risk of tic disorders (IRR, 1.25; 95% CI, 1.12-1.41;  $P < .001$ ) compared with individuals who did not undergo a streptococcal test. However, the risk of any mental disorder and OCD was still highest for individuals with positive

test results compared with those with negative test results. The risk of any mental disorder, OCD, and tic disorders increased linearly in a dose-response manner with an increasing number of negative streptococcal test results (Table 2). Likewise, the risk of any mental disorder increased linearly with the number of positive test results. The IRRs for all outcomes tended to increase throughout the time after a positive test result; in particular, the risk did not appear to be highest in the proximate period following the test (Table 3). Case-sibling analyses displayed a 94% increased risk of OCD (odds ratio, 1.94; 95% CI, 1.18-3.20) for children with positive test results compared with siblings with a negative test result, while the remaining estimates were insignificant (eTable 4 in the Supplement).

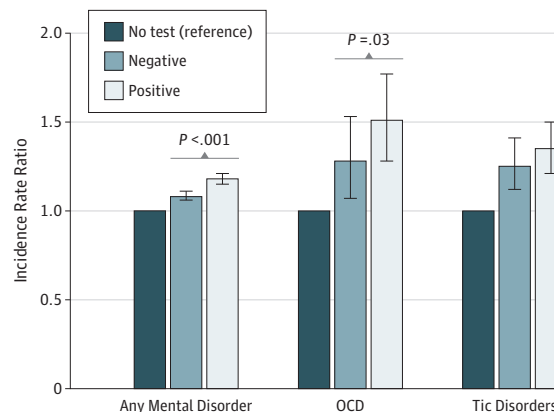
Individuals 3 to 11 years of age with positive streptococcal test results had the largest IRRs for OCD (1.55; 95% CI, 1.30-1.83) and tic disorders (1.41; 95% CI, 1.25-1.58) (Table 4); however, the differences across age groups were not significant. The risk of any mental disorder was highest for individuals with a positive test result at 12 years of age or older (IRR, 1.73; 95% CI, 1.60-1.86;  $P < .001$ ). Moreover, there was an interaction between undergoing a streptococcal test and sex with regard to the risk of any mental disorder, with a significantly larger risk for female compared with male individuals with positive test results and a greater risk in male rather than female individuals with negative test results (eTable 5 in the Supplement). We did not find an interaction between a positive or negative test result and a parental or personal history of autoimmune disease regarding any of the outcomes (eTable 5 in the Supplement).

## Discussion

This large population-based cohort study showed that individuals with positive streptococcal test results and thereby probable streptococcal throat infections had an 18% increased risk of any mental disorder, a 51% increased risk of OCD, and a 35% increased risk of tic disorders compared with individuals who had never been tested for streptococcal infection. However, individuals with a negative streptococcal test result who thereby most likely had a nonstreptococcal throat infection also had an increased risk of mental disorders. Nonetheless, individuals with a streptococcal infection had a greater risk of any mental disorder and OCD compared with those with a nonstreptococcal throat infection. The associations persisted after adjusting for possible confounders, and the risk of OCD was 94% larger for individuals with positive test results compared with siblings with negative test results.

Our findings that individuals with a streptococcal infection had an increased risk of OCD and tic disorders support the PANDAS hypothesis to some extent, in line with findings of previous studies.<sup>9,25-28</sup> Obsessive-compulsive disorder, tic disorders, and Tourette syndrome have been associated with an increased occurrence of streptococcal infection 3 to 12 months before a psychiatric diagnosis compared with controls, based on a study of 742 cases<sup>27</sup> and a study of 144 cases.<sup>26</sup> The association was even stronger after multiple streptococcal

**Figure. Risk of Mental Disorders in Individuals With Positive or Negative Streptococcal Test Results Compared With Individuals Who Did Not Undergo Streptococcal Tests**



Individuals with positive or negative streptococcal test results had a significantly increased risk of any mental disorder, obsessive-compulsive disorder (OCD), and tic disorders compared with individuals who did not undergo a test. However, the risk of any mental disorder (incidence rate ratio [IRR], 1.18; 95% CI, 1.15-1.21;  $P < .001$ ) and OCD (IRR, 1.51; 95% CI, 1.28-1.77;  $P = .03$ ) was still largest in individuals with positive test results compared with individuals with negative test results (any mental disorder: IRR, 1.08; 95% CI, 1.06-1.11; and OCD: IRR, 1.28; 95% CI, 1.07-1.53). The streptococcal test was the rapid antigen diagnostic test for group A  $\beta$ -hemolytic streptococcal throat infections. The incidence rate ratio was adjusted for sex, age, and calendar year. Error bars indicate 95% CIs.

infections,<sup>26</sup> similar to our findings of a dose-response association with the number of streptococcal infections and any mental disorder. A follow-up study of 45 individuals with Tourette syndrome and/or OCD found that streptococcal infections were associated with worsening of neuropsychiatric symptoms.<sup>25</sup> The diagnostic criteria of PANDAS state that the neuropsychiatric symptoms debut from the age of 3 years until the beginning of puberty<sup>4</sup>; we also found that individuals 3 to 11 years of age had the greatest tendency of an increased risk of OCD and tic disorders, whereas the risk of any mental disorder was highest in the group older than 11 years of age.

Nonetheless, our findings that the risk of mental disorders is only slightly less elevated after a nonstreptococcal throat infection than after a streptococcal infection suggest that other, possibly viral, infectious agents are also linked with the development of OCD and tic disorders. This finding might instead support the recently proposed concept of pediatric acute-onset neuropsychiatric syndrome, even though the main diagnostic criteria exclude tic disorders and include a restricted food intake.<sup>29</sup> Pediatric acute-onset neuropsychiatric syndrome offers an alternative to PANDAS with wider diagnostic criteria; it is primarily thought to be a postinfectious condition but without restriction to streptococcal infections. In our study, individuals with negative streptococcal test results had an 8% increased risk of any mental disorder, a 28% increased risk of OCD, and a 25% increased risk of tic disorders compared with individuals who had never been tested for streptococcal throat infection. Furthermore, the nonstreptococcal throat infections also displayed a dose-response

**Table 2. Risk of Mental Disorders in Individuals With Positive or Negative Streptococcal Test Results, by the Number of Tests Performed<sup>a</sup>**

Result of Streptococcal Tests, No.	Any Mental Disorder		OCD		Tic Disorders	
	No.	IRR <sup>b</sup> (95% CI)	No.	IRR <sup>b</sup> (95% CI)	No.	IRR <sup>b</sup> (95% CI)
No test performed	13 712	1 [Reference]	206	1 [Reference]	522	1 [Reference]
Positive						
1	8551	1.13 (1.09-1.16) <sup>c</sup>	292	1.50 (1.25-1.79) <sup>c</sup>	549	1.35 (1.19-1.52) <sup>c</sup>
2	3496	1.16 (1.12-1.20) <sup>c</sup>	111	1.28 (1.01-1.61) <sup>c</sup>	196	1.16 (0.99-1.37)
≥3	3361	1.21 (1.16-1.26) <sup>c</sup>	153	1.71 (1.39-2.12) <sup>c</sup>	248	1.59 (1.36-1.85) <sup>c</sup>
Negative						
1	5988	1.01 (0.98-1.04)	147	1.16 (0.94-1.44)	320	1.11 (0.96-1.27)
2	2873	1.11 (1.07-1.16) <sup>c</sup>	80	1.26 (0.98-1.64)	202	1.51 (1.29-1.78) <sup>c</sup>
≥3	2454	1.22 (1.17-1.28) <sup>c</sup>	89	1.58 (1.23-2.02) <sup>c</sup>	140	1.33 (1.10-1.60) <sup>c</sup>

Abbreviations: IRR, incidence rate ratio; OCD, obsessive-compulsive disorder.

<sup>b</sup> Adjusted for sex, age, and calendar year.

<sup>a</sup> The streptococcal test was the rapid antigen diagnostic test for group A β-hemolytic streptococcal throat infections.

<sup>c</sup> The reference interval did not include 1 [Reference].

**Table 3. Risk of Mental Disorders in Individuals With Positive Streptococcal Test Results, by Time Since the Last Positive Test Result<sup>a</sup>**

Time Since the Last Positive Streptococcal Test, y	Any Mental Disorder		OCD		Tic Disorders	
	No.	IRR <sup>b</sup> (95% CI)	No.	IRR <sup>b</sup> (95% CI)	No.	IRR <sup>b</sup> (95% CI)
No test performed	13 712	1 [Reference]	316	1 [Reference]	522	1 [Reference]
<1	2482	1.09 (1.04-1.14) <sup>c</sup>	57	1.38 (1.03-1.86) <sup>c</sup>	128	1.17 (0.96-1.42)
1-2	4094	1.19 (1.15-1.24) <sup>c</sup>	96	1.30 (1.02-1.65) <sup>c</sup>	263	1.34 (1.15-1.55) <sup>c</sup>
3-5	4376	1.25 (1.20-1.30) <sup>c</sup>	155	1.53 (1.24-1.89) <sup>c</sup>	368	1.57 (1.37-1.79) <sup>c</sup>
6-10	3596	1.19 (1.14-1.24) <sup>c</sup>	202	1.67 (1.37-2.04) <sup>c</sup>	213	1.19 (1.01-1.41) <sup>c</sup>
≥11	860	1.17 (1.08-1.26) <sup>c</sup>	46	1.57 (1.12-2.21) <sup>c</sup>	21	1.17 (0.74-1.86)

Abbreviations: IRR, incidence rate ratio; OCD, obsessive-compulsive disorder.

<sup>b</sup> Adjusted for sex, age, and calendar year.

<sup>a</sup> The streptococcal test was the rapid antigen diagnostic test for group A β-hemolytic streptococcal throat infections.

<sup>c</sup> The reference interval did not include 1 [Reference].

**Table 4. Risk of Mental Disorders in Individuals With Positive Streptococcal Test Results, by Age at the First Positive Test<sup>a</sup>**

Age at the First Positive Streptococcal Test, y	Any Mental Disorder		OCD		Tic Disorders	
	No.	IRR <sup>b</sup> (95% CI)	No.	IRR <sup>b</sup> (95% CI)	No.	IRR <sup>b</sup> (95% CI)
No test performed	13 712	1 [Reference]	206	1 [Reference]	522	1 [Reference]
0-2	4666	1.14 (1.10-1.18) <sup>c</sup>	113	1.47 (1.17-1.85) <sup>c</sup>	258	1.23 (1.06-1.42) <sup>c</sup>
3-11	9889	1.19 (1.15-1.22) <sup>c</sup>	417	1.55 (1.30-1.83) <sup>c</sup>	723	1.41 (1.25-1.58) <sup>c</sup>
≥12	853	1.73 (1.60-1.86) <sup>c</sup>	26	1.12 (0.73-1.71)	12	1.18 (0.65-2.14)

Abbreviations: IRR, incidence rate ratio; OCD, obsessive-compulsive disorder.

<sup>b</sup> Adjusted for sex, age, and calendar year.

<sup>a</sup> The streptococcal test was the rapid antigen diagnostic test for group A β-hemolytic streptococcal throat infections.

<sup>c</sup> The reference interval did not include 1 [Reference].

association. Other studies have found that the debut and worsening of OCD and tic disorders can also be linked to nonstreptococcal infectious agents,<sup>27,28,30,31</sup> including the study by Swedo et al<sup>4</sup> describing the first 50 cases of PANDAS. Another aspect that does not seem to entirely confirm PANDAS in our study is the increased risk of any mental disorder, not only OCD and tic disorders, after a streptococcal infection. In line with this finding, psychiatric comorbidity is common when investigating children who received a diagnosis of PANDAS.<sup>4,17,18,25</sup> However, in our study, individuals with streptococcal infection did have a larger risk of the subsequent development of OCD and tic disorders than of any mental disorders; this finding favors a specific association between streptococcal infection and OCD and tic disorders. Furthermore, not all previous

studies have supported the PANDAS hypothesis.<sup>15-18</sup> The previously largest study of streptococcal infection and mental disorders investigated 2596 individuals with streptococcal infection based on a research database and found that only inpatients (ie, patients with severe streptococcal infections) had an increased risk of all outcomes as a combined group and an increased risk of attention-deficit/hyperactivity disorder, whereas the risk of OCD and tic disorders was only insignificantly increased.<sup>32</sup> Other studies did not find a temporal link between neuropsychiatric worsening and streptococcal infection<sup>17</sup> or found a temporal link in only a few of the cases but with more than 75% of the neuropsychiatric worsening occurring without an association with streptococcal infection.<sup>18</sup> We did not find the risk of the outcomes to be highest in close

proximity to the streptococcal infection, which can probably not be explained merely by a diagnostic delay.

The association between streptococcal and nonstreptococcal infections and mental disorders could also be an epiphenomenon instead of representing causality. Some parents might have an increased focus on somatic and psychiatric symptoms, prompting more frequent visits to the general practitioner in spite of only few symptoms of throat infection, inducing the registration of streptococcal tests and likewise more frequent examination and diagnosis by a psychiatrist. We might partially adjust for this medical care-seeking behavior by adjusting for socioeconomic factors and probably adjusting even more in our case-sibling design, which still found an increased risk of OCD in patients with a streptococcal throat infection compared with control siblings. However, our results for both positive and negative streptococcal test results did not change significantly in the fully adjusted model that included socioeconomic factors and a family history of mental disorders, which is also in line with previous contradictory findings regarding socioeconomic status as a risk factor for OCD.<sup>33</sup> Moreover, mental disorders have been linked to immune-related genes and genetic susceptibility to infections.<sup>34</sup> Autoimmune diseases might account for the increased occurrence of infections in these individuals; previous studies have also found that a family history of autoimmune diseases appears more frequently among children who received a diagnosis of PANDAS.<sup>18,35</sup> However, we did not find that individuals with a history of personal or parental autoimmune diseases had a more elevated risk of any of the outcomes after a streptococcal or nonstreptococcal throat infection.

### Strengths and Limitations

This large nationwide cohort had up to 17 years of follow-up without any loss to follow-up, which are major strengths of our study and make selection bias an unlikely explanation for our findings. In addition, information on streptococcal tests and outcomes were registered prospectively, which excludes recall bias. The inclusion of a case-sibling design allowed us to account for unmeasured social and environmental factors even though these analyses included fewer cases and the control siblings might also have been exposed to a streptococcal throat infection without receiving treatment. The limitations of the study include the use of a proxy method for defining a posi-

tive streptococcal test result, which allowed us to interpret this finding only as a presumed streptococcal throat infection. Furthermore, misclassification would occur in cases in which an antibiotic was prescribed to an individual with a negative test result to treat a nonstreptococcal bacterial infection or in cases in which an individual received an antibiotic for a streptococcal throat infection based only on the clinical symptoms without undergoing a streptococcal test. Hence, it might have been appropriate to perform sensitivity analyses excluding individuals in the control group who were receiving antibiotics; however, such analyses were beyond the extent of our study. The streptococcal test is targeted at group A  $\beta$ -hemolytic streptococcus, so throat infection with other types of streptococcus would lead to a negative test result, which probably dilutes the effect of a positive test result. Also, a meta-analysis<sup>36</sup> found that 14% of the streptococcal test results are false negatives, which might add to the diluting effect. Only hospital contacts for mental disorders are covered by the registers; hence, individuals treated by general practitioners or private pediatricians or psychiatrists are not included in our study. Even though the onset of OCD and tic disorders might have been abrupt and accompanied by other co-occurring psychiatric symptoms, which are important elements of PANDAS,<sup>4</sup> the registers did not provide such information, which is why we were able to explore only key aspects of PANDAS, and might not have been able to identify the rare and true cases of PANDAS. Although we found an association, the absolute risk of OCD and tic disorders after a streptococcal throat infection is still small. In addition, other noninfectious environmental factors that we were not able to include could have influenced the association with OCD, tic disorders, and Tourette syndrome.<sup>33,37,38</sup>

### Conclusions

We found that both individuals with a streptococcal throat infection and individuals with a nonstreptococcal throat infection had an increased risk of any mental disorder, OCD, and tic disorders; however, the risk of all mental disorders and of OCD was greatest in individuals with streptococcal throat infections. Our results could favor essential elements of the wider diagnostic concept of pediatric acute-onset neuropsychiatric syndrome.

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