

## Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

## **eAppendix. Statistical Analyses**

The risk of mental disorders was estimated according to age with particular focus on the age group of 3-11 years since the diagnostic working criteria for PANDAS imply that the neuropsychiatric symptoms debut from the age of 3 years to the beginning of puberty.<sup>1</sup> We investigated the importance of time since the streptococcal test was performed and a dose-response relationship by testing for a linear relationship between the number of tests and the following risk of the outcomes. In order to investigate a possible interaction between a streptococcal test and respectively sex and a personal or parental history of autoimmune disease, we stratified for these variables and made comparisons of the IRRs for exposure to a positive or negative test between the stratification groups and estimated statistical differences by P-values.

## **eReference**

1. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry*. 1998;155(February):264-271. <http://www.ncbi.nlm.nih.gov/pubmed/9464208>.

**eTable 1.** Diagnosis Codes Based on the World Health Organization International Classification of Diseases Codes from the *ICD-10* Period and Antibiotics According to the Anatomical Therapeutic Chemical System from the World Health Organization

<b>Outcome diagnoses</b>	<b>ICD-10</b>
Any mental disorder	F00-F99
Tic disorders including Tourette syndrome	F95
OCD	F42
<b>Other diagnoses</b>	<b>ICD-10</b>
Infections	A00-B99, E23.6A, G00, I02, J00–J18, K35, L00–L08, M00, N30.0, N51.8B, N70– N72, N76, N77.0D, N77.1B, N77.1L, O23, O26.4, O85, O86, O98, P35.2A
Autoimmune diseases	D51.0, D59.1, D69.3, E05.0, E06.3, E10, E27.1, G35, G61.0, G70.0, H20, K50, K51, K73, K74.3, K90.0, L10, L12, L40.0-3, L40.5-9, L63, L80, M05, M06, M08, M31.3, M31.5, M31.6, M32.1, M32.9, M33, M34, M35.0, M35.3, M45.9
Family history of psychiatric disorders	F00-F99
<b>Antibiotic</b>	<b>ATC code</b>
Phenoxyethylpenicillin	J01CE02
Amoxicillin	J01CA04
Amoxicillin/clavulanic acid	J01CR02
Clarithromycin	J01FA09
Roxithromycin	J01FA06
Clindamycin	J01FF01

**eTable 2.** Demographic Variables for Individuals Without a Streptococcal Test and Individuals With a Negative or Positive Test

<b>Covariates</b>	<b>No test</b>	<b>Negative test</b>	<b>Positive test</b>
<b>N (%)</b>	429,478 (40.2)	288,283 (27.0)	349,982 (32.8)
<b>Sex (female), N (%)</b>	208,141 (48.5)	142,838 (49.5)	168,842 (48.2)
<b>Birth year, N (%)</b>			
1996-2001	113,792 (26.5)	101,208 (35.1)	148,814 (42.5)
2002-2007	131,833 (30.7)	97,828 (33.9)	123,969 (35.4)
2008-2013	183,853 (42.8)	89,247 (31.0)	77,199 (22.1)
<b>Maternal education, N (%)</b>			
≤10 years	74,009 (17.2)	46,292 (16.1)	54,623 (15.6)
>10 and ≤15 years	183,468 (42.7)	132,741 (46.0)	165,658 (47.3)
>15 years	160,760 (37.4)	104,857 (36.4)	125,646 (35.9)
Unknown	11,241 (2.6)	4,393 (1.5)	4,055 (1.2)
<b>Maternal marital status, N (%)</b>			
Married	265,108 (61.7)	191,195 (66.3)	243,359 (69.5)
Divorced	26,317 (6.1)	25,026 (8.7)	35,118 (10.0)
Unmarried	137,006 (31.9)	71,085 (24.7)	70,089 (20.0)
Widow	1,047 (0.2)	977 (0.3)	1,416 (0.4)
<b>Maternal income in deciles, N (%)</b>			
1-3	33,489 (7.8)	13,432 (4.7)	12,223 (3.5)
4-7	212,170 (49.4)	127,832 (44.3)	141,935 (40.6)
8-10	183,819 (42.8)	147,019 (51.0)	195,824 (56.0)
<b>Parental mental disorder (yes), N (%)</b>	88,691 (20.7)	66,918 (23.2)	82,036 (23.4)
<b>Parental autoimmune disease (yes), N (%)</b>	32,437 (7.6)	26,102 (9.1)	34,841 (10.0)
<b>Personal autoimmune disease (yes), N (%)</b>	1,548 (0.4)	1,912 (0.7)	2,989 (0.9)

Streptococcal test=rapid antigen diagnostic test for group A beta-hemolytic streptococcal throat infections. N=number of individuals.

**eTable 3.** Risk of Any Mental Disorder in Persons With Positive Streptococcal Tests, Stratified by the Specific Diagnostic *ICD-10* Codes Included in the Category of any Mental Disorder

Specific <i>ICD-10</i> codes in the category of any mental disorder	No streptococcal test (reference)		Positive streptococcal test	
	N	IRR <sup>a</sup> (95% CI)	N	IRR <sup>a</sup> (95% CI)
<b>F00-09: Organic, including symptomatic, mental disorders</b>	20	1.00	31	1.91 (0.99-3.67)
<b>F10-19: Mental and behavioral disorders due to psychoactive substance use</b>	313	1.00	453	<b>1.25</b> (1.06-1.49)
<b>F20-29: Schizophrenia, schizotypal, and delusional disorders</b>	48	1.00	137	1.40 (1.00-1.95)
<b>F30-39: Mood disorders</b>	145	1.00	507	<b>1.64</b> (1.36-1.98)
<b>F40-49: Neurotic, stress-related, and somatoform disorders</b>	2,448	1.00	2,933	<b>1.24</b> (1.16-1.32)
<b>F50-59: Behavioral syndromes associated with physiological disturbances and physical factors</b>	1,187	1.00	724	1.03 (0.92-1.16)
<i>F50: Eating disorders</i>	813	1.00	542	0.91 (0.80-1.04)
<b>F60-69: Disorders of adult personality and behavior</b>	42	1.00	95	<b>1.85</b> (1.23-2.80)
<b>F70-79: Mental retardation</b>	938	1.00	634	1.05 (0.94-1.18)
<b>F80-89: Disorders of psychological development</b>	3,005	1.00	2,826	1.06 (1.00-1.12)
<b>F90-99: Behavioral and emotional disorders with onset usually occurring in childhood and adolescence</b>	5,566	1.00	7,068	<b>1.21</b> (1.17-1.26)
<i>F90: Hyperkinetic disorders</i>	1,984	1.00	3,337	<b>1.24</b> (1.17-1.31)

Streptococcal test=rapid antigen diagnostic test for group A beta-hemolytic streptococcal throat infections. N=number of individuals.

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

Boldface indicates that the reference interval did not include 1.00 (reference).

**eTable 4.** Risk of Mental Disorders in Cases Compared With Siblings With Positive and Negative Streptococcal Tests

Result of streptococcal test	Any mental disorder			OCD			Tic disorders		
	OR <sup>a</sup>	95%CI	N, Cases/siblings	OR <sup>a</sup>	95%CI	N, Cases/siblings	OR <sup>a</sup>	95%CI	N, Cases/siblings
<b>No test (reference, sibling)</b>	1.00	-	8,405/9,889	1.00	-	178/190	1.00	-	402/452
<b>Positive (case)</b>	1.05	0.96-1.16		1.22	0.69-2.18		1.10	0.72-1.68	
<b>Negative (reference, sibling)</b>	1.00	-	6,519/7,188	1.00	-	199/211	1.00	-	474/520
<b>Positive (case)</b>	1.07	0.99-1.16		<b>1.94</b>	1.18-3.20		0.97	0.71-1.32	

Streptococcal test=rapid antigen diagnostic test for group A beta-hemolytic streptococcal throat infections. N=number of individuals.

<sup>a</sup>Adjusted for sex and calendar year.

Boldface indicates that the reference interval did not include 1.00 (reference).

**eTable 5.** Risk of Mental Disorders in Individuals With Positive and Negative Streptococcal Tests, by Sex and Parental History of Autoimmune Disease

Sex	Result of streptococcal test	Any mental disorder			OCD			Tic disorders		
		N	IRR <sup>a</sup>	95%CI	N	IRR <sup>a</sup>	95%CI	N	IRR <sup>a</sup>	95%CI
Female	No test (reference)	5,255	1.00	-	115	1.00	-	118	1.00	-
	Negative	4,164	1.04	1.00-1.09	176	1.26	1.00-1.60	154	<b>1.30</b>	1.02-1.66
	Positive	5,878	<b>1.24</b>	1.19-1.29	306	<b>1.51</b>	1.22-1.88	230	<b>1.50</b>	1.20-1.87
Male	No test (reference)	8,457	1.00	-	91	1.00	-	404	1.00	-
	Negative	7,151	<b>1.11</b>	1.08-1.15	140	1.31	1.00-1.70	508	<b>1.24</b>	1.09-1.41
	Positive	9,530	<b>1.15</b>	1.11-1.19	250	<b>1.50</b>	1.18-1.90	763	<b>1.31</b>	1.16-1.48
<b>Parental autoimmune disease</b>										
Yes	No test (reference)	1,101	1.00	-	19	1.00	-	41	1.00	-
	Negative	1,007	1.02	0.94-1.12	39	1.57	0.91-2.71	66	1.46	0.99-2.15
	Positive	1,598	<b>1.19</b>	1.10-1.29	60	1.52	0.91-2.54	82	1.22	0.84-1.78
No	No test (reference)	12,611	1.00	-	187	1.00	-	481	1.00	-
	Negative	10,308	<b>1.09</b>	1.06-1.12	277	<b>1.25</b>	1.04-1.50	596	<b>1.23</b>	1.09-1.39
	Positive	13,810	<b>1.18</b>	1.15-1.21	496	<b>1.50</b>	1.27-1.78	911	<b>1.36</b>	1.21-1.52

Streptococcal test=rapid antigen diagnostic test for group A beta-hemolytic streptococcal throat infections. N=number of individuals.

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

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