

Parental Psychiatric Disorders Associated With Autism Spectrum Disorders in the Offspring

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The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

Previous literature has noted that psychiatric disorders are more common among family members of individuals with autism. Previous studies have used small clinic-based samples and been unable to distinguish whether associations are more common among mothers or fathers.

What This Study Adds

The Swedish registry system allowed data linkage to study a population less prone to selection bias than previous clinical samples. This large, population-based study had power to distinguish associations between psychiatric history among mothers versus fathers in relation to autism.

ABSTRACT

OBJECTIVE. Autism is a developmental disorder defined by impaired social interaction, communication, and behavior. Causes and correlates of autism are largely unknown, but elevated frequencies of psychiatric disorders and distinct personality traits have been reported among the family members of individuals with autism. Linkage of data from Swedish registries was used to investigate whether hospitalization for psychiatric conditions was higher among parents of children with autism compared with control subjects.

METHODS. Data sources included the Swedish Medical Birth Register (child's birth), the Swedish Multi-Generation Register (linking parents to children), and Swedish Hospital Discharge Register (hospitalization records). Children born between 1977 and 2003 who had a hospitalization record indicating autism before 10 years of age ($n = 1227$) were matched with 30 693 control subjects from the Swedish Medical Birth Register by gender, year of birth, and hospital. Parent diagnoses were based on an inpatient hospital diagnostic evaluation and included schizophrenia, other nonaffective psychoses, affective disorders, neurotic and personality disorders and other non-psychotic disorders, alcohol and drug addiction and abuse, and autism. Odds ratios and 95% confidence intervals were estimated by using conditional logistic regression, adjusted for child's age, gender, hospital of birth, parents' age, country of birth and socioeconomic status, and diagnosis of a mental disorder in the other parent.

RESULTS. Parents of children with autism were more likely to have been hospitalized for a mental disorder than parents of control subjects. Schizophrenia was more common among case mothers and fathers compared with respective control parents. Depression and personality disorders were more common among case mothers but not fathers.

CONCLUSIONS. This large population study supports the potential for familial aggregation of psychiatric conditions that may provide leads for future investigations of heritable forms of autism.

AUTISM IS A developmental disorder defined by impaired social interaction, communication, and behavior.¹ The strong genetic contribution to autism has been well supported by twin studies noting high concordance among monozygotic twins.² However, the etiology of autism is complex and likely involves multiple genes in combination with external factors.^{3–6} This allows for the possibility that autism and other psychiatric disorders result from some common genes, possibly varying in expression and in combination with other factors.

Personality traits similar to, but not as severe as, the defining features of autism have been found to be more common among the family members of some individuals with autism. These subclinical traits have become known as the broader autism phenotype.^{7–12} In addition, elevated rates of clinical psychiatric disorders, distinct from autism, have been reported among the relatives of individuals with autism, including schizophrenia, anxiety, depression, and social phobias.^{13–18} Specific genes that might contribute to the complex constellation of factors leading to autism or other psychiatric disorders have yet to be confirmed.^{4,19} However, identifying specific psychiatric disorders among the parents of individuals with autism could help distinguish familial cases from sporadic cases. This study evaluates

www.pediatrics.org/cgi/doi/10.1542/peds.2007-2296

doi:10.1542/peds.2007-2296

Key Words

autism, psychiatric disorders, schizophrenia, depression, epidemiology, registry

Abbreviations

ICD—*International Classification of Diseases*

OR—odds ratio

CI—confidence interval

Accepted for publication Nov 12, 2007

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2008 by the American Academy of Pediatrics

whether hospital diagnosis of psychiatric disorders is more common among the parents of children with hospital-diagnosed autism than the general population, and, if so, which disorders are most strongly associated with autism.

METHODS

A population-based case-control study was nested within a Swedish cohort of children born between 1977 and 2003 and their parents. Several Swedish registries were linked to facilitate the study. All of the linkages were possible because of the unique national registration number that is assigned to all Swedish residents at the time of birth or immigration and is consistently used in all types of registers and registrations in Sweden.²⁰ First, children with a diagnosis of autism were identified through the Swedish Hospital Discharge Registry. This register has nearly complete nationwide coverage for inpatient hospital care for psychiatric disorders from 1973 onward and records the treating physician's discharge diagnosis on the basis of the *International Classification of Diseases (ICD)*.²⁰ The Swedish health care system has a strong network among outpatient service, inpatient care, and school health service for individuals with autism and psychiatric conditions. No private clinics are used.

Children were considered case subjects if they were born between 1977 and 2003 and had a diagnosis of autism disorder, Asperger syndrome, or pervasive developmental disorder not-otherwise-specified at or before 10 years of age that was recorded in the registry between 1987 and 2003 (see Appendix for ICD classification).

Case children were linked by the unique registration number to the Swedish Medical Birth Registry, operated by the National Board of Health and Welfare. From the same registry, 25 control children were randomly selected for each case subject from among children of the same gender, birth year, and birth hospital. The control subjects were alive and did not have any hospital diagnosis consistent with autism at the time of the diagnosis of their respective case.

All of the children were linked to their biological parents through the Swedish Multi-Generation Register, which contains familial relationship data and is maintained by Statistics Sweden. The register contains entries for an "index person," along with the biological parents. To be included in the register, an index person had to be registered in Sweden after 1961 and to have been born after 1932. Paternity is assumed to be the husband of the mother at the time of birth or "by acknowledgment" for unwed mothers. Parents were then linked back to the Swedish Hospital Discharge Register to identify inpatient hospital diagnoses related to the parent's psychiatric disorders. Parents' diagnoses were classified into categories defined a priori to cover psychotic and nonpsychotic psychiatric disorders including schizophrenia, affective disorders, other nonaffective psychoses, neurotic and personality disorders and other nonpsychotic disorders, alcohol and drug addition/abuse, and autism (see Appendix for ICD classification). Records between 1968 and 2003 were extracted for each parent from the Swedish Hospital Discharge Register, and additional data on the parents' socioeconomic status and country of birth was obtained from Statistics Sweden.

The timing of both children's and parent's diagnoses was defined as the year of first recorded diagnosis. For parents who had multiple diagnoses, the year could have varied in the analysis depending on whether the model was specifying "any" disorder or a specific disorder subgroup. To evaluate the timing of the parent's diagnosis relative the child's diagnosis, the year of the case child's first diagnosis served as the reference year for both the case and the matched control subjects.

Conditional logistic regression analyses estimated odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for child's age, gender and hospital of birth, parents' age at delivery, socioeconomic status, country of birth, and any mental disorder for the other parent. The study was approved by the University of North Carolina at Chapel Hill Office of Human Research Ethics Institutional Review Board and by the Karolinska Institutet Research Ethics Committee.

RESULTS

Both biological parents were linked for 1227 (99%) of 1237 identified case subjects and 30 693 (99%) of 30 925 identified control subjects. Seventy-seven percent of the children were boys. Half were 4 to 6 years of age at the time of diagnosis or reference date, 20% were <4 years of age, and 30% were >6 years of age. Parents of case and control subjects were of similar socioeconomic status, but case subject parents were generally more likely to be of African, Asian, and South American nativity compared with Nordic nativity. The fathers of children with autism were older than control fathers (Table 1).

Overall, psychiatric disorders were more common among the parents of children with autism than among the parents of control subjects (OR: 1.7; 95% CI: 1.5–2.0). The OR for autism was slightly greater if both parents had been diagnosed with a psychiatric disorder (OR: 2.0; 95% CI: 1.2–3.1), adjusted for child's age, gender, reference year, parental age, socioeconomic status, and country of birth (data not shown in tables).

Schizophrenia among both the mothers (OR: 1.9; 95% CI: 0.8–4.7) and the fathers (OR: 2.1; 95% CI: 0.9–4.9) was associated with autism in their children (Table 2). Among mothers, depression (OR: 1.7; 95% CI: 1.0–2.6) and neurotic and personality disorder and other nonpsychotic disorders (OR: 1.7; 95% CI: 1.3–2.2) were associated with increased risk of autism among the children but not among the fathers. Other evaluated parental psychiatric disorders were not associated with autism in the children. Associations between parental psychiatric disorders and autism did not vary by the child's birth order or by the early (1987–1996) versus the late (1997–2004) cohorts, in which the diagnostic practices might have differed (data not shown).

The positive association between any parental psychiatric disorder and the child's diagnosis of autism was present regardless of the timing of the parent's diagnosis relative to the child's diagnosis (Table 3). The ORs for autism were slightly higher if the parent had been diagnosed before the child's diagnosis or before the child's birth, rather than after.

TABLE 1 Distribution of Parental Characteristics and Their Association With Autism

Characteristic	Mothers			Fathers		
	<i>n</i>	%	Autism OR (95% CI) ^a	<i>n</i>	%	Autism OR (95% CI) ^a
Age at delivery, y						
≥25	8812	28.0	Reference	4535	14.0	Reference
25–30	11 864	37.0	0.9 (0.7–1.0)	10 192	32.0	1.4 (1.1–1.7)
31–35	7828	25.0	0.9 (0.8–1.1)	9521	30.0	1.7 (1.3–2.1)
36–40	2929	9.0	1.1 (0.8–1.4)	4985	16.0	1.8 (1.4–2.4)
41–50	487	2.0	1.0 (0.6–1.6)	2470	8.0	1.9 (1.4–2.5)
≥50	—	—	—	217	1.0	2.7 (1.5–4.8)
Socioeconomic status						
Unskilled in goods and service	8083	25.0	Reference	7488	23.0	Reference
Skilled in goods and service	3554	11.0	0.9 (0.7–1.1)	7288	23.0	1.0 (0.8–1.2)
Assistant, nonmanual	4255	13.0	0.8 (0.6–0.9)	2547	8.0	0.9 (0.7–1.1)
Intermediate, nonmanual	4727	15.0	0.8 (0.6–1.0)	4543	14.0	0.9 (0.7–1.1)
Upper-level executives	1686	5.0	1.0 (0.8–1.4)	3416	11.0	0.9 (0.7–1.2)
Self-employed	389	1.0	0.8 (0.5–1.5)	1349	4.0	1.0 (0.8–1.4)
Agriculture	101	0.3	0.5 (0.1–2.0)	448	1.0	1.0 (1.6–1.7)
Miscellaneous and unclassified	9170	29.0	1.1 (0.9–1.3)	4841	15.0	1.1 (0.9–1.3)
Parents' country of birth						
Nordic countries	28 617	90.0	Reference	28 149	88.0	Reference
Europe and North America	1423	4.0	1.0 (0.7–1.4)	1688	5.0	1.0 (0.7–1.3)
Africa	445	1.0	1.6 (0.9–2.8)	563	2.0	1.6 (1.0–2.8)
Asia	1093	3.0	1.3 (0.9–2.0)	1176	4.0	1.4 (1.0–2.1)
South America	272	1.0	1.6 (0.8–2.9)	299	1.0	1.1 (0.6–2.2)
Other	70	0.2	0.7 (1.2–2.9)	45	0.1	—

— indicates category comprised too few individuals for analysis.

^a Data were adjusted for children's age, gender, and reference year, both parents' age at delivery, socioeconomic status, both parents' country of birth, and any mental disorder among mother or father.

TABLE 2 Association Between Parental Psychiatric Disorders and Children's Autism Diagnosis: Adjusted ORs and 95% CIs

Disorder	Maternal Diagnoses Among			Paternal Diagnoses Among		
	Autism Case Subjects, <i>n</i>	Control Subjects, <i>n</i>	OR (95% CI) ^a	Autism Case Subjects, <i>n</i>	Control Subjects, <i>n</i>	OR (95% CI) ^a
Schizophrenia	7	55	1.9 (0.8–4.7)	8	61	2.1 (0.9–4.9)
Other nonaffective psychoses	13	174	1.1 (0.6–2.1)	11	126	1.2 (0.6–2.5)
Affective disorders	42	631	1.2 (0.8–1.7)	28	480	1.0 (0.6–1.5)
Not including depression	20	392	1.1 (0.8–1.4)	21	293	1.2 (0.7–2.0)
Only depression	22	239	1.7 (1.0–2.6)	7	187	0.6 (0.3–1.4)
Neurotic and personality disorders and other non psychotic disorders	68	882	1.7 (1.3–2.2)	44	756	1.0 (0.6–1.5)
Alcohol and drug addiction or abuse	31	478	1.1 (0.8–1.7)	58	953	1.2 (0.8–1.9)
Autism	1	5	2.3 (0.3–20.5)	—	—	—

— indicates category comprised too few individuals for analysis.

^a Data were adjusted for child's age, gender, and hospital of birth and parents' ages at delivery, country of birth, socioeconomic status, other psychiatric disorders of the parent under analysis, and any psychiatric disorder among the opposite parent.

DISCUSSION

In these data, parental psychiatric diagnoses in the aggregate were associated with a twofold increased risk of autism among the children. For both parents, schizophrenia was associated with autism. For other disorders, such as depression and nonpsychotic personality disorders, the positive association between psychiatric disorders and childhood autism was found only for maternal disorders, not for paternal disorders.

We hypothesized that having a psychiatric condition might influence parents to have their child evaluated for psychiatric conditions and consequently result in increased diagnosis of autism or, conversely, that a child's disorder may lead to depression among the parents and

elevate the association between the parent's and child's diagnosis. The magnitude of the association between any parental diagnosis and autism was higher when the parent's diagnosis was set before the child's but remained elevated for maternal psychiatric diagnoses after the child's birth and diagnosis. This temporal analysis may indicate some modest increase in the children's rate of diagnosis if the parents were already in the psychiatric care system and counters that parental difficulty resulting from caring for the child's disorder would increase depression or other clinical psychiatric symptoms. These results support the hypothesis that there is a familial predisposition, perhaps genetic, that presents differently in the parent than in the child and probably requires a

TABLE 3 Association Between Parental Psychiatric Disorders and Children's Autism by the Timing of the Parent's First Diagnosis

Timing of Parent's First Diagnosis	Maternal Diagnosis			Paternal Diagnosis		
	Autism Case Subjects, <i>n</i>	Control Subjects, <i>n</i>	OR (95% CI) ^a	Autism Case Subjects, <i>n</i>	Control Subjects, <i>n</i>	OR (95% CI) ^a
Any time	115	1557	1.9 (1.6–2.4)	101	1686	1.5 (1.2–1.9)
Before child's diagnosis/reference year	81	981	2.2 (1.7–2.7)	71	1040	1.7 (1.3–2.2)
After child's diagnosis/reference year	34	576	1.5 (1.1–2.2)	30	646	1.2 (0.8–1.8)
Before child's birth	57	695	2.1 (1.6–2.8)	59	723	2.0 (1.5–2.6)
After child's birth	58	862	1.8 (1.3–2.3)	42	963	1.1 (0.8–1.6)

^aData were adjusted for child's age, gender, and hospital of birth and parents' ages at delivery, country of birth, socioeconomic status, and any psychiatric disorder among the opposite parent.

constellation of other genetic or environmental factors for expression.

These results are consistent with other studies that have shown associations between parent's psychiatric disorders and children's diagnosis of autism; however, the specific disorders associated with autism vary by study and may reflect methodologic differences.²¹ The study most similar to this study, which also relied on population-based record linkage, reported a nearly threefold increased risk of autism associated with parental schizophrenia, affective disorder, and an "other" category of disorders but was unable to distinguish whether maternal or paternal diagnoses were responsible for the association.¹³ These results may be consistent with our finding of an association with schizophrenia in both parents and depression among mothers, but detail is lacking for full comparison. Other case-control studies have implicated various psychiatric disorders, including schizophrenia, depression, social phobia, and affective disorder, but results have been inconsistent, and the smaller sample sizes have limited the ability to consistently distinguish the diagnostic categories most associated with autism.^{14–17} The social impairments and adherence to rigid routines experienced by individuals with autism may reflect a more severe presentation of social discomfort and the interpersonal challenges common to those with anxiety disorders and schizophrenia. Studies of altered brain morphology and candidate genes have been inconsistent but suggestive for both disorders.^{4,22–25} Distinguishing familial cases of autism, characterized by a family history of psychiatric disorders, may enhance progress in understanding whether some anatomic and genetic factors are common to both disorders.

The variability in results among the studies has been attributed to differences in the diagnostic standards for the children, reporting bias in classifying the parents, and the characteristics of the study population and control selection.²¹ The present study relied on diagnoses recorded in the Swedish Hospital Discharge Register. The register represents nationwide coverage of inpatient treatment facilities during the study period and includes care in psychiatric hospitals, child psychiatric clinics, special units for treatment of autism disorders, and pediatric and other somatic clinics but does not include case subjects only diagnosed and treated as outpatients. During the majority of the period under evaluation, it was common for children suspected of autism in Sweden to be hospitalized for more careful diagnostic evaluation,

but in the 1990s, outpatient evaluation and treatment began to replace services that were previously conducted in the hospitals. The temporal analysis indicates that it is unlikely that an association with hospitalized autism would be artificially induced because of a shift from outpatient to inpatient treatment over time. An earlier study of autism using the Swedish Hospital Discharge Register estimated inclusion of ~50% of expected case subjects on the basis of prevalence figures of Gillberg and Wing²⁶ and Fombonne,²⁷ considering the study period, geographic area, definition of autism, and age of case subjects.²⁰ Because all residents have equal access to both inpatient and outpatient services that are well coordinated, the decision about whether the child is hospitalized is unlikely to be related to parental resources or abilities (including psychiatric diagnoses). The present study was unable to validate the diagnoses in the registry by personal review, but the discharge diagnosis, which is the basis for the register data, reflects the final assessment by a psychiatric specialist. A previous validation of schizophrenia diagnoses indicated that registry data were reliable and valid for psychiatric research,²⁸ but such a validation has not been conducted for autism.

Diagnostic practices in psychiatry continue to change, and case definitions become more narrow for both adult and childhood psychiatric disorders. Thus, it will be important to assess the relationships between parental psychiatric disorders and an offspring's risk of autism in other data with more detailed and complete ascertainment of psychiatric disorders for parents and offspring.

Analyses based on hospital diagnoses recorded in the registry may miss more mildly affected individuals, among both parents and children, consequently reflecting more severe cases of autism and parental psychiatric disorders. Accordingly, the generalizability of the results might be somewhat limited to associations among psychiatric diagnoses severe enough to require hospitalization. We could not evaluate parents with mild disorders treated as outpatients or those with subclinical personality traits consistent with the broader autism phenotype. The influence of misclassified autism case subjects was diminished, however, because control subjects were oversampled from the population. Given the nature of these design limitations, the reported associations between parental and child psychiatric conditions are likely to be underestimates of the extent of these relationships within families.

Despite these limitations, the study benefits from its large size and population representation. Most other reports reflect a select group of clinical participants and often compare autism case subjects with control subjects with other disabilities.¹⁴⁻¹⁷ This population-based study was possible because of universal access to health care and availability of disease and demographic characteristics for the entire base population. The registries cover >99% of the Swedish population with essentially complete linkage among parents, children, and hospital discharge data.²⁰ Although the details of the parent's and child's diagnoses are limited in such data sets, they are not likely to be biased by recall and reporting differences among case and control subjects. Data in these registers allowed control for parental characteristics shown to be associated with autism by other studies, such as immigrant status and paternal age. In addition, the size and population representation improve precision in estimating the relationship among these rare diagnoses in a less select population than in some previously published research.

These results support those of smaller studies that indicated an increase in psychiatric conditions among parents of children with autism, specifically schizophrenia, neurotic disorders, and depression. Identifying families with a propensity for rare psychiatric conditions may help uncover rare genes that contribute to the susceptibility of both disorders. Future studies that have the ability to contact families directly for detailed information should confirm both parent's and child's diagnosis, consider more extended family members, and consider more mild psychiatric conditions treated on an outpatient basis, as well as subclinical personality traits consistent with the broader autism phenotype, which were not assessed here. It will also be important to reevaluate these findings among children with more mild symptoms of autism.

ACKNOWLEDGMENT

This work was supported partially by the Centers for Disease Control and Prevention.

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APPENDIX Detailed Description of Psychiatric Categories

Diagnostic Group	Current Classification, ICD-10 (1997 to Present)	Previous Classifications	
		ICD-9 (1987–1996)	ICD-8 (1968–1986)
Autism	F84 autistic disorder, F84.5 Asperger's syndrome, F84.9 pervasive developmental disorder not otherwise specified (excludes F84.2 Rett's syndrome and F84.3 childhood disintegrative disorder)	299	
Schizophrenia	F20 schizophrenia, F21 schizotypal disorder, F23.1 acute polymorphic psychotic disorder with symptoms of schizophrenia, F23.2 acute schizophrenia-like psychotic disorder, F25 schizoaffective disorder	295	295
Other nonaffective psychoses	F22 delusional disorder, F23 acute polymorphic psychotic disorder without symptoms of schizophrenia (excluding F23.1 and F23.3 noted above), F24 induced delusional disorder, F28 other nonorganic psychotic disorders, F29 unspecified nonorganic disorders	297–299, excluding 298	297–299, excluding 298
Affective disorders	F30 hypomania, F31 bipolar affective disorder, F32 depressive episode, F33 recurrent depressive episode, F34 cyclothymia, F38 other single mood (affective) disorder, F39 unspecified mood (affective) disorder	296, 298, 300.4, 311	296, 298.00, 298.10, 300.41
Neurotic and personality disorders and other nonpsychotic disorders	F40 phobic anxiety disorders, other anxiety disorders, F42 obsessive-compulsive disorders, F43 Reaction to severe stress and adjustment disorders, F44 dissociative amnesia, F45 somatoform disorders, F48 other neurotic disorders, F50 eating disorders, F51 nonorganic sleep disorders, F52 lack or loss of sexual desire, F53 mental and behavioral disorders associated with the puerperium, not elsewhere classified, psychological and behavioral factors associated with disorders or diseases classified elsewhere, F55 abuse of nondependence producing substances, F59 unspecified behavioral syndromes associated with physiological disturbances, F60 specific personality disorders, F61 mixed and other personality disorders, F62 enduring personality changes, not attributable to brain damage and diseases, F63 habit and impulse disorders, F64 gender identity disorders, F65 fetishism, F66 psychological and behavioral disorders associated with sexual development and orientation, F68 other disorder of adult personality and behavior, F69 unspecified disorder of adult personality and behavior, F99 mental disorder not otherwise specified	300–301, 306–316, excluding 300.4 and 311	300–301, excluding 300.41
Alcohol and drug addiction/abuse	Mental and behavioral disorders due to use of . . . F10 alcohol, F11 opioids, F12 cannabinoids, F13 sedatives or hypnotics, F14 cocaine, F15 other stimulants, including caffeine, F16 hallucinogens, F17 tobacco, F18 volatile solvents, F19 multiple drug use and use of other psychoactive substances	303–305	303–305

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Pediatrics 2008;121:e1357-e1362

DOI: 10.1542/peds.2007-2296

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