

Family History of Schizophrenia and Bipolar Disorder as Risk Factors for Autism

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Context: The clinical and etiologic relation between autism spectrum disorders (ASDs) and schizophrenia is unclear. The degree to which these disorders share a basis in etiology has important implications for clinicians, researchers, and those affected by the disorders.

Objective: To determine whether a family history of schizophrenia and/or bipolar disorder is a risk factor for ASD.

Design, Setting, and Participants: We conducted a case-control evaluation of histories of schizophrenia or bipolar disorder in first-degree relatives of probands in 3 samples—population registers in Sweden, Stockholm County (in Sweden), and Israel. Probands met criteria for ASD, and affection status of parents and siblings for schizophrenia and bipolar disorder were established.

Results: The presence of schizophrenia in parents was associated with an increased risk for ASD in a Swedish national cohort (odds ratio [OR], 2.9; 95% CI, 2.5-3.4) and a Stockholm County cohort (OR, 2.9; 95% CI, 2.0-4.1). Similarly, schizophrenia in a sibling was associated with an increased risk for ASD in a Swedish national cohort (OR, 2.6; 95% CI, 2.0-3.2) and an Israeli conscription cohort (OR, 12.1; 95% CI, 4.5-32.0). Bipolar disorder showed a similar pattern of associations but of lesser magnitude.

Conclusions: Findings from these 3 registers along with consistent findings from a similar study in Denmark suggest that ASD, schizophrenia, and bipolar disorder share common etiologic factors.

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AUTISM SPECTRUM DISORDERS (ASDs) and schizophrenia are currently considered as distinctive and infrequently overlapping.^{1,2} Historically, ASD was often regarded as childhood schizophrenia because the impaired social interactions and bizarre behavior found in ASD were reminiscent of symptoms of schizophrenia.³ Indeed, the psychiatrist who coined the term schizophrenia counted autism (an active turning away from the external world) as an important distinguishing feature of schizophrenia.^{4,5} Around 1980, the nosologic status of ASD and schizophrenia was revised so that these disorders were separated.⁶ The separation was strongly influenced by developmental trajectory and delineated infantile autism present from very early in life⁷ from schizophrenia where psychotic symptoms developed after an extended period of normal or near-normal development.

Several lines of evidence suggest that this distinction is not absolute, and that there

are important overlaps between ASD and schizophrenia. Some family history studies^{8,9} (although not all)¹⁰ found that the relatives of probands with ASD were more likely to have a history of schizophrenia. However, these studies tended to be small and relatively underpowered. Childhood-onset schizophrenia is a rare subtype, and a sizable fraction have premorbid ASD.¹¹ More directly, genomewide copy number variation studies have identified rare mutations that are strong risk factors for both ASD and schizophrenia (eg, 15q13.3, 16p11.2, 22q11.21, and in neurexin 1).¹²⁻¹⁵ These points of overlap are quite uncommon, and they apply to only a fraction of clinical samples.

The degree to which ASD and schizophrenia share etiologic factors has important implications for clinicians, researchers, and those affected by these diseases. Therefore, we investigated whether a family history of schizophrenia and/or bipolar disorder in first-degree relatives was a risk factor for ASD. Bipolar disorder was included given its etiologic and clinical

overlap with schizophrenia.^{16,17} We conducted parallel analyses in 3 samples to evaluate the consistency and generalizability of the findings.

METHODS

The overall goal of this study was to evaluate the impact of the exposure of family history of schizophrenia and bipolar disorder (psychotic disorders) on the outcome of ASD. This relation was evaluated in 3 complementary samples. Study 1 has Swedish national coverage of inpatient and outpatient admissions. Study 2 is based on an inclusive set of primarily outpatient ASD treatment facilities but limited to the largest population center in Sweden (Stockholm County). Study 3 uses standardized psychiatric assessment of conscripts in Israel. Autism spectrum disorder outcomes were assessed using register data, and exposures were measured using register data on parents (studies 1 and 2) or siblings (studies 1 and 3). These studies were approved by research ethics committees at Karolinska Institutet and Sheba Medical Center.

Study 1 (Sweden National Patient Register [NPR]) was conducted using Swedish national registers. An analysis of 27% of these cases was published previously.⁸ The primary key for register linkage was the unique personal identification number assigned to each Swedish citizen at birth or upon arrival in Sweden for immigrants.¹⁸ The NPR^{19,20} contains discharge diagnoses for all inpatient (since 1973) and outpatient (since 2001) psychiatric treatment in Sweden including admissions for assessment or treatment to any psychiatric or general medical hospital (including forensic psychiatric hospitals and the few private providers of inpatient health care). Biological relationships were established using the Multi-Generation Register,²¹ which identifies the relatives of an index person through linkage of a child to his or her parents and includes all individuals born in Sweden since 1932, those registered as living in Sweden after 1960, and immigrants who became Swedish citizens before age 18 years. Vital status was defined using the national Cause of Death Register. Cases were defined by the presence of a discharge diagnosis of an ASD (*International Classification of Diseases, Ninth Revision [ICD-9]* code 299 or *International Statistical Classification of Diseases, 10th Revision [ICD-10]* code F84). To avoid bias due to diagnostic uncertainty, 2147 ASD cases who had ever received a discharge diagnosis of schizophrenia (eighth revision of the ICD [ICD-8] codes 295.0-295.4, 295.6, or 295.8-295.9; ICD-9 codes 295A-295E, 295G, or 295W-295X; or ICD-10 code F20) or bipolar disorder (ICD-8 codes 296.1, 296.3, or 296.8; ICD-9 codes 296A, 296C-296E, or 296W; or ICD-10 codes F30-F31) were excluded. Ten control relative pairs were randomly selected and matched to each case-relative pair. Control participants met the following criteria: same sex and year of birth as the index case; alive, living in Sweden, and no ASD diagnosis up to the time of the proband's initial diagnosis (to avoid bias owing to left truncation and to ensure equivalent follow-up times for relatives of probands and controls)^{22,23}; and control subjects who had ever received a discharge diagnosis of schizophrenia or bipolar disorder were excluded to avoid bias due to diagnostic uncertainty. Control participants were also required to have a relative individually matched to the relative of a case by biological relationship, sex, and year of birth. We estimated the relation between the exposure (family history of schizophrenia or bipolar disorder) and the outcome (ASD) using odds ratios (ORs) with 95% confidence intervals from conditional logistic regression models in PROC PHREG in SAS version 9.2 (SAS Institute).²⁴ We adjusted the confidence intervals for nonindependence within family clusters using a robust sandwich estimator function (PHREG covsandwich option).

Study 2 (Stockholm inpatient and outpatient) was also conducted using Swedish registries.²⁵ The base for study 2 was all youth aged 0 to 17 years registered in Stockholm County from 1984 through 2007 (N=589 114). Cases were drawn from health services registers from Stockholm County and they had DSM-IV diagnosis of pervasive development disorder in the Stockholm County Council Child and Adolescent Mental Health Service Register²⁶; treatment at the Autism Centre for Young Children, Asperger Centre, or Autism Centre within Stockholm County Council Handicap and Habilitation services; or NPR diagnosis of ASD (ICD-9 code 299 or ICD-10 code F84). Because mental retardation is a source of heterogeneity in ASD,²⁷ cases were also stratified by the presence or absence of clinically significant mental retardation (ie, treatment at clinical centers specifically for ASD comorbid with mental retardation, a diagnosis of mental retardation in any register, or ASD subtype other than Asperger syndrome). We randomly selected 10 control relative pairs for each case. Control participants also resided in Stockholm County, had no evidence of ASD (ie, no treatment or NPR diagnosis), and were matched to cases by year of birth and sex as well as by the year of birth of the father and mother. The main exposures were schizophrenia (ICD-8 codes 295.0-295.9, ICD-9 codes 295A-295X, and ICD-10 code F20) or bipolar disorder (ICD-8 codes 296.0-296.9, ICD-9 codes 296A-296W, and ICD-10 code F31) in the parents of cases and control participants. These exposures were assessed using the NPR supplemented by psychiatric outpatient treatment registers available in Stockholm County. The statistical analysis paralleled that used in study 1.

Study 3 (Israeli conscripts) included all Jewish persons born in Israel who are required to participate in an assessment at age 17 years prior to compulsory military service. Participation rates are 98% for males and 75% for females (women adhering to Orthodox Judaism are exempted).²⁸ The preinduction assessment determines intellectual, medical, and psychiatric eligibility for compulsory military service. The draft board registry data were used to obtain the diagnostic outcomes for ASD probands and their siblings at age 17 years. Psychiatric diagnostic procedures are described elsewhere, and ICD-10 psychiatric diagnoses for ASD and schizophrenia were assigned by a board-certified psychiatrist experienced in treating adolescents.^{28,29} Mood disorder diagnoses for bipolar and major depressive disorder could not confidently be assigned. Draft board psychiatrists had access to additional information for subjects under specialty care for developmental disorders. Eligible subjects were born during 10 consecutive years, beginning in the 1980s. Sibships within the cohort were identified using the parental national identification numbers, which are assigned to all citizens at birth or upon immigration. There were 436 697 sibships with at least 2 siblings per sibship, 386 ASD sibships where 1 sibling had a diagnosis of ASD, and 436 311 control sibships where no sibling had a diagnosis of ASD. For analysis, 1 non-ASD sibling was randomly selected from ASD sibships, and 1 sibling was randomly selected from control sibships. As in studies 1 and 2, the association between the exposure of sibling diagnosis of schizophrenia with proband ASD was tested using logistic regression.

Swedish register diagnoses have been subjected to extensive scrutiny. The NPR is of high quality.¹⁹ For schizophrenia, the definition of affection has passed peer review on multiple occasions; direct review of case notes yields very high agreement; ^{20,30} the prevalence and recurrence risks to relatives²² are nearly identical to that accepted by the field³¹⁻³⁴; and most importantly, genomic findings in Swedish samples are highly consistent with those from conventionally phenotyped cases.^{16,35,36} For ASD, NPR diagnoses have good validity,³⁷ and we have shown high agreement via review of case notes (96%). Similarly, for the Israeli register, validity has been established.^{28,29}

Table 1. Description of Samples

	Study 1	Study 2	Study 3
Sampling frame	Sweden (national)	Stockholm County	Israel
Calendar, y	1973-2009	1984-2007	Born in 1980s
Case definition	Inpatient and outpatient registers	Treatment registers, Swedish NPR	Preinduction assessment
Cases, No.	25 432	4982	386
Male, %	69.1	72.9	86.3
Age, mean (SD), y	18.8 (14.1)	NA	17, by definition
Parent-offspring relative pairs	47 614	9964	NA
Sibling-sibling relative pairs	30 067	NA	539
Mental retardation, %	NA	41.8	NA
Control subjects, No.		49 844 ^a	436 311
Parent-offspring relative pairs	475 965 ^a		
Sibling-sibling relative pairs	300 571 ^a		

Abbreviations: NA, not available; NPR, National Patient Register.

^aTen control participants were matched to cases by sex, year of birth, and birth year and sex of relatives.

RESULTS

We investigated the association of schizophrenia and bipolar disorder in first-degree relatives (parents or siblings) with ASD using 3 samples. Descriptive data for the 3 studies are given in **Table 1**. Study 1 used a Swedish national sampling frame with outcome and exposure diagnoses defined using a national patient register. Study 2 provided complementary data based on Stockholm County outpatient and inpatient health service registers. Study 3 capitalized on a standardized national pre-prescription assessment in Israel. Male sex predominated in all samples, consistent with a US survey (76-88%).³⁸

Table 2 shows associations between family history exposures and ASD outcome for all 3 studies. The exposure of schizophrenia in parents was a significant risk factor for ASD in probands with ORs of 2.9 in both studies 1 and 2. Studies 1 and 2 had modest overlap (approximately 22% of the Swedish population live in Stockholm County). Re-analysis of study 2 after removal of inpatient ASD cases also in study 1 yielded consistent ORs. Sibling data were available in studies 1 and 3, and the exposure of schizophrenia in siblings was also a significant risk factor for ASD (ORs of 2.6 and 12.1 in studies 1 and 3, respectively). The estimate from study 3 was numerically larger, but the smaller sample size gave relatively large confidence intervals. Notably, the ORs for parents and siblings in study 1 were numerically similar.

Studies 1 and 2 had data on the exposure of bipolar disorder in parents as a risk factor for proband ASD. These associations were positive (ORs of 1.9 and 1.6, respectively, with overlapping confidence intervals). Study 1 showed similar effects for the exposure of sibling bipolar disorder.

Additional data available in study 2 allowed stratification of ASD cases by the presence (41.8%) or absence (58.2%) of mental retardation. The exposure of family history of schizophrenia or bipolar disorder with ASD was principally in cases without clinical indication of mental retardation. For ASD cases without mental retardation, ORs were 2.6 for schizophrenia and 1.5 for bipolar disorder compared with 1.6 for schizophrenia and 1.1 for bipolar disorder for ASD cases with mental retardation.

Table 2. Relation Between Exposures (Family History of Schizophrenia or Bipolar Disorder) and ASD Outcomes in 3 Studies

	Odds Ratio (95% CI)	
	Schizophrenia	Bipolar Disorder
Study 1: Sweden national outpatient + inpatient		
Parent	2.9 (2.5-3.4) ^a	1.9 (1.7-2.1) ^a
Sibling	2.6 (2.0-3.2) ^a	2.5 (2.1-3.0) ^a
Study 2: Stockholm County outpatient + inpatient		
Parent	2.9 (2.0-4.1) ^a	1.6 (1.1-2.1) ^a
Parents of ASD cases + MR	2.6 (1.6-4.3) ^a	1.1 (0.7-2.0)
Parents of ASD cases – MR	2.6 (1.6-4.2) ^a	1.7 (1.2-2.5) ^a
Study 2: Stockholm outpatient only		
Parent	2.4 (1.6-3.6) ^a	1.5 (1.1-2.0) ^a
Parents of ASD cases + MR	2.7 (1.3-5.5) ^a	1.1 (0.7-1.8)
Parents of ASD cases – MR	2.0 (1.1-3.4) ^a	1.7 (1.2-2.4) ^a
Study 3: Israeli conscripts		
Sibling	12.1 (4.5-32.5) ^a	NA

Abbreviations: ASD, autism spectrum disorder; MR, mental retardation.

^a95% confidence intervals exclude 1.0.

Analyses evaluating the effect of sex did not reveal marked differences in associations between the exposures and ASD in studies 1 through 3 as the adjusted ORs were relatively homogeneous with respect to the sex of the ASD case and the sex of the relative.

COMMENT

The purpose of our study was to evaluate whether a family history of schizophrenia or bipolar disorder in first-degree relatives was associated with ASD. We analyzed 3 samples to understand whether an association was specific to 1 sample or generalized across samples.

The findings were clear. The presence of schizophrenia or bipolar disorder in first-degree relatives was a consistent and significant risk factor for ASD in all 3 samples. Moreover, a comparable register-based study from Den-

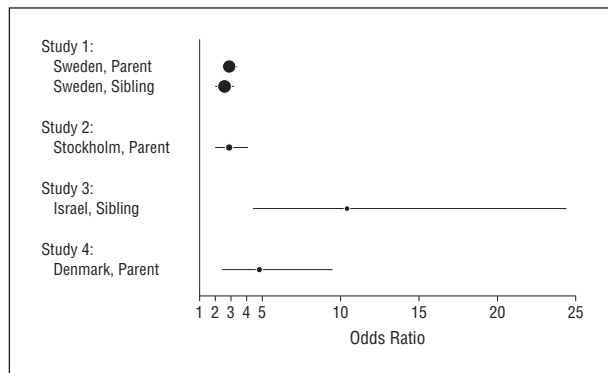


Figure. Forest plot of effects of exposure of schizophrenia in first-degree relatives on autism spectrum disorder outcomes in probands. The 3 samples reported here are shown along with a similarly conducted study from Denmark.⁹

mark showed similar findings for the association of parental schizophrenia-like psychosis with ASD (OR, 4.8; 95% CI, 2.4-9.5).⁹ We speculate that the higher sibling OR from Israel resulted from subjects with earlier onset schizophrenia, which has a higher sibling recurrence risk.³⁹ The findings from these 4 samples are depicted in the **Figure**. These remarkably consistent findings have a number of immediate implications.

These findings have implications for etiologic research. The statistical model we used to calculate the risk associated with exposure to the presence of schizophrenia in parents or siblings on the outcome of ASD was one of convenience. This model is likely incomplete. We speculate that the true underlying etiologic model contains an unmeasured confounder and moreover, does not explicitly model etiologic heterogeneity (which is plausible and generally assumed for these complex disorders). The confounder could be DNA sequence variation shared between the ASD probands and their parents or siblings, a common environmental risk factor to which all family members are exposed, or a gene-environment interaction. Genetic effects may be more likely given substantial heritability estimates for ASD,^{40,41} schizophrenia,^{23,42} and bipolar disorder^{23,43} along with evidence for relatively lesser but significant environmental effects (empirical data suggest a significant role of common environment in the etiology of both ASD and schizophrenia).^{42,44}

Our findings indicate that ASD, schizophrenia, and bipolar disorders share etiologic risk factors. We suggest that future research could usefully attempt to discern risk factors common to these disorders. As one example, the Psychiatric Genomics Consortium is now conducting an integrated and relatively well-powered meta-analysis of all available genomewide association data to evaluate whether there are associations common to more than 1 of ASD, schizophrenia, and bipolar disorder.⁴⁵

Family history has historically served as an important validator for definitions of psychiatric disorders. If ASD, schizophrenia, and bipolar disorder share etiologic risk factors, it does not necessarily follow that the disorders should be lumped into an aggregate classification. However, it is tenable that these disorders are more similar phenotypically than currently appreciated, and it might prove interesting to reevaluate the degrees of de-

marcation between these 3 disorders. Indeed, our findings are consistent with genomic data showing that the same rare copy number variants of strong effect are risk factors for both disorders. It may be that the clinical definitions of ASD and schizophrenia are derived from exemplars, individuals who have particularly distinctive and unequivocal symptoms. Definitions derived from exemplars may not be applicable to many cases seen clinically whose complex and mutable combinations of symptoms may not respect these boundaries. For individuals with ASD, assessment of psychotic symptoms is challenging particularly when language and intelligence are compromised, and some individuals with ASD cannot be evaluated. Even if assessment of psychosis is possible, the decision of whether a particular sensation, cognition, or behavior constitutes a hallucination, delusion, or thought disorder is a matter of interpretation and judgment.⁴⁶ Some individuals with schizophrenia have developmental histories not inconsistent with ASD.⁴⁷

In the discussion, we focused on family history of schizophrenia as a risk factor for ASD because the associations were generally stronger for schizophrenia than bipolar disorder. However, given increasing evidence for etiologic overlap between schizophrenia and bipolar disorders,^{16,22} we note that the analyses also support a common etiology between bipolar disorder and ASD. One potential limitation of study 1 is that the outpatient data in the Swedish NPR is relatively new (started in 2001) and not yet complete. Thus, these data cannot be used for prevalence estimates but should be unbiased with regard to the analyses presented here (we believe it unlikely that the variation in reporting from different health care providers would be correlated with family history of psychotic symptoms).

In conclusion, our findings suggest that ASD, schizophrenia, and bipolar disorder share common etiologic factors. This conclusion is supported by the results of the 3 studies reported here along with a fourth from the literature.

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