Family History of Psychiatric Illness as a Risk Factor for Schizoaffective Disorder

A Danish Register-Based Cohort Study

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Background: Schizoaffective disorder may be related to both schizophrenia and bipolar disorders, but no population-based studies, to our knowledge, have investigated this association in families.

Objectives: To determine whether a psychiatric history of schizoaffective disorder, bipolar disorder, or schizophrenia among parents and siblings is a risk factor for developing a schizoaffective disorder, and whether a specific pattern of family history of psychiatric illness exists in persons with schizoaffective disorder compared with persons with bipolar disorder or schizophrenia.

Design: Register-based cohort study.

Setting: Denmark.

Cohort: The 2.4 million persons born in Denmark after 1952.

Main Outcome Measures: Relative risks of the 3 illnesses estimated by Poisson regression.

Results: In total, 1925 persons had a schizoaffective disorder, 3721 had a bipolar disorder, and 12 501 had schizophrenia. The relative risk of schizoaffective disorder was 2.76 (95% confidence interval, 2.49-3.06) if a first-degree relative had a history of mental illness compared with a person with no first-degree relatives with such a history. There was an additional risk (95% confidence interval) of 2.57 (2.11-3.13), 3.23 (2.63-3.95), or 1.92 (1.43-2.57) if the first-degree relative had schizophrenia, bipolar disorder, or schizoaffective disorder, respectively, compared with other psychiatric admissions. When bipolar disorder was the outcome, bipolar disorder in first-degree relatives was by far the significantly strongest risk factor. When schizophrenia was the outcome, the significantly strongest risk factor was schizophrenia among first-degree relatives.

Conclusion: Schizoaffective disorder is not simply a subgroup of either bipolar disorder or schizophrenia but may be genetically linked to both, with schizoaffective disorder being a subtype of each or a genetic intermediate form.

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METHODS

All live-born children and new residents in Denmark are assigned a unique personal identification number, and vital status, on an individual level, is recorded in the Civil Registration System. The unique personal identification number is used to link to registers, which ensures accurate linkage of information between registers.7 From the Civil Registration System and the Danish Psychiatric Central Register, we identified our study populations. The Danish Psychiatric Central Register contains computerized data on all admissions to Danish psychiatric inpatient facilities since April 1, 1969. Outpatients were included from 1995.8 The diagnostic system used until December 31, 1993, was ICD-8. Beginning January 1, 1994, the ICD-10 classification was used. There are no private psychiatric inpatient facilities in Denmark, ensuring that all psychiatric admissions are represented in the register.

STUDY POPULATION

Using data from the register, we established a population-based cohort of all individuals who were born in Denmark between January 1, 1932, and January 1, 1987, who had a link to a mother, and who were alive at their 15th birthday, for a total of 2,207,862 persons. Follow-up started on the cohort members' 15th birthday or on April 1, 1970, whichever came later, and ended on the date of first schizoaffective disorder diagnosis for the study population of patients with schizoaffective disorder, first bipolar disorder diagnosis for the study population of patients with bipolar disorder, and first schizophrenia diagnosis for the study population of patients with schizophrenia; the date of death; the date of emigration; or January 1, 2002, whichever came first. Of all 2,207,862 persons in the cohort, 97.66% (2,156,212) had a registered link to a father. Siblings were identified through the link to the mother.

ASSESSMENT OF SCHIZOAFFECTIVE DISORDER, SCHIZOPHRENIA, AND BIPOLAR DISORDER IN PROBANDS AND FIRST-DEGREE RELATIVES

Cohort members and their parents and siblings were recorded by their diagnosis at discharge. They were categorized as having schizoaffective disorder if they were given an ICD-8 diagnosis code of 295.79 or 296.8 or an ICD-10 diagnosis code of F25; having schizophrenia if they received an ICD-8 diagnosis code of 295 (excluding 295.79) or an ICD-10 diagnosis code of F20; or having bipolar disorder if they had an ICD-8 diagnosis code of 296.19 or 296.39 or an ICD-10 diagnosis code of F30 or F31. They were categorized in the "any contact" group if they had any psychiatric diagnosis and were admitted; beginning in 1995, this group also included outpatients.

We used parents' and siblings' diagnoses as time-dependent indicator variables allowing the relatives to be categorized into 1 or more of the 4 groups; ie, categories are not mutually exclusive.

STATISTICAL ANALYSIS

Data were analyzed by means of the log-linear Poisson regression, with person-years as an offset variable,9,10 in the SAS GENMOD version 8.1 procedures (SAS Institute Inc, Cary, NC). All relative risks (RRs) were adjusted for calendar period (1970-1979, 1980-1984, 1985-1989, 1990-1991, 1992-2001 in 1-year groups), age (3-year groups), sex, and interaction between age and sex. Furthermore, we controlled for parents' and siblings' history of mental illness, age of the mother (<20, 20-24, 25-29, 30-34, and ≥35 years) and father (<20, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, and ≥50) at the time of the child's birth, whether the father was included in the register, number of siblings, birth order, and the person's birth municipality. Age, calendar year, number of siblings, and mother's, father's, and sibling's history of diagnosis of mental illness were treated as time-dependent variables, whereas the rest were treated as variables independent of time. P values were based on likelihood ratio tests, and 95% confidence intervals were calculated by Wald test. We used the likelihood ratio method in the test of interaction between the diagnoses of the family members. In the calculation of the cumulative incidence rate, we assume that an individual is alive throughout the whole study period. We used the standard survival function in the calculations of the cumulative incidence rate.11

RISK OF SCHIZOAFFECTIVE DISORDER

The cohort was followed up to more than 30 years and resulted in nearly 38 million person-years and 1925 persons with schizoaffective disorder. The incidence rate for a schizoaffective disorder peaked at a relatively later age in women than in men. A total of 86% of the 1925 persons had been admitted before the admission where schizoaffective disorder was first diagnosed. More than half (males, 38%; females, 51%) of the 1925 persons had previously been admitted for either a bipolar disorder and/or schizophrenia (Table 1). The changing diagnoses could be due to ambiguous or varying clinical symptoms, but they could also reflect differences between clinicians. Our
The distribution of the number of persons with schizoaffective disorder and person-years, as well as crude rates according to family history of schizoaffective disorder, bipolar disorder, schizophrenia, or any contact, is shown in Table 3. For example, 30 persons with a schizoaffective disorder had a mother with a schizoaffective disorder during 48,454 person-years of risk. Table 3 also shows the RR, adjusted for calendar time and the interaction between sex and age, associated with having a family member with schizoaffective disorder, bipolar disorder, schizophrenia, or any contact. For these persons the adjusted RR of developing a schizoaffective disorder was 10.60. In the model adjusted for sex, age, and calendar period, having a mother, father, or sibling with a schizoaffective disorder was associated with a high RR of having a schizoaffective disorder.

Because patients with a schizoaffective disorder often had a psychiatric history that included bipolar disorder or schizophrenia, we examined psychiatric illness in mother, father, and siblings in the following model: bipolar disorder, schizophrenia, schizoaffective disorder diagnosis, or any contact. No pairwise interactions were found between bipolar disorder, schizophrenia, and schizoaffective disorder in mothers, fathers, and siblings, respectively (P = .72 in a likelihood ratio test). As this is a test for departure from a multiplicative model, this finding implies the following, for example: If a person had a mother with bipolar disorder and schizophrenia, the RR of the person developing a schizoaffective disorder was 2.28 (RR if mother had any contact) \times 2.32 (RR if mother had a bipolar disorder) \times 1.94 (RR if mother had schizophrenia) = 10.26, compared with a person with a mother who had never been admitted to a psychiatric hospital.

There was no significant additional effect of father or siblings having a schizoaffective disorder (P = .79 and P = .20, respectively) compared with other admissions. The RRs of having a parent with bipolar disorder, a parent with schizophrenia, and a sibling with schizophrenia were not significantly different from each other. The RR was higher if a person had a sibling with bipolar disorder than if the sibling had schizophrenia. There was no difference between male and female patients when the impact of family history of psychiatric admission was examined (Table 5).

### RISK OF BIPOLAR DISORDER AND SCHIZOPHRENIA

The cumulative incidence of bipolar disorder, at age 47 years, was 3.36% if there was a family member with bipolar disorder and 0.31% if no family members had bipolar disorder (Table 2). When we examined bipolar disorder as the outcome variable, we found a highly increased RR of developing bipolar disorder when the mother, father, or sibling had a bipolar disorder (Table 4). There was only a minor increase in risk if the first-degree relatives had schizoaffective disorder or schizophrenia.

When the outcome was schizophrenia, we found a cumulative incidence rate (at age 47 years) of 6.11% if a family member had schizophrenia and 0.88% if no family members had schizophrenia (Table 2). Schizophrenia among first-degree relatives was the strongest risk factor. There was now only a minor increase in risk associated with having a first-degree relative with a bipolar disorder or schizoaffective disorder (Table 4).

### KEY FINDINGS

In this cohort, which covers all Danes born in Denmark after 1952 and their parents and siblings, we found that there...
was a high individual RR associated with developing schizoaffective disorder, if the mother, father, and sibling had a history of psychiatric illness. At a first glance, the highest RR was associated with parents having schizoaffective disorder and siblings having schizoaffective or bipolar disorder. After repeating the analysis in a mutually adjusted model, ie, taking into account that family members with a schizoaffective disorder diagnosis also frequently had a schizophrenia diagnosis and/or a bipolar disorder diagnosis, the highest RR was associated with having parents and siblings with a bipolar disorder diagnosis and/or a schizophrenia diagnosis. The increase in the RR when a parent had bipolar disorder was not significantly different from the increase when a parent had schizophrenia.

When bipolar disorder was the outcome, bipolar disorder in the first-degree relatives was by far the strongest risk factor; however, schizophrenia among first-degree relatives was a small but significant risk factor. When schizophrenia was the outcome, the strongest risk factor was schizophrenia among first-degree relatives, but still with bipolar disorder as a smaller but significant risk factor.

### COMPARISON WITH OTHER RESULTS

There seems to be general agreement that there is a genetic factor in schizoaffective disorders with increased schizophrenia and affective disorder morbid risks. Since schizoaffective disorder shares many features with both bipolar disorder and schizophrenia, comparisons with these illnesses have been made. Berrettini found that there was evidence of 4 susceptibility loci (18p11.2,
22q11-13, 13q32, and 10p14) shared between bipolar disorder and schizophrenia. Evidence of susceptibility loci unique to bipolar disorder and unique to schizophrenia was also found. In accordance with these results, we found that bipolar disorder in relatives was a large risk factor for bipolar disorder, but also a minor risk factor for schizophrenia and vice versa. A review by Bramon and Sham also concluded that there was an increased risk of schizophrenia among relatives of probands with bipolar disorder.4 Especially for the ICD-8, ICD-9, and DSM-III classifications, they found that there seemed to be a tendency toward an equal distribution of affective disorder and schizophrenia in first-degree relatives of patients with schizophrenia. A slightly different result was found by Tsuang, who compared the morbid risk of schizophrenia and affective disorders among first-degree relatives of persons with schizophrenia, schizoaffective disorder, and affective disorder. Tsuang found a morbid risk of schizophrenia of the same size in first-degree relatives of probands with schizoaffective disorder and schizophrenia, but a lower morbid risk of schizophrenia among first-degree relatives of probands with affective disorder. The morbid risk of affective disorder shows a tendency to have an intermediate position for relatives of probands with schizoaffective disorder, between the higher risk in relatives of probands with affective disorder and lower risk in probands with schizophrenia. They concluded that schizoaffective disorder was not solely a variant of schizophrenia or of affective disorders. Coryell and Zim-
merman compared relatives of probands with major depression, schizoaffective disorder, and schizophrenia and those who were never ill. They found that data supported the separation of schizophrenia and psychotic affective disorder in the sense that schizophrenic patients had no more familial clustering of depression, and depressed probands had no more clustering of schizophrenia than controls.

It seems possible to distinguish schizoaffective disorder from affective disorder and schizophrenia. Several studies have compared the outcome of the 3 illnesses. For example, Jäger et al compared schizoaffective disorder with schizophrenia and affective disorder. They found that it was possible to prognostically distinguish schizoaffective disorder from affective disorder and schizophrenia. When examining the long-term outcome, they found that schizoaffective disorder had a significantly more favorable outcome than schizophrenia. There was only a minor difference when affective disorder and schizoaffective disorder were compared, leading to the conclusion that schizoaffective disorder showed a similar outcome to affective disorder. Kendler et al also found it possible to distinguish between schizoaffective disorder and the other illnesses.

In summary, in the literature schizoaffective disorder has been considered in a number of different ways: as schizophrenia with affective symptoms, as an affective disorder with schizophrenic symptoms, as a genetic intermediate form with a mixture of schizophrenic and affective symptoms, as an intermediate step between schizophrenia and affective disorder in a continuum psychosis, as a chance occurrence of schizophrenia and affective disorder in the same patient at the same time, and as an independent illness with its own symptoms.

In the literature, many studies have shown a familial aggregation of bipolar disorder in families of probands with bipolar disorder and a familial aggregation of schizophrenia in families of probands with schizophrenia. We found the same pattern in our study. Furthermore, we found that schizoaffective disorder was equally strongly associated with bipolar disorder and schizophrenia among first-degree relatives; there were no significant differences between the RRs. This contrasted our results regarding schizophrenia and bipolar disorder, with a strong and more specific association with family history of schizophrenia and bipolar disorder, respectively. The RR was significantly higher for the same diagnosis than for other diagnoses in first-degree relatives. In the discussion of whether schizoaffective disorder is a subgroup of schizophrenia or a subgroup of bipolar disorder, our findings suggest that schizoaffective disorder is equally related to both disorders, because bipolar disorder and schizophrenia coexist in the families of patients with schizoaffective disorder with the same increased risk for schizoaffective disorder. Schizoaffective disorder seems to coexist as an intermediate disorder sharing family risk factors with both schizophrenia and bipolar disorder.

If the group of patients diagnosed as having schizoaffective disorder were composed of a mixture of patients with schizophrenia and bipolar disorder, this could give the same result as we present in this study. If so, however, the results suggest that information about family history of psychiatric illness may indicate which category they most probably belong to. Otherwise, the results from our study could suggest that schizoaffective disorder may represent a separate clinical manifestation of genetic intermediate forms of schizophrenia and bipolar disorder. The result gives little support to schizoaffective disorder being a separate disorder of its own, which would have produced results with definite separation between the 3 disorders. Chance occurrence simultaneously in the patients would be extremely rare, and a

Table 5. Adjusted RR Associated With Family History of Psychiatric Illness for Developing Schizoaffective Disorder, Bipolar Disorder, and Schizophrenia by Sex

<table>
<thead>
<tr>
<th>Family History of Psychiatric Diseases, Total*</th>
<th>Schizoaffective Disorder</th>
<th>Bipolar Disorder</th>
<th>Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>RR† (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not admitted (reference)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Any contact</td>
<td>2.83 (2.44-3.29)</td>
<td>2.37 (2.11-2.65)</td>
<td>2.38 (2.26-2.51)</td>
</tr>
<tr>
<td>Additional effect of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>3.90 (2.97-5.12)</td>
<td>5.14 (4.20-6.28)</td>
<td>1.44 (1.24-1.68)</td>
</tr>
<tr>
<td>S</td>
<td>2.63 (2.00-3.47)</td>
<td>1.70 (1.32-2.19)</td>
<td>3.15 (2.84-3.50)</td>
</tr>
<tr>
<td>SA</td>
<td>1.69 (1.11-2.56)</td>
<td>1.57 (1.12-2.19)</td>
<td>1.08 (0.86-1.36)</td>
</tr>
<tr>
<td>Females</td>
<td>RR† (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not admitted (reference)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Any contact</td>
<td>2.69 (2.33-3.11)</td>
<td>2.41 (2.16-2.68)</td>
<td>2.47 (2.29-2.65)</td>
</tr>
<tr>
<td>Additional effect of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>2.59 (1.90-3.52)</td>
<td>5.22 (4.33-6.30)</td>
<td>1.43 (1.16-1.76)</td>
</tr>
<tr>
<td>S</td>
<td>2.51 (1.89-3.32)</td>
<td>1.67 (1.31-2.13)</td>
<td>3.35 (2.92-3.85)</td>
</tr>
<tr>
<td>SA</td>
<td>2.20 (1.45-3.33)</td>
<td>1.15 (0.81-1.62)‡</td>
<td>1.43 (1.08-1.89)</td>
</tr>
</tbody>
</table>

Abbreviations: BP, bipolar disorder; CI, confidence interval; RR, relative risk; S, schizophrenia; SA, schizoaffective disorder.
*At least 1 family member (mother, father, siblings).
†Mutually adjusted for family history of psychiatric admissions, birth order, paternal/maternal age at birth, place of birth, number of siblings, calendar year, and sex × age interaction.
‡Not significant (P = .45).
clinical intermediate form of a continuum psychosis would be expected to have lower rates of schizoaffective disorder in the relatives.

REMARKS ABOUT THE DESIGN

An important issue to address when looking at schizoaffective disorder in a register-based study is to determine which diagnostic codes should be used in the definition. We used ICD-10 codes F25 and corresponding ICD-8 codes 295.79 and 296.8. These ICD-8 diagnoses are broadly accepted (World Health Organization ICD-10 to ICD-8 conversion table) as being equivalent to ICD-10 code F25.

When RRs are estimated in family history studies, misclassification should always be considered as a potential problem. In particular, schizoaffective disorder is a clinical diagnosis ofunknown validity from 2 classification periods. For the diagnoses of schizophrenia and bipolar disorder, 2 studies have validated the clinical diagnosis in the Psychiatric Central Register against research criteria diagnoses, showing high agreement between the diagnoses. In this study, we assume a possible misclassification to be nondifferential, ie, measurement error in exposed and unexposed persons is the same. Family members of a proband with schizoaffective disorder do not have a higher degree of measurement error than family members of probands without schizoaffective disorder. Because of this, the RR would be “conservative,” that is, biased toward the null hypothesis (RR=1.00). Only the most severe cases of the psychiatric diseases are included in this study, as we investigated only persons in contact with the psychiatric system in Denmark. Thus, we minimize the risk of false-positive results. Beginning in 1995 we included outpatients because treatment of psychiatric illness in Denmark tends toward outpatient treatment instead of inpatient treatment. We thereby introduce a problem in terms of incidence vs prevalence of the persons categorized as outpatients. We have no indication of whether the person was an outpatient before 1995. We believe, however, that this problem is very small because persons with these severe illnesses in the early follow-up period were seldom outpatients only. Analyses were performed with outpatients excluded, and results were almost identical regarding the RRs. We had 1536, 2975, and 10,813 inpatients with schizoaffective disorder, bipolar disorder, and schizophrenia, respectively.

The Danish Psychiatric Central Register has complete computerized records from 1969 to the present. Parents of children in this cohort could have been born as far back as the start of the 20th century. By definition of the cohort, their children should be born after 1952. These facts can create a problem in assessing family history. For example, a person born in 1940 was 29 years old in 1969 and could have been admitted before 1969. This admission would not be registered in the electronic part of the register if the person was discharged before 1969. This kind of misclassification will, however, again bias the results toward the null hypothesis. The risk of false-negative findings among parents in the register is at the same level for bipolar disorder, schizophrenia, and schizoaffective disorder admissions. This is not a problem of the cohort members, as they were born after 1952, and the risk of receiving a diagnosis of schizoaffective disorder, schizophrenia, or bipolar disorder before the age of 17 years is generally very low.

CONCLUSIONS

A large number of cases were included in our study during a long period, giving a solid numerical basis for studying whether the psychiatric history of the first-degree relatives affects the risk of schizoaffective disorder. We found that the risk of schizoaffective disorder was equally strongly associated with schizophrenia and bipolar disorder among the first-degree relatives. We also found that bipolar disorder in the family was a strong risk factor for developing a bipolar disorder and that schizophrenia in the family was a strong risk factor for developing schizophrenia. However, the risk of bipolar disorder was not strongly associated with schizophrenia in the family and vice versa, although a significant association was present in both directions.

On the basis of our results, we assume that there is an equal aggregation of bipolar disorder and schizophrenia in families of persons admitted with schizoaffective disorder and that schizoaffective disorder may be genetically linked to both, with schizoaffective disorder being a subtype of each or a genetic intermediate form.

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REFERENCES


Errors in Tables. In the Original Article by Nurnberger et al titled “A Family Study of Alcohol Dependence: Co-aggregation of Multiple Disorders in Relatives of Alcohol-Dependent Probands,” published in the December issue of the ARCHIVES (2004;61:1246-1256), there were errors in Tables 2 and 3. In Table 2, the heading for column 4 should have read “Prevalence, %.” In Table 3, under the heading “Prevalence, %,” the value for ASPD in Relatives should have read 8.79. The journal regrets the error.