

Severe Mental Disorders in Offspring With 2 Psychiatrically Ill Parents

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Background: Studies of couples of psychiatric patients with children allow us to calculate the effects of double predispositions on morbid risk in the offspring, which is of interest for molecular genetic research and for genetic counseling.

Objective: To determine the risks in offspring of receiving a diagnosis of schizophrenia, bipolar disorder, unipolar depressive disorder, or any diagnosis from parents who both have received a diagnosis of schizophrenia or bipolar disorder.

Design: National register-based cohort study.

Setting: Denmark.

Participants: A population-based cohort of 2.7 million persons born in Denmark, alive in 1968 or born later than 1968, with a register link to their mother and father and aged 10 years or older in 2007.

Main Outcome Measure: Risk of schizophrenia or bipolar disorder, calculated as cumulative incidences by age 52 years.

Results: The risk of schizophrenia in 270 offspring of

196 parent couples who were both admitted to a psychiatric facility with a diagnosis of schizophrenia was 27.3% (increasing to 39.2% when schizophrenia-related disorders were included) compared with 7.0% in 13 878 offspring from 8006 couples with only 1 parent ever admitted for schizophrenia and 0.86% in 2 239 551 offspring of 1 080 030 couples with neither parent ever admitted. The risk of bipolar disorder was 24.9% in 146 offspring of 83 parent couples who were ever admitted with bipolar disorder (increasing to 36.0% when unipolar depressive disorder was included) compared with 4.4% in 23 152 offspring from 11 995 couples with only 1 parent ever admitted and 0.48% in 2 239 553 offspring of 1 080 030 couples with neither parent ever admitted. Risks of schizophrenia and bipolar disorder in offspring of couples with 1 parent with schizophrenia and the other with bipolar disorder were 15.6% and 11.7%, respectively. The maximal risks of any psychiatric disorders in the offspring of parents both with schizophrenia or both with bipolar disorder were 67.5% and 44.2%, respectively.

Conclusions: Derived risks may be informative for counseling. Patterns of transmission may support evolving assumptions about genetic overlap for traditional categories.

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GENETICALLY ORIENTED studies of offspring of 2 psychiatric patients followed into adulthood represent a super-high-risk strategy compared with studies of children with only 1 affected parent. The dual-mating study permits calculating the effects of double predispositions on the lifetime morbid risk (age-corrected) in the offspring of couples with the same or different mental disorders. Such risks will be of use to genetic counselors to inform personal decisions with regard to marriage, family formation, adoption, and health insurance planning. Studies of the outcome in the offspring of parents with homotypic disorders, eg, schizophrenia \times schizophrenia and bipolar affective disorder \times bipolar affective disorder, may elucidate modes of transmission and possible genetic heterogeneity.^{1,2} Matings between those with heterotypic disorders, eg, schizophrenia \times bipolar disorder,

may reveal the presence and risk of possible spectrum interforms or other atypical forms of parental criterion diagnoses in the offspring^{3,4} and may be of interest to researchers intrigued by the overlap in offspring phenotypes between schizophrenia and bipolar affective disorder.⁵⁻⁷

Infrequent psychiatric dual-mating studies during the last century have relied on case histories of small clinical samples. They were all central European studies with diagnostic evaluations based on the German and Swiss concepts of Kraepelin and Bleuler, which are quite similar to the descriptions from the *International Classification of Diseases, Eighth Revision (ICD-8)* and *International Classification of Diseases, Ninth Revision (ICD-9)*.^{8,9} Morbid risks (ie, age-corrected) of schizophrenia in offspring of 2 schizophrenic parents varied between 28% and 58% in 8 studies (on average, 48% in pooled data). Risk of manic-depressive disorder in offspring of 2 such

parents varied between 22% and 80% in 4 studies (on average 28% in pooled data),* that is, between 2 and 4 times the risk in contemporary studies of children with only 1 affected parent.¹⁰ In offspring of 1 parent with schizophrenia and 1 parent with manic-depressive disorder, the risks of schizophrenia and manic-depressive disorder were similar to the risks in children with only 1 parent with schizophrenia or only 1 parent with manic-depressive disorder, 13% to 14% and 18% to 20% respectively.³ The present study is conducted within the context of genetic epidemiology¹¹ to obtain maximum sample sizes, using all register-based diagnoses for each patient reported in the nationwide Danish Central Psychiatric Register.

METHODS

SOURCE OF DATA

A cohort of more than 2.6 million persons with a link to their biological parents, ignoring legal marital status, and with information on all psychiatric admissions among offspring and parents was established from 2 Danish registers with privacy guaranteed by meticulous safeguards in place. The Danish Civil Registration System¹² was established in 1968. All persons living in Denmark are assigned a unique identification number, and data on their date of birth, sex, vital status (continuously updated), and identity of parents and siblings are recorded. The identification number is used in all national registers, thus guaranteeing accurate linkage of information among registers.

The Danish Psychiatric Central Register contains data on psychiatric inpatient and outpatient admissions (currently about 650 000 persons with 2.8 million admissions), computerized since 1969 with complete registration from April 1, 1970, of all admissions to Danish psychiatric inpatient facilities; it has included outpatients since 1995.¹³ As there are no private psychiatric inpatient or outpatient units, all admissions in Denmark are contained in the register. From 1966 until December 31, 1993, ICD-8 was used for diagnostic classification¹⁴; ICD-10 has been used since January 1, 1994.¹⁵

STUDY POPULATION

A population-based cohort of all persons born in Denmark, alive in 1968 or born later than 1968, and with a link to their mother and father was established from the Civil Registration System for a total of 3 391 018 persons. The investigation was restricted to persons who were aged 10 years before January 1, 2007, for a total of 2 685 301 persons and their parents. The number of unique parent couples (counted only once) was 1 278 977 couples, some of whom had more than 1 offspring.

STUDY DESIGN

Those who had ever received diagnoses of schizophrenia, bipolar affective disorder, or unipolar depressive disorder were identified from the Psychiatric Central Register among a group of parent couples with both parents ever having been admitted to a psychiatric facility from April 1, 1970, to January 1, 2007. For each of these groups of parent couples, their offspring, the eldest reaching age 52 years at follow-up, were checked in the register for admissions with similar or related diagnoses, and cumulative incidences were calculated.

For comparison, cumulative incidences were calculated in the offspring of couples with only 1 parent ever having been admitted to a psychiatric facility for the selected diagnoses and the other parent never having been admitted. To create base

rates from the general population for comparison, cumulative incidences were calculated in the offspring of parent couples with neither parent ever having been admitted (cleaned population) and parent couples with no restrictions on parent diagnoses (uncleaned population).

Cumulative incidences of schizophrenia and bipolar disorder in offspring of both parents with heterotypic disorders were calculated in parent couples in which 1 parent was admitted for schizophrenia and the other parent was admitted for bipolar disorder to inform discussions about genetic overlap between schizophrenia and bipolar disorder. To get an estimate or impression of normality in the offspring of the various groups of parent couples, the cumulative incidences of any psychiatric diagnosis in the offspring were calculated.

Because both the parents and their offspring may have been admitted more than once with different diagnoses, they may appear in more than 1 of the groups of parent couples or offspring; thus the groups are not mutually exclusive. Furthermore, some of the offspring may have their own children in this longitudinal design; therefore, the same person may have dual status as both offspring and in one of the groups of parent couples.

ASSESSMENT OF PSYCHIATRIC DIAGNOSES

Parents and offspring were classified according to their diagnoses at discharge from admissions to inpatient or outpatient treatment facilities. Each admissions diagnosis was defined by the corresponding codes from ICD-8 and ICD-10 the first time the parents and offspring were recorded with that diagnosis in the Danish Psychiatric Central Register. Disorders were categorized as schizophrenia if they were given an ICD-8 code of 295 (schizophrenia) or an ICD-10 code of F20 (schizophrenia); as schizophrenia-related disorders if they received an ICD-8 diagnosis of 297 (paranoid states), 298.3 (acute paranoid reaction), 298.9 (reactive psychosis unspecified), 299 (unspecified psychosis), 301.0 (paranoid personality disorder), 301.2 (schizoid personality disorder), or 301.83 and 301.84 (special Danish categories for borderline cases [*casus limitares pseudoneuroticae sive pseudopsychopathicae* or *casus limitares psychicae aliae*]), or an ICD-10 code of F21 (schizotypal disorder), F22 (persistent delusional disorders), F23 (acute and transient psychotic disorders), F25 (schizoaffective disorders), F28 (other nonorganic psychotic disorders), F29 (unspecified nonorganic psychotic disorder), F60.0 (paranoid personality disorder), or F60.1 (schizoid personality disorder); as bipolar affective disorder if they received an ICD-8 code of 296.1 (manic-depressive psychosis, manic type), 296.3 (manic-depressive psychosis, circular type), or 296.8 (manic-depressive psychosis, other), or an ICD-10 code of F30 (manic episode), F31 (bipolar affective disorder), or F38.00 (mixed affective episode); as unipolar depressive disorder if they received an ICD-8 code of 296.0 (involuntary melancholia) or 296.2 (manic-depressive psychosis, depressed type), or an ICD-10 diagnosis of F32 (depressive episode) or F33 (recurrent depressive disorder), and as any psychiatric disorder if they had received any ICD-8 code between 290 and 315 or any ICD-10 F code (F00-99).

STATISTICAL ANALYSIS

The incidence of psychiatric admission was calculated from the number of new cases occurring for each age in the cohort members.^{16,17} Cumulative incidences at age t are calculated as

$$S(t) = \exp\left[-\sum_{i \leq t} \lambda(t_i)\right]$$

$\lambda(t_i)$ is the incidence at time t_i , which is based on the Nelson-Aalen estimator.^{18,19} The cumulative incidence reported in the tables and henceforth in the text can be interpreted as, at a given age,

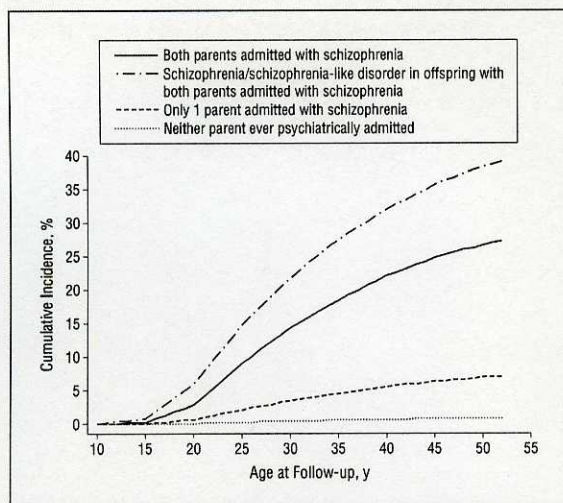


Figure 1. Cumulative incidence of admission with schizophrenia in offspring by age.

the proportion of people in a population (eg, those with both parents admitted with schizophrenia) who have received a diagnosis prior to follow-up. Version 9 of SAS (SAS Institute Inc, Cary, North Carolina) was used in the estimation. Cumulative incidences cannot be calculated from the raw data on sample sizes.

ETHICS

This study was approved by the Danish Data Protection Agency. Because data available for register-based research do not include information that can lead to the identification of individuals, approval from the National Scientific Ethical Committee was not required.

RESULTS

RISK AS CUMULATIVE INCIDENCES OF DEVELOPING SCHIZOPHRENIA

For 196 couples with both individuals admitted with a diagnosis of schizophrenia (270 children), the cumulative incidence by age 52 years for 26 of their children being admitted with a diagnosis of schizophrenia was 27.3% (95% confidence interval [CI], 18.3-36.2) (**Figure 1**). Including schizophrenia-related disorders, the number of affected children increased to 40 and the cumulative incidence to 39.2% (95% CI, 28.8-48.6).

For 8006 couples with 1 of them admitted with schizophrenia and the other never having been admitted (13 878 offspring), the cumulative incidence for 473 of their offspring being admitted with schizophrenia was 7.0% (95% CI, 6.4-7.7). For 1 080 030 couples with neither individual ever having been admitted (2 239 551 offspring), 9384 offspring were admitted with schizophrenia; the cumulative incidence was 0.86% (95% CI, 0.83-0.88). In the general population with no restrictions on parental admissions (1 282 934 couples with 2 701 593 offspring and 14 938 offspring admitted with schizophrenia) the cumulative incidence was 1.12% (95% CI, 1.09-1.14). The last 2 values taken

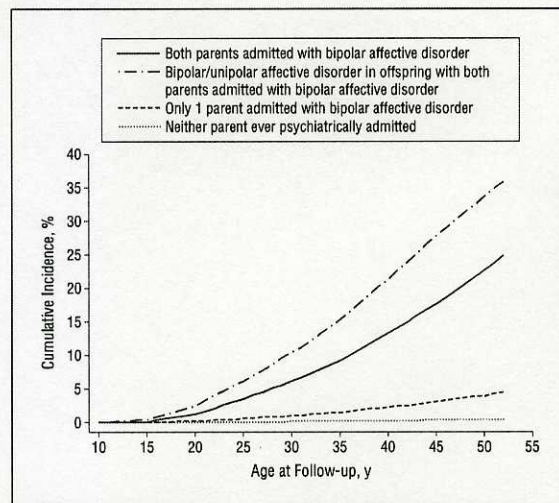


Figure 2. Cumulative incidence of admission with bipolar affective disorder in offspring by age.

as base population rates correspond closely with the classic literature in genetic epidemiology.¹¹

The risk estimated as cumulative incidence percentage by age 52 years of being admitted with a diagnosis of schizophrenia in offspring of 2 parents admitted with a diagnosis of schizophrenia is clearly (3.9 times) higher than in offspring with only 1 schizophrenic parent and 31.7-fold higher than in the general population with no parents ever having been admitted. Including schizophrenic spectrum disorders in the offspring raises the ratio to 45.6. The incidence in offspring with only 1 schizophrenic parent is also higher (8.2 times) than in the general population with no parents admitted.

In couples in which 1 individual was admitted with schizophrenia and the other was admitted with bipolar disorder, the cumulative incidence in their offspring admitted with schizophrenia was 15.6% (95% CI, 7.1-24.0). This is more than twice the value for the offspring of couples with 1 individual with schizophrenia. The difference shows a marked trend but is not statistically significant (overlapping CIs) because of low numbers. In couples with both parents admitted with bipolar disorder, the cumulative incidence in offspring for schizophrenia was 4.8% (95% CI, 0.2-9.4), 4 times the value for the general population.

RISK AS CUMULATIVE INCIDENCES OF DEVELOPING BIPOLAR AFFECTIVE DISORDER

For 83 couples with both individuals admitted with a diagnosis of bipolar disorder (146 offspring), the cumulative incidence of being admitted with bipolar disorder by age 52 years in 15 of their children was 24.95% (95% CI, 14.0-35.8) (**Figure 2**). With the inclusion of unipolar depressive disorder, the number of affected children increased to 24 and the cumulative incidence increased to 36.0%; 95% CI, 24.6-47.4).

In 11 995 couples with 1 individual admitted with bipolar disorder and the other never admitted, 400 in their 23 152 offspring were admitted with bipolar disorder; the

