

Bipolar Disorder, Schizoaffective Disorder, and Schizophrenia Overlap: A New Comorbidity Index

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Objective: Growing evidence of an etiologic overlap between schizophrenia, schizoaffective disorder, and bipolar disorder has become increasingly difficult to disregard. We investigated the magnitude of the overlap between the clinical diagnoses of bipolar affective disorder, schizoaffective disorder, and schizophrenia over a 35-year period based on the entire Danish population.

Method: We established a register-based prospective cohort study of more than 2.5 million persons born in Denmark after 1954. Risks for the 3 psychiatric disorders were estimated by survival analysis using the Aalen-Johansen method. Cohort members were followed from 1970 to 2006. We introduced a new comorbidity index measuring the magnitude of the overlap between the 3 disorders.

Results: Overall, 12,734 patients were admitted with schizophrenia, 4,205 with bipolar disorder, and 1,881 with schizoaffective disorder. A female bipolar patient's risk of also being admitted with a schizoaffective disorder by the age of 45 years was approximately 103 times higher than that of a woman at the same age in the general population. Thus, we defined the comorbidity index between schizoaffective disorder and bipolar disorder at age 45 years to be 103. At age 45 years, the index between schizophrenia and schizoaffective disorder was 80 and between schizophrenia and bipolar disorder was 20. Similar large comorbidity indexes were found for men.

Conclusions: A large comorbidity index between schizophrenia and schizoaffective disorder was found, as well as a large index between bipolar disorder and schizoaffective disorder. But, more surprisingly, it was clear that a substantial comorbidity index between bipolar disorder and schizophrenia was present. This study supports the existence of an overlap between bipolar disorder and schizophrenia and thus challenges the strict categorical approach used in both *DSM-IV* and *ICD-10* classification systems.

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The classification of mental disorders and especially the concept of psychosis has been debated for more than 100 years. Psychoses have historically been dichotomized, as originally proposed by Emil Kraepelin¹: dementia praecox (schizophrenia) and manic depressive insanity (bipolar disorder). In the World Health Organization *ICD-10* classification,² psychosis (occasionally denoted *functional psychosis*) is categorized in 2 different chapters: schizophrenia in the F2 chapter and bipolar disorder in the F3 chapter. However, this dichotomization with assumptions of different illness processes and treatment has been questioned from the beginning, as Kraepelin recognized that many patients presented symptoms from both disorders.³ As a response to these “in-between” patients, Kasanin introduced the concept of schizoaffective disorder in 1933.⁴

The definition of schizoaffective disorder has changed during the last decades, and it is a highly “unstable” diagnosis, defined in different ways in Europe and in the United States. In short, the *DSM-IV-TR*⁵ definition requires a co-occurrence of an affective episode and a schizophrenia active phase and at least 2 weeks without mood symptoms. At the same time, affective disorders with psychotic mood-incongruent symptoms could include schizophrenia symptoms. The *ICD-10* classification defines only the co-occurrence of an affective syndrome and schizophrenia symptoms for 2 weeks of about the same extent and intensity as the affective symptoms. Schizophrenia symptoms are not allowed in psychotic affective disorders.⁶ However, despite the problems with the validity of the diagnosis, probably because of the large number of “in-between” patients, the diagnostic category of schizoaffective disorder is upheld.

Discussions on this dichotomization versus an overlapping etiology between schizophrenia and bipolar disorder were reiterated in the early 1980s. Studies have shown that a family history of psychiatric disorders, recent stress, child birth, and perinatal complications are risk factors for both disorders,^{6–11} which further questions the concept of dichotomization.¹² On the other hand, risk factors operating solely on one of the disorders have been found; urban birth, paternal age (> 50 years), and physical anomalies have been proposed to affect only the risk of schizophrenia,^{8,9,13} while higher social status decreases the risk of bipolar disorder.⁹

With the possibility to study genetic polymorphisms, new methods to approach the overlap of the 3 disorders

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have become available. Over the last decade, it has become clear that neither schizophrenia nor bipolar affective disorders are results of a single cause or single gene.¹² Rather, both disorders might be the result of epistatic effects with a number of genes with relatively small impact compounded by environmental hazards.¹² Some of these genes are believed to confer susceptibility toward both disorders, whereas other genes may only increase the risk of one of the disorders.^{14–16} Results from studies on the overlap are, however, rather inconclusive.^{14–16}

We aimed to investigate the magnitude of the overlap between the clinical diagnoses of bipolar affective disorder, schizoaffective disorder, and schizophrenia. Linking Danish nationwide population-based registers, we followed up Danes for 35 years. In Denmark, psychiatric hospitalization is paid for via the tax system, and, thus, all persons have, in principle, equal access to psychiatric treatment. Similar data including the entire population of a country can be obtained only in Sweden and Finland.

We introduced a new comorbidity index measuring the magnitude of the overlap between the 3 disorders, enabling us to make a new and important contribution to the discussion of dichotomization versus overlapping diseases.

METHOD

Study Population, Assessment of Psychiatric Admission, and Follow-Up

We identified all persons born in Denmark between January 1, 1955, and January 1, 1991, who were alive at their 15th birthday using data from the Danish Civil Registration System.¹⁷ This search yielded a total of 2,508,280 persons in the population-based cohort.

Using The Danish Psychiatric Central Register,¹⁸ all psychiatric inpatient admissions in Denmark from January 1, 1970, to December 31, 2006, were identified. The diagnostic system used in the Danish registers until December 31, 1993, was the Danish adaptation of *ICD-8*.¹⁹ From January 1, 1994, the *ICD-10*² classification was used. The psychiatric disorders of interest were bipolar disorder (*ICD-8*: 296.19 or 296.39, *ICD-10*: F30 or F31), schizoaffective disorder (*ICD-8*: 295.79 or 296.8, *ICD-10*: F25), and schizophrenia (*ICD-8*: 295 [excluding 295.79], *ICD-10*: F20). We examined only inpatient stays. A person was, for example, “admitted with schizophrenia” from the first day of the first admission for which the discharge diagnosis was schizophrenia (main or auxiliary diagnosis). If the person later was admitted with, for example, a bipolar disorder diagnosis, an overlap was registered from that day.

The follow-up for psychiatric admission of the cohort members began on their 15th birthday and ended on December 31, 2006, at the day of death, day of psychiatric disorder under investigation, or day of emigration, whichever came first. Thus, cohort members were at the most 52 years old at the end of follow-up in 2006.

Statistical Analyses

Data were analyzed as a prospective cohort study using the Aalen-Johansen²⁰ method to estimate the probability (cumulative incidence) of psychiatric admission. The Aalen-Johansen method generalizes the Kaplan-Meier method taking competing risks from death and emigration into account. Aalen-Johansen survival curves were obtained using the SAS macro presented by Rosthøj et al.²¹

Our comorbidity index, which measures the overlap between the psychiatric disorders, was constructed on the basis of the definition of independence between 2 events. The probability of having been admitted with, for example, both bipolar disorder and schizophrenia divided by the product of having been admitted with 1 of the disorders, in mathematical terms, $P(\text{schizophrenia} | \text{bipolar disorder}) / P(\text{schizophrenia}) \times P(\text{bipolar disorder})$ equals 1 only if the disorders are independent. That is, admission with 1 of the disorders does not influence probability of being admitted with the other disorder. Furthermore, this expression also equals the fraction between the probabilities of being admitted with 1 of the disorders among patients who already have the other disorder divided by the probability of this disorder in general. Thus, for bipolar disorder and schizophrenia, the fraction expresses how common schizophrenia is among bipolar patients compared to the general population. In brief mathematical form, this latter fraction can be expressed as $P(\text{schizophrenia} | \text{bipolar disorder}) / P(\text{schizophrenia}) = P(\text{bipolar disorder} | \text{schizophrenia}) / P(\text{bipolar disorder})$.

If the fraction $P(\text{schizophrenia} | \text{bipolar disorder}) / P(\text{schizophrenia})$ is greater than 1, then the numerator is larger than the denominator, and the probability of schizophrenia among persons with a bipolar disorder is larger than the unconditional probability of being diagnosed with schizophrenia. That is, a person with bipolar disorder has a larger risk of being diagnosed with schizophrenia than a person from the general population. For example, $P(\text{schizophrenia} | \text{bipolar disorder}) / P(\text{schizophrenia}) = 20$ implies that persons in the cohort with a bipolar disorder have a 20 times higher risk of being diagnosed with schizophrenia than a randomly picked person in the cohort. Equally, $P(\text{schizophrenia} | \text{bipolar disorder}) / P(\text{schizophrenia}) = P(\text{bipolar disorder} | \text{schizophrenia}) / P(\text{bipolar disorder})$,²² so the comorbidity index describes not only the shift from, for example, bipolar disorder to schizophrenia, but also the shift from schizophrenia to bipolar disorder in 1 number.

We calculated this comorbidity index for the 3 disorders by comparing pairwise, and the fraction was calculated according to age.

RESULTS

Overall, 16,890 cohort members were admitted to a psychiatric hospital with at least 1 diagnosis of schizophrenia, bipolar disorder, or schizoaffective disorder. The cumulative

Figure 1. Cumulative Incidence (%) of Admissions With Schizophrenia, Bipolar Disorder, or Schizoaffective Disorder According to Age: Women

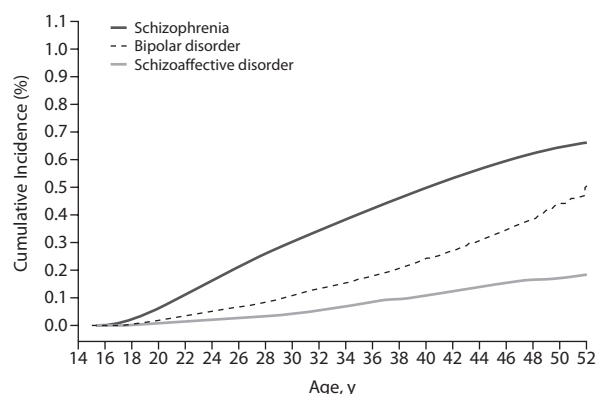
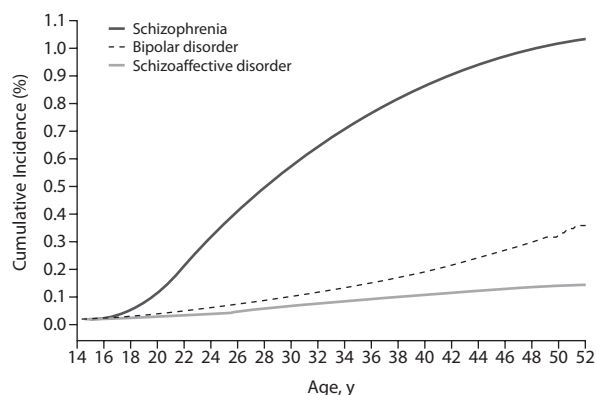


Figure 2. Cumulative Incidence (%) of Admissions With Schizophrenia, Bipolar Disorder, or Schizoaffective Disorder According to Age: Men



incidence measured the probability of having a history of the psychiatric diagnosis in question at a specified point in time. Figures 1 and 2 show the cumulative incidence according to age for the 3 disorders and for both women and men, respectively. At age 52 years, the probability of previous admission to a psychiatric hospital with a diagnosis of schizophrenia was 0.85% (men = 1.03%, women = 0.66%); for bipolar disorder, it was 0.42% (men = 0.34%, women = 0.50%); and for schizoaffective disorder, it was 0.16% (men = 0.13%, women = 0.19%). Schizophrenia was more common among men, while women had a higher risk of being diagnosed with a bipolar disorder. The risk of schizoaffective disorder was of the same magnitude in the 2 genders.

The diagnostic overlap resulted in 18,820 first-time admissions with 1 of the 3 disorders. The most frequent admission type was schizophrenia (N = 12,734), followed

Table 1. Diagnostic Course of the 16,890 Cohort Members With 18,820 First-Time Admissions With Schizophrenia, Bipolar Disorder, or Schizoaffective Disorder^a

Diagnostic Course	N	%
BP	3,228	19.11
BP → SA	248	1.47
BP → SA → SZ	63	0.37
BP → SZ	190	1.12
BP → SZ → SA	72	0.43
SA	570	3.37
SA → BP	110	0.65
SA → BP → SZ	18	0.11
SA → SZ	243	1.44
SA → SZ → BP	7	0.04
SZ	11,422	67.63
SZ → BP	169	1.00
SZ → BP → SA	59	0.35
SZ → SA	450	2.66
SZ → SA → BP	41	0.24
Total	16,890	100

^aUnadjusted numbers in a dynamic cohort.

Abbreviations: BP = bipolar disorder, SA = schizoaffective disorder, SZ = schizophrenia.

by bipolar disorder (N = 4,205) and schizoaffective disorder (N = 1,881). The diagnostic course of the cohort members during the follow-up period is shown in Table 1. Note that the numbers and percentages are unadjusted and do not take the dynamic structure of the cohort into account. In total, 67.6% of patients were diagnosed only with schizophrenia, 19.1% only with bipolar disorder, and 3.4% only with schizoaffective disorder. The most frequent (in percent of total) diagnostic course involving more than 1 disorder was having a diagnosis of schizophrenia and then schizoaffective disorder (2.7%).

A female bipolar patient's risk of being admitted with a schizoaffective disorder, and vice versa, by age 45 years was approximately 103 times higher than the risk for a woman of the same age in the general population (Figure 3). We express this as the comorbidity index between bipolar disorder and schizoaffective disorder. The comorbidity index between schizophrenia and schizoaffective disorder was smaller, and a 45-year-old person with schizophrenia had an 80 times higher risk of also receiving a schizoaffective disorder diagnosis, or vice versa (Figure 3). Among women, the index between schizophrenia and bipolar disorder was a 20 times higher risk at that age (Figure 3). The index was of similar proportion among men; the index at age 45 years between bipolar disorder and schizophrenia was 20, between schizophrenia and schizoaffective disorder was 61, and between schizoaffective disorder and bipolar disorder was 146 (Figure 4).

DISCUSSION

Key Findings

Our comorbidity index showed substantial overlap between the diagnostic categories of schizophrenia,

Figure 3. Comorbidity Index Between Schizoaffective Disorder and Bipolar Disorder, Schizoaffective Disorder and Schizophrenia, and Schizophrenia and Bipolar Disorder According to Age: Women

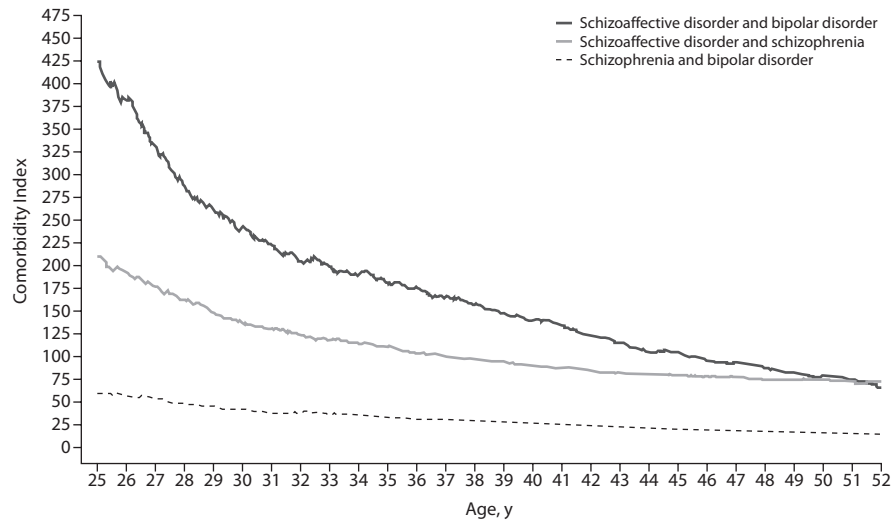
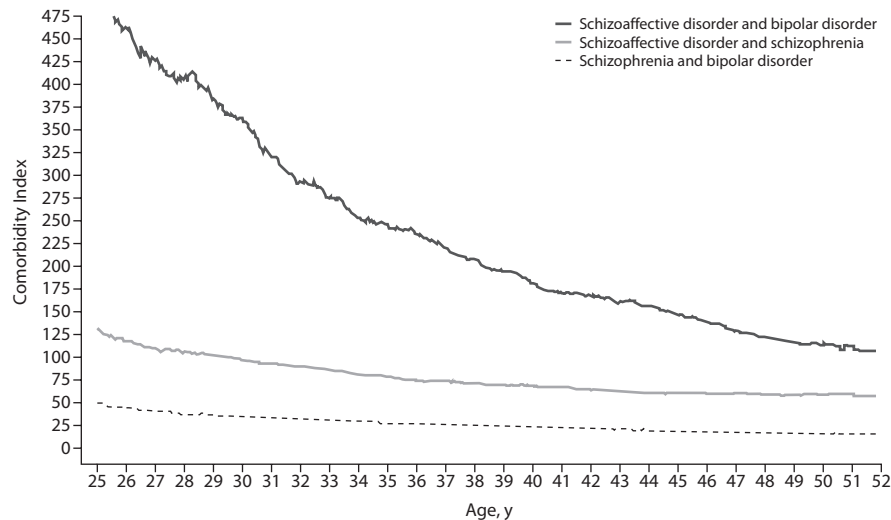


Figure 4. Comorbidity Index Between Schizoaffective Disorder and Bipolar Disorder, Schizoaffective Disorder and Schizophrenia, and Schizophrenia and Bipolar Disorder According to Age: Men



schizoaffective disorder, and bipolar disorder in the cohort. The largest comorbidity index, indicating the largest overlap, was found between schizoaffective disorder and bipolar disorder, but there was also a high index between schizophrenia and schizoaffective disorder. Most surprisingly, a large index was also found between bipolar disorder and schizophrenia. The index was highest in the younger age group, but remained high in the older age groups.

Statistical Model

The association between psychiatric disorders has often been estimated in traditional regression models in which one disorder has been used as a covariate (ie, risk factor) and the other as an outcome. In schizophrenia and bipolar disorders, the premorbid and prodromal phases often occur many years before the actual onset of the disorder.^{23,24} An advantage in our comorbidity index, as opposed to the

more traditional regression models, was that it described the overlap between the 2 disorders regardless of which disorder had the first onset. Moreover, if, as proposed, the disorders were on the same causal pathway, using 1 disorder as a risk factor for the other would be meaningless. Our index furthermore took follow-up time of the persons in the cohort into account.

We made additional tests of the “stability” of the comorbidity index by examining the second admission with the disorder in question (we assumed that a person had the diagnosis only from the date of the second admission). As expected, results showed a slightly lower incidence of the 3 disorders, but the comorbidity indexes between the disorders were of similar magnitude with women (men) at 45 years old: schizoaffective disorder and bipolar disorder, 135 (230); schizophrenia and schizoaffective disorder, 82 (70); and schizophrenia and bipolar disorder, 15 (18). These results suggest that the high comorbidity index is not due only to diagnostic uncertainty in the first diagnosis.

Diagnostic Course, Dichotomization, and Overlap

Patients with schizoaffective disorder showed a tendency to accumulate diagnoses of bipolar disorder and schizophrenia; patients with schizoaffective disorder were often admitted with bipolar disorder and/or schizophrenia before or after their first admission with schizoaffective disorder. This finding indicates the presence of persons who display a phenotype “between” bipolar disorder and schizophrenia. Of the patients with schizoaffective disorder, 30% (570 of 1,881) did not have (or later changed diagnostic category to) bipolar disorder or schizophrenia. This low percentage would probably be even lower if follow-up of all cohort members was complete, as some cohort members were censored. Our comorbidity index, modeling the overlap in a statistical model and taking follow-up time and censoring into account, also showed an overlap between schizoaffective disorder and schizophrenia/bipolar disorder. The overlap was largest in the younger age groups, indicating that younger patients were more likely to change from, or to, a schizoaffective disorder from one of the other 2 diagnostic categories (compared to the general population). This finding was not surprising, as older patients often have a longer course of psychiatric system contacts, making the diagnosis more reliable. However, a substantial overlap between the disorders was still present at the age of 52 years.

As mentioned previously, the *ICD-10* and *DSM-IV* define schizoaffective disorders in different ways. Thus, the overlap between schizophrenia/bipolar disorder and schizoaffective disorder is not necessarily the same in, for example, the United States and in Denmark. However, the most important feature in both classification systems is that persons with schizoaffective disorders have both schizophrenia and affective symptoms,²⁵ and, thus, similar results might be expected in countries using the *DSM-IV* classification. We expected that schizoaffective disorder was a poorly defined diagnosis,

and one of the objectives of this article was to describe this instability. In the *ICD-10* diagnostic classification system, schizoaffective disorder (F25) is placed as a subgroup in the F2 (schizophrenia, schizotypal, and delusional disorders) section in which schizophrenia (F20) is also placed and not as a subgroup of F3 (mood [affective] disorders) in which bipolar disorder is placed. However, our results suggest a higher comorbidity index between schizoaffective disorder and bipolar disorder than between schizoaffective disorder and schizophrenia. This finding could indicate that schizoaffective disorder is misplaced, but it could also indicate that the dichotomization of psychosis into bipolar disorder and schizophrenia is potentially not correct.

Different theories in opposition to the Kraepelinian dichotomization have recently gained momentum. The developmental model suggests shared susceptibility genes between schizophrenia and bipolar disorder, but on this common genetic background, different “environmental” factors operate to cause the person to develop either schizophrenia or bipolar disorder.²⁶ The continuum model assumes that all the major psychiatric disorders are linked by the existence of a continuum ranging from unipolar disorder, to bipolar disorder, to schizoaffective disorder, to schizophrenia, with increasing severity across the spectrum.^{27,28} A third explanatory model is the possible presence of psychopathological dimensions, that is, the presence of groups of, for example, psychotic symptoms occurring together (more often than would be expected) across the diagnostic entities.²⁹

Our results showed that a substantial overlap between bipolar disorder and schizophrenia was present, which supports all the above-mentioned models. If one assumes the continuum model or the developmental model to be correct, a substantial overlap between the 3 disorders, exactly as found, would be expected. In combination with the evidence of overlapping disorders on both the genetic and phenotypic level,^{8,28,30–35} it is likely that an overlap between the 2 disorders is present. Moreover, an overlap could also be attributable to psychopathological dimensions between the 3 diagnostic groups examined.

If we examine the 4 basic validity criteria (content, concurrent, predictive, and discriminant) of a psychiatric diagnostic entity first proposed by Robins and Guze³⁶ and used by Vieta and Phillips³⁷ in their review of validity of the diagnosis of bipolar disorder, the last 2 items, predictive validity (stability over time) and discriminant validity (delimitations from other illnesses), obviously fail for schizoaffective disorder and seem poor for bipolar disorder and schizophrenia with a large comorbidity of the other disorders.

Our study does not answer the question of whether this overlap is based on a common genetic basis, or on the disorders being part of a continuum, or on the existence of psychopathological dimensions alongside categorical entities. However, our study shows a clear overlap between bipolar disorder and schizophrenia in a new setup, taking

time of follow-up, mortality, and emigration into account. Moreover, we have confirmed that schizoaffective disorder is a very unstable diagnosis and thus challenged the categorical approach used in the *DSM-IV* and *ICD-10* classification systems.

Limitations

In register-based studies, we only have access to clinical diagnoses. Although high agreement has been shown between the psychiatric clinical diagnoses in the Danish Psychiatric Central Register and research criteria diagnoses,^{18,38,39} some of the patients with 2 different psychiatric diagnoses are probably shifting from 1 disorder to another because of erroneous decisions in relation to diagnosing. Consequently, we cannot distinguish between diagnostic errors and patients actually displaying characteristics from both disorders. Part of the high comorbidity indexes might be explained by such errors. However, when we restricted analysis to the second admission, we obtained similar results, suggesting that such errors had limited effect on our results.

CONCLUSION

In the cohort, the proposed comorbidity index revealed a large overlap between the diagnostic categories of schizophrenia, schizoaffective disorder, and bipolar disorder. There was a large comorbidity index between schizophrenia and schizoaffective disorder as well as a large index between bipolar disorder and schizoaffective disorder. But, more surprisingly, it was clear that a substantial comorbidity index in persons with a bipolar disorder diagnosis and a diagnosis of schizophrenia was present. On this basis, we conclude that this study supports the existence of an overlap between bipolar disorder and schizophrenia and thus challenges the categorical approach used in both *DSM-IV* and *ICD-10* classification systems.

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