A Comparison of Selected Risk Factors for Unipolar Depressive Disorder, Bipolar Affective Disorder, Schizoaffective Disorder, and Schizophrenia From a Danish Population-Based Cohort

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Objective: Growing evidence of an etiologic overlap between schizophrenia and bipolar disorder has become increasingly difficult to disregard. In this study, we examined paternal age, urbanicity of place of birth, being born "small for gestational age," and parental loss as risk factors for primarily schizophrenia and bipolar disorder, but also unipolar depressive disorder and schizoaffective disorder. Furthermore, we examined the incidence of the disorders in a population-based cohort and evaluated our results in the context of the Kraepelinian dichotomization.

Method: We established a register-based cohort study of more than 2 million persons born in Denmark between January 1, 1955, and July 1, 1987. Overall follow-up began on January 1, 1973 and ended on June 30, 2005. Relative risks for schizophrenia, bipolar disorder, unipolar depressive disorder, and schizoaffective disorder (ICD-8 or ICD-10) were estimated by survival analysis, using Poisson regression.

Results: Differences were found in age-specific incidences. Loss of a parent (especially by suicide) was a risk factor for all 4 disorders. High paternal age and urbanization at birth were risk factors for schizophrenia. Children born preterm had an excess risk of all disorders except schizophrenia if they were born "small for gestational age."

Conclusions: An overlap in the risk factors examined in this study was found, and the differences between the phenotypes were quantitative rather than qualitative, which suggests a genetic and environmental overlap between the disorders. However, large gender differences and differences in the age-specific incidences in the 4 disorders were present, favoring the Kraepelinian dichotomization.

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Schizophrenia and bipolar disorder have been dichotomized since Kraepelin introduced a classification of psychotic symptoms more than 100 years ago. However, growing evidence of an overlap between schizophrenia and bipolar disorder has become increasingly difficult to disregard. Most notably, genetic overlap and familial co-aggregation of bipolar disorder and schizophrenia have been shown in several studies,[1–4] and consequently, classification theories alternative to the Kraepelinian dichotomization have been proposed, especially in Europe.[5] These include the continuum theory[6–8] and the developmental theory.[9]

Studies of schizophrenia and bipolar disorder have shown both overlap and differences in risk factors, but most studies have only focused on either bipolar disorder or schizophrenia. Risk factors studied are age of the father, urbanicity of place of birth, being born small for gestational age, and loss of a parent, which are risk factors supposed to operate at different stages in life. However, different conclusions have emerged, and a direct comparison between schizophrenia and bipolar disorder has not been made. Advanced paternal age is a risk factor for schizophrenia,[10,11] whereas it is unclear whether the same is true for bipolar disorder. Place of birth is a well-established risk factor for schizophrenia in the way that birth in a rural area is associated with a lower risk compared to birth in an urbanized area.[12] The risk of bipolar disorder, on the other hand, is probably not affected in the

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same way.[3] Being born small for gestational age has been shown to be a risk factor for schizophrenia in some studies. However, in an extensive meta-analysis by Cannon et al.,[13] no significant effect of being born small for gestational age was present. Little is known about being born small for gestational age as a risk factor for bipolar disorder. Loss of a parent is believed to be a risk factor for both schizophrenia[10,14] and bipolar disorder,[14,15] although mostly in connection with suicide of a parent. An often used explanation of the increased risk associated with the above-mentioned factors is selection of mothers and fathers suffering from a psychiatric disorder,[16] but a way to account for this is to control for family history of psychiatric admission in all analyses.

The aim of this study was to make a description of incidence (measured as incidence of first hospital contact) of affective and schizophrenic disorders and test risk factors that are supposed to operate at different stages of life. In this study, we have chosen paternal age, place of birth (both of which operate before conception), being born small for gestational age (which most likely operates during pregnancy), and parental loss (which operates during upbringing) as risk factors for unipolar depressive disorder, bipolar disorder, schizoaffective disorder, and schizophrenia, focusing on a comparison between bipolar disorders and schizophrenia. Furthermore, the aim was to make an evaluation of our results in the context of the Kraepelinian dichotomization of bipolar disorder and schizophrenia versus other explanations, by examining if the selected risk factors influenced the risk of developing bipolar disorder or schizophrenia differently.

METHOD

From the Danish civil registration system, we established a cohort of more than 2 million persons.[17] We linked this information to the Danish Psychiatric Central Register,[18] from where we obtained information on inpatient psychiatric treatment of all cohort members and their parents and siblings (outpatient contacts included from 1995). From the Cause of Death Register, cause-specific deaths of parents were acquired. Information on birth weight and gestational age was obtained from the Danish Medical Birth Register.[19] Linkage between registers was made using the unique personal identification number assigned to all people living in Denmark.

Study Population

The population-based cohort comprised all individuals born in Denmark between January 1, 1955, and July 1, 1987, with a known link to their mother in the register and alive at their 18-year birthday. The overall follow-up began on January 1, 1973, and ended on June 30, 2005. However, follow-up of cohort members did not start until their 18th birthday and stopped at the day of death, emigration, or admission with the psychiatric disorder under study (e.g., at first admission with a unipolar disorder when unipolar disorder is the outcome), whichever came first. A little more than 2.1 million persons were included in the cohort. Mean time of follow-up was 16.2 years.

Information on gestational age and weight at birth was only available from 1973 and onward, so a subcohort for investigating the impact of being born small for gestational age was established limiting the cohort to persons born in 1973 or later.

Assessment of Psychiatric Disorder and Risk Factors

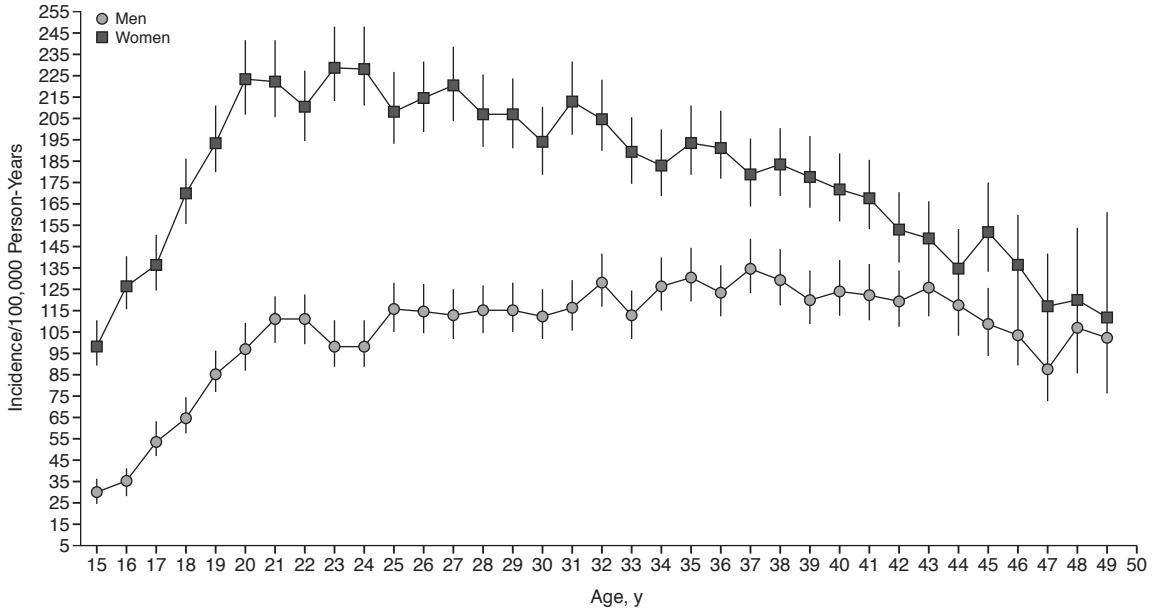
Cohort members were categorized as suffering from a psychiatric disorder if they were admitted to a psychiatric hospital. The diagnostic system used until December 31, 1993, was ICD-8,[20] and from January 1, 1994, the ICD-10[21] classification was used. From 1995, we also included outpatient contact. The following diagnostic categories were used: unipolar disorder (ICD-8: 296.09, 296.29, 296.99, 298.09, 300.49, or 300.19; ICD-10: F32 or F33), 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), schizophrenia (ICD-8: 295 [excluding 295.79]; ICD-10: F20). A cohort member was categorized as having a family history of psychiatric disorder if the father, mother, or sibling(s) had any admission to or outpatient contact with a psychiatric hospital.

Paternal age at birth of child was subdivided into 5-year groups. We adjusted all relative risks for maternal age in 5-year groups. This classification is similar to that of Byrne et al.[10] and Malaspina et al.[11] Place of birth was divided into 5 groups (Copenhagen, suburbs to Copenhagen, larger cities with more than 100,000 inhabitants, smaller cities with more than 10,000 inhabitants, and rural areas), similar to that of Pedersen et al.[22]

Gestational age was divided into 2 groups: birth before week 37 and birth within week 37 or later. In each of the 2 groups, boys and girls in the lower 10% of birth weight (cut points: girls preterm = 1335 grams, boys preterm = 1375 grams; girls term = 2850 grams, boys term = 2900 grams, respectively) were categorized as small for gestational age. The rest were categorized as not small for gestational age. Approximately 7.5% of the 1973 cohort had missing information on "small for gestational age."

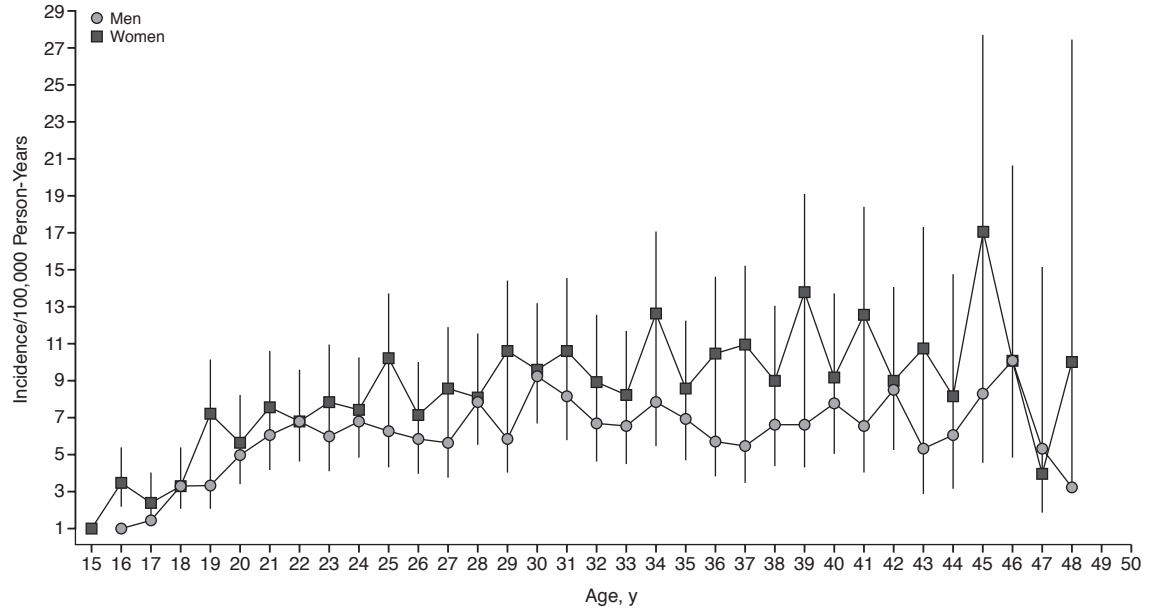
When examining all causes of death in parents as a risk factor, we divided loss of a parent into 4 groups (loss of a parent in the age group 0–5 years, 6–11 years, and 12–17 years and no loss of parent before the age of 18), and into 3 groups when we examined cause-specific death of the parents (loss of parent from unnatural cause of death before the age of 18, from natural cause of death before the age of 18, and no loss before 18 years old). Unnatural death comprised suicide, accidents, and homicide.

Figure 1. Age-Specific Incidence of Admission With Unipolar Depressive Disorder[a]



[a]Adjusted for calendar time. Vertical lines represent 95% confidence intervals.

Figure 2. Age-Specific Incidence of Admission With Schizoaffective Disorder[a]

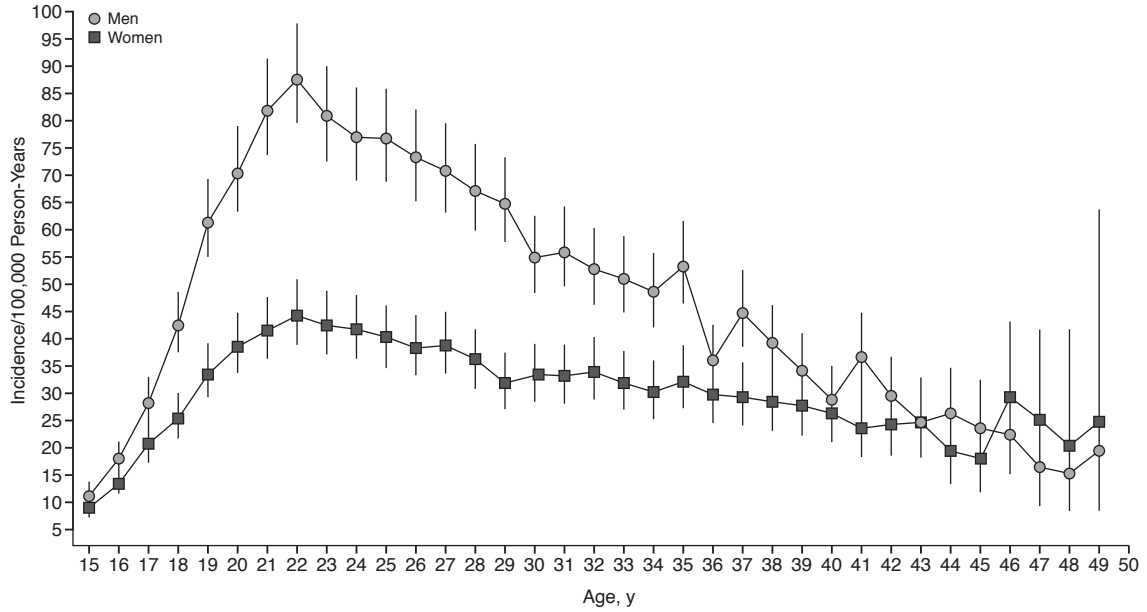


[a]Adjusted for calendar time. Vertical lines represent 95% confidence intervals.

Statistical Analyses

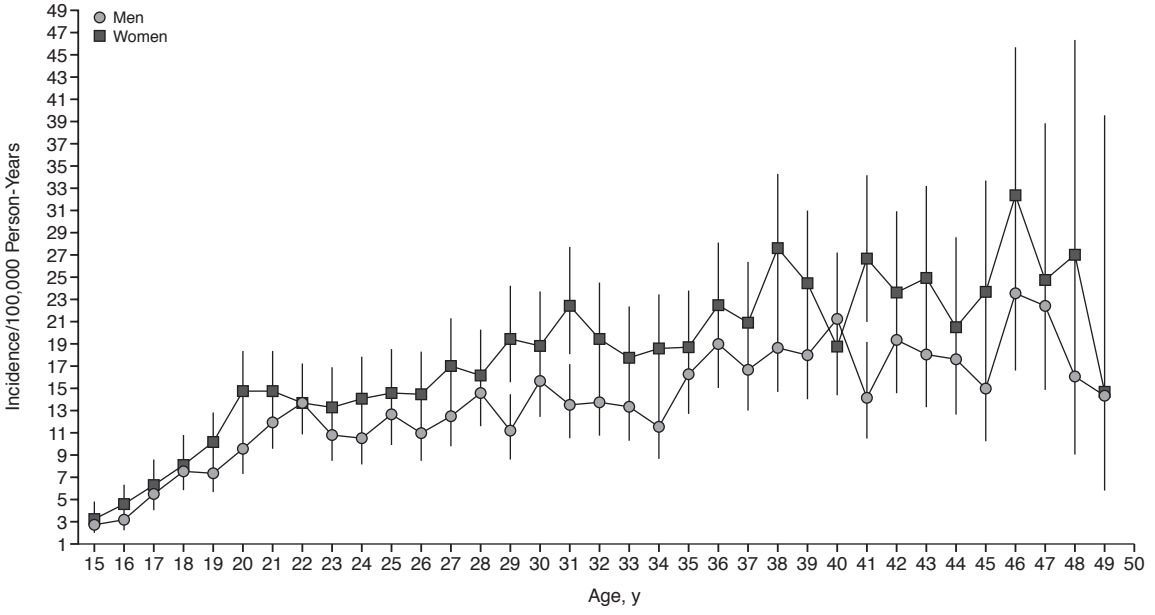
We analyzed data as a cohort study with survival analysis techniques, using Poisson regression with the logarithm of the person-years as an offset. This method approximates a Cox regression when analyzing large data sets.[23,24] Using a Poisson regression and person-years takes into account the different lengths of follow-up in the cohortees. The GENMOD procedure in SAS version 9.1 (SAS Institute Inc., Cary, N.C.) was used. All relative risks were adjusted for gender, calendar time (1973–1974, 1975–1979, 1980–1984, 1985–1989, 1990–1991, and 1992–2005 in 1-year groups), and age in 5-year groups. Furthermore, an adjustment was made for the variables family history of psychiatric admission, place of birth, maternal age, paternal age, and loss of a parent according to the above-defined groups. Relative risks were calcu-

Figure 3. Age-Specific Incidence of Admission With Schizophrenia[a]



[a]Adjusted for calendar time. Vertical lines represent 95% confidence intervals.

Figure 4. Age-Specific Incidence of Admission With Bipolar Disorder[a]



[a]Adjusted for calendar time. Vertical lines represent 95% confidence intervals.

lated by log-likelihood estimation and confidence intervals by Wald's test. All risk factors were tested for interaction with family history of psychiatric admission, but analyses revealed no interaction on a multiplicative scale. Population-attributable risk (or fraction) was calculated, measuring the percentage of all cases in the population, which would not have occurred if the specific risk factor had not been present.[25]

RESULTS

Overlap

During the follow-up period, approximately 35 million person-years were observed, and 31,752 persons (women = 19,394; men = 12,358) were recorded as having unipolar disorder. A total of 4490 persons (women = 2444; men = 2046) had bipolar disorder, 2115 (women = 1108;

men = 1007) had schizoaffective disorder, and 13,297 (women = 4592; men = 8705) were recorded as having schizophrenia. There was an overlap between the admission groups. Especially persons admitted with schizoaffective disorder had previously been admitted with schizophrenia (38.0%), bipolar disorder (26.2%), and/or unipolar disorder (35.9%). The listed percentages add up to more than 100%, because the 3 admission groups are not mutually exclusive. Thirty-two percent of persons admitted with bipolar disorder had previously been admitted with unipolar disorder. A smaller overlap of approximately 2% to 10% was present between the other illnesses.

Incidence

Women had a much higher incidence of unipolar depressive disorder compared with men (Figure 1), but the genders were equally distributed in the schizoaffective disorder group (Figure 2). The incidence of schizophrenia was more than twice as high in men as in women. A peak occurred in men aged 20 to 25 years (Figure 3). In contrast to this, women had a higher incidence of bipolar disorder in all age groups compared with men. Bipolar disorder had a steadily increasing incidence with age in both men and women (Figure 4). Overall, schizophrenia peaked at an earlier age than bipolar disorder.

Risk Factors

Family history of psychiatric admission was associated with a highly elevated incidence and risk in the 4 disorders, but no interactions with the examined risk factors were found on a multiplicative scale. That is, risk factors had the same pattern of influence on cohortees with or without a family history of psychiatric admission, but cohortees with a family history had a generally higher risk for the disorders.

Paternal age had no influence on the risk of unipolar disorder. A slightly increased risk for bipolar disorder was present if the father was 51 to 55 years old. In schizophrenia, a linear trend toward higher risk was present with increasing age of the father (Table 1). The attributable risk of paternal age was almost 0 for unipolar disorder but approximately 10% in the other disorders (Table 2).

Place of birth had none or only little influence on the risk of unipolar disorder, but being born in a rural area was associated with a slightly lesser risk. A small, increased risk for bipolar disorder was associated with being born in Copenhagen

Table 1. Paternal Age, Place of Birth, and Loss of a Parent as Risk Factors for Onset of Psychiatric Disorders

	Unipolar Disorder			Bipolar Disorder			Schizoaffective Disorder			Schizophrenia		
Variable	No. of Cases	Rate[a]	RR[b] (95% CI[c])	No. of Cases	Rate[a]	RR[b] (95% CI[c])	No. of Cases	Rate[a]	RR[b] (95% CI[c])	No. of Cases	Rate[a]	RR[b] (95% CI[c])
Paternal age, y												
≤ 20	1,459	1.04	1.06 (1.00 to 1.12)	152	0.11	0.89 (0.75 to 1.07)	77	0.05	0.97 (0.76 to 1.25)	597	0.43	1.06 (0.96 to 1.16)
21–25	8,148	0.93	1.00 reference	996	0.11	1.00 reference	467	0.05	1.00 reference	3,167	0.36	1.00 reference
26–30	9,856	0.88	0.96 (0.93 to 0.99)	1,357	0.12	1.08 (0.98 to 1.18)	643	0.06	1.10 (0.97 to 1.26)	4,014	0.36	1.04 (0.99 to 1.10)
31–35	6,374	0.89	1.01 (0.97 to 1.05)	986	0.14	1.21 (1.09 to 1.34)	451	0.06	1.21 (1.04 to 1.41)	2,655	0.37	1.12 (1.05 to 1.19)
36–40	3,123	0.86	1.02 (0.97 to 1.07)	521	0.14	1.25 (1.09 to 1.42)	237	0.07	1.21 (1.00 to 1.47)	1,369	0.38	1.17 (1.09 to 1.27)
41–45	1,322	0.85	1.01 (0.95 to 1.09)	213	0.14	1.14 (0.96 to 1.36)	111	0.07	1.29 (1.01 to 1.65)	633	0.40	1.27 (1.14 to 1.40)
46–50	490	0.89	1.04 (0.94 to 1.15)	87	0.16	1.26 (0.99 to 1.61)	41	0.07	1.34 (0.95 to 1.91)	256	0.46	1.42 (1.23 to 1.63)
51–55	160	0.96	1.07 (0.91 to 1.26)	37	0.22	1.71 (1.21 to 2.41)	14	0.08	1.43 (0.82 to 2.48)	82	0.49	1.36 (1.08 to 1.71)
≥ 56	73	1.15	1.18 (0.93 to 1.49)	9	0.14	1.03 (0.53 to 2.01)	3	0.05	0.74 (0.23 to 2.31)	47	0.74	1.86 (1.39 to 2.50)
Place of birth												
Copenhagen	6,237	0.97	1.11 (1.08 to 1.15)	935	0.14	1.20 (1.09 to 1.31)	523	0.08	1.47 (1.29 to 1.67)	3,773	0.59	1.94 (1.84 to 2.04)
Suburb to Copenhagen	2,961	0.97	1.05 (1.01 to 1.10)	357	0.12	1.01 (0.90 to 1.14)	181	0.06	1.14 (0.95 to 1.35)	1,352	0.44	1.47 (1.38 to 1.58)
City with population > 100,000	4,077	0.91	1.06 (1.02 to 1.10)	654	0.15	1.33 (1.20 to 1.47)	277	0.06	1.25 (1.07 to 1.45)	1,719	0.39	1.35 (1.27 to 1.43)
City with population > 10,000	11,122	0.91	1.04 (1.01 to 1.07)	1,529	0.12	1.12 (1.04 to 1.22)	695	0.06	1.13 (1.00 to 1.27)	4,016	0.33	1.13 (1.07 to 1.19)
Rural area	7,355	0.81	1.00 reference	1,015	0.11	1.00 reference	439	0.05	1.00 reference	2,437	0.27	1.00 reference
Loss of parent												
At age 0–5 y	335	1.72	1.42 (1.28 to 1.58)	44	0.22	1.57 (1.16 to 2.11)	23	0.12	1.59 (1.05 to 2.40)	151	0.77	1.48 (1.26 to 1.74)
At age 6–11 y	692	1.22	1.20 (1.11 to 1.30)	104	0.18	1.23 (1.01 to 1.50)	66	0.12	1.59 (1.24 to 2.04)	350	0.62	1.33 (1.20 to 1.48)
At age 12–17 y	1,389	1.15	1.22 (1.15 to 1.29)	204	0.17	1.12 (0.97 to 1.30)	96	0.08	1.10 (0.90 to 1.36)	643	0.53	1.22 (1.12 to 1.32)
No loss	29,336	0.88	1.00 reference	4,138	0.12	1.00 reference	1,930	0.06	1.00 reference	12,153	0.36	1.00 reference

[a]Rate = cases per 1,000 person-years.
[b]RR = relative risk adjusted for age, calendar time, gender, family history of psychiatric admission, and maternal age. Furthermore, mutually adjusted for loss of parent, paternal age, and place of birth.
[c]95% Confidence interval not including 1.00 indicates statistically significant differences at a 5% level from reference group.

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Table 2. Attributable Risk[a]

Variable	Unipolar Disorder, %	Bipolar Disorder, %	Schizoaffective Disorder, %	Schizophrenia, %
Paternal age (reference = 21–26 y)	0.06	10.06	11.65	8.81
Place of birth (reference = rural)	4.48	10.83	15.22	23.73
Loss of parent (reference = no loss)	1.46	1.29	1.99	1.89
Small for gestational age (reference = not small for gestational age)	0.46	0.15	4.08	1.74

[a]Measures the percentages of cases that would not occur if all cohort members had the same risk as those in the reference group.

Table 3. Being Born Small for Gestational Age as Risk Factor for Onset of Psychiatric Disorders

	Unipolar Disorder			Bipolar Disorder			Schizoaffective Disorder			Schizophrenia		
Variable	No. of Cases	Rate[a]	RR[b] (95% CI)	No. of Cases	Rate[a]	RR[b] (95% CI)	No. of Cases	Rate[a]	RR[b] (95% CI)	No. of Cases	Rate[a]	RR[b] (95% CI)
Upper 90%	8028	1.52	1.00 reference	670	0.13	1.00 reference	331	0.06	1.00 reference	2726	0.51	1.00 reference
Lower 10% within week 37 or later	1012	1.51	1.01 (0.95 to 1.08)	82	0.12	0.94 (0.75 to 1.19)	49	0.07	1.07 (0.79 to 1.44)	432	0.64	1.09 (0.98 to 1.20)
Lower 10% before week 37	49	4.16	2.23 (1.68 to 2.95)	9	0.76	5.32 (2.75 to 10.29)	4	0.34	4.59 (1.71 to 12.31)	9	0.76	1.22 (0.63 to 2.35)
Unknown	760	1.76	1.01 (0.93 to 1.09)	53	0.12	0.98 (0.74 to 1.30)	38	0.09	1.41 (1.00 to 1.99)	260	0.60	1.10 (0.96 to 1.25)

[a]Rate = Cases per 1000 person-years.
[b]RR = Relative risk adjusted for unknown small for gestational age, loss of parent, parental age, place of birth, age, gender, and calendar time.

Table 4. Cause-Specific Loss of Parent as Risk Factor for Onset of Psychiatric Disorders

	Unipolar Disorder			Bipolar Disorder			Schizoaffective Disorder			Schizophrenia		
Variable	No. of Cases	Rate[a]	RR[b] (95% CI)	No. of Cases	Rate[a]	RR[b] (95% CI)	No. of Cases	Rate[a]	RR[b] (95% CI)	No. of Cases	Rate[a]	RR[b] (95% CI)
From natural causes	1,659	1.06	1.13 (1.08 to 1.19)	227	0.14	1.01 (0.88 to 1.16)	112	0.07	1.04 (0.86 to 1.27)	802	0.51	1.20 (1.12 to 1.29)
From unnatural causes	757	1.86	1.55 (1.44 to 1.66)	125	0.31	1.78 (1.48 to 2.12)	73	0.18	2.02 (1.59 to 2.56)	342	0.84	1.51 (1.35 to 1.68)
No loss	29,336	0.88	1.00 reference	4,138	0.12	1.00 reference	1,930	0.06	1.00 reference	12,153	0.36	1.00 reference

[a]Rate = Cases per 1,000 person-years.
[b]RR = Relative risk adjusted for age, calendar time, gender, family history of psychiatric admission, maternal age, paternal age, and place of birth.

or other larger cities compared with rural areas, and this tendency was even more pronounced in schizoaffective disorder. In schizophrenia, there was a trend toward a higher risk associated with higher degree of urbanization. Being born in Copenhagen was associated with a doubling of the risk of schizophrenia compared with birth in a rural area (Table 1). Attributable risk of place of birth was approximately 4% in unipolar disorder, but increasing over bipolar disorder and schizoaffective disorder, to 24% in schizophrenia (Table 2).

Being born small for gestational age was associated with a higher risk for all disorders except schizophrenia for children born preterm. We found no increased risk associated with being born small for gestational age for children born at term (Table 3). Attributable risk of small for gestational age was diminutive for unipolar disorder and bipolar disorder (Table 2).

Loss of a parent had similar patterns of excess risk for all 4 disorders irrespective of age of the proband at the time of loss (Table 1). We also made separate analyses that showed that loss of a mother was a stronger risk factor than loss of a father (data not shown). A subdivision of the cause of death in the deceased parent showed that loss of a parent because of unnatural causes was associated with a higher risk than loss of a parent from natural causes, and this pattern was the same for all 4 disorders. Loss of a parent by natural causes as a risk factor was only significant for unipolar disorder and schizophrenia (Table 4). The exact same pattern emerged when we only examined cohortees without a history of family psychiatric admission (data not shown). Attributable risk for loss of a parent was around 1% to 2% for all 4 disorders (Table 2).

DISCUSSION

Key Findings

A difference was found in age at first admission and gender distribution of the 4 disorders. Risk factors differed for the 4 disorders and high paternal age as a risk factor was most pronounced in schizophrenia. Urbanization became increasingly strongly associated with outcome, from virtually no difference in unipolar disorder to a 2-fold risk of schizophrenia associated with birth in Copenhagen (compared with a rural area). In children born at term, small for gestational age was not significantly associated with higher risk of the 4 disorders, but preterm children had an excess risk of all disorders except schizophrenia if they were small for gestational age. Loss of a parent was a risk factor for all 4 disorders, especially after unnatural death of a parent.

Comments and Comparison With Other Results

A Danish population-based study found an increased risk of schizophrenia associated with advanced paternal age (> 50 years). However, no monotonic linear trend was present, only a peak in the oldest fathers.[10] Two other studies found a monotonic linear trend with increasing paternal age as a risk factor for schizophrenia.[11,26] A population-based study from Sweden also found a linear trend in subjects with no family history of psychiatric admissions but not in subjects with a family history.[27] Two possible reasons for the increased risk of schizophrenia associated with older fathers have often been pointed out: older fathers may be a selected segment of the population with respect to overall risk of mental disorders, or older fathers have a higher mortality thereby causing adverse psychological problems for the child following loss of a parent.[10] As we have taken family history of psychiatric admission and loss of a parent into account in our analyses, these are not likely explanations of the peak in the oldest fathers found in the present study. Moreover, most of the abovementioned studies suggest that de novo mutations in the germ cells in the oldest fathers could be leading to the excess risk of schizophrenia. To our knowledge, no previous population-based studies on paternal age as a risk factor for bipolar disorder exist.

Urbanicity of place of birth has been shown to be a solid proxy variable for urbanicity during upbringing,[12] which makes this variable suitable for describing the risk associated with urbanicity during upbringing. Urbanicity has been shown to be associated with schizophrenia in many studies,[12,28–30] but no effect was found in bipolar disorder or affective disorder (including bipolar disorder) in Danish population-based studies.[3,30,31] In our study, the association with bipolar disorder was much less prominent than with schizophrenia. Urbanization has been linked to schizophrenia since the 1930s; however, the cause of the increased risk is still unclear. Social isolation, drift of individuals who develop schizophrenia toward the city, nutrition, drug abuse, or a higher exposure to influenza have been proposed explanations.[30] More recently, risk factors related to the family have been examined[32]; however, no conclusive evidence of an environmental or genetic origin of the excess risk associated with urbanicity has been found.

A meta-analysis by Cannon et al.[13] including 5 studies on small for gestational age revealed a nonsignificantly increased risk in relation to schizophrenia. In our study, we had more statistical power to detect a slightly increased risk, but we did not find a statistically significant association with schizophrenia. Only when we examined persons without a family history of psychiatric admission was a significantly increased risk for schizophrenia found (data not shown). In the study by Eaton et al.,[30] small for gestational age was examined in relation to urbanization. They found an increased risk of "light for age" in schizophrenia and a negative association with affective psychosis, although the results were not statistically significant. We found no population-based studies with bipolar disorder as the outcome, but an Irish case-register study found

no association between bipolar disorder and obstetric complications in general.[33]

A Danish study found that parental death by suicide was a risk factor for schizophrenia in the children later in life, whereas no association with parental death by natural causes was found.[10] The same tendency emerged in bipolar disorder in a similar Danish population-based study.[15] In a case-control study conducted at an Israeli hospital, increased risk of major depression, bipolar disorder, and schizophrenia was observed for probands who experienced early parental loss. The increased risk of major psychiatric disorders following parental loss has often been described as a proxy measure of other problems in the family.[14] However, we also found an increased risk in families with no history of psychiatric admission. Death of a parent by natural causes was a risk factor, although not significant for bipolar disorder and schizoaffective disorder, and not as prominent as death of a parent by unnatural causes. However, these results indicate that parental loss in itself is a risk factor for all 4 disorders.

Dichotomization or Not?

There was an overlap between the 4 diagnostic groups studied, since risk factors were shared between the disorders. Risk factors operating both before and after conception were more or less shared. Furthermore, persons suffering from schizoaffective disorder had a tendency to accumulate diagnoses of bipolar disorder and schizophrenia prior to their schizoaffective disorder diagnosis, indicating the existence of persons displaying a phenotype "between" bipolar disorder and schizophrenia that is difficult for clinicians to classify. These observations could indicate that the dichotomization should be reconsidered. We therefore evaluated the results on the basis of alternative explanation.

The developmental model, as proposed by Murray et al., suggests that certain susceptibility genes are shared between bipolar disorder and schizophrenia, and these genes predispose an individual to psychosis in general; other genes/environmental factors may act on this background resulting in schizophrenia, but in the absence of these additional genes/environmental factors, a pathway toward bipolar disorder is the result.[9] Our results were not in conflict with this hypothesis since the susceptibility genes shared between bipolar disorder and schizophrenia should result in some common risk factors due to genes acting before conception (in our study, age of the father, e.g., by de novo mutations in the germ cells) and some acting only on the risk of schizophrenia (in our study, place of birth). According to the model, some environmental factors during pregnancy and childhood should only be risk factors for one of the disorders and some for both disorders (in our study, parental loss). In the present study, the risk factor profile for schizoaffective disorder had a tendency to be a mixture of the risk factor profile for bipolar disorder and schizophrenia (where differences were found), indicating that schizoaffective disorder may be genetically linked to both and share the same susceptibility genes, as a study (in the same cohort) of family aggregation of bipolar disorder, schizophrenia, and schizoaffective disorder also suggested.[1]

The continuum model[6] assumes the major psychiatric disorders to be a continuum from unipolar disorder, to bipolar disorder, to schizoaffective disorder, to schizophrenia, with increasing severity across the spectrum. When considering this model, we would expect some risk factors to show the same dose-response characteristic, and urbanicity especially shows that characteristic across the diagnostic groups.

Along with evidence especially from family studies[1,4] and genetic studies,[2] the agreement of our results with alternative explanations to the Kraepelinian dichotomization could justify a reconsideration of the dichotomization of bipolar disorder and schizophrenia. However, the very different gender distribution and differences in onset of the disorders (despite the overlap in persons in the diagnostic groups) indicate that, at least for the time being, a dichotomization should be upheld until further studies have examined the differences.

Remarks About the Design

Three studies[18,34,35] have validated the clinical diagnoses of affective disorder and schizophrenia in the Danish Psychiatric Central Register against research criteria diagnoses and found high agreement between them. Because cohort members were not older than 50 years (32 years when we examined small for gestational age) and bipolar disorder had a later onset than schizophrenia, we found lower rates of bipolar disorder compared with schizophrenia than those reported in the literature.

CONCLUSION

An overlap in the risk factors examined in this study was found, and the differences in terms of risk factors associating between the phenotypes were quantitative rather than qualitative; that is, only the magnitude, and not the direction of the risk factors, differed. This finding could suggest a genetic and environmental overlap between the disorders. However, large gender differences and differences in the age at onset in the 4 disorders were present. Especially bipolar disorder and schizophrenia had different patterns of age-specific incidence rates and gender distributions.

Results were not conflicting when held up against other models, but the huge differences in incidence could indicate that the Kraepelinian dichotomization could be upheld, not only in the clinical context, but also when studying the causes of schizophrenia and bipolar disorder, respectively.

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