Increased Mortality Among Patients Admitted With Major Psychiatric Disorders: A Register-Based Study Comparing Mortality in Unipolar Depressive Disorder, Bipolar Affective Disorder, Schizoaffective Disorder, and Schizophrenia

Thomas Munk Laursen, M.Sc., Ph.D.; Trine Munk-Olsen, M.Sc.; Merete Nordentoft, M.P.H., Ph.D.; and Preben Bo Mortensen, Dr.Med.Sc.

Context: Persons suffering from severe mental disorder have an excess mortality compared to persons with no mental disorder. However, the magnitude of the excess mortality differs from one mental disorder to another, and the impact on mortality if a first-degree family member suffers from a mental disorder has never been examined in a population-based study.

Objective: Our objective was to examine and compare mortality rates after admission with schizophrenia, schizoaffective disorder, unipolar depressive disorder, or bipolar affective disorder and to examine the impact of family history of psychiatric admission on mortality.

Method: We established a register-based cohort study of 5.5 million persons born in Denmark who were alive on or born after January 1, 1973 and alive on their 15th birthday. Mortality rate ratios were estimated by survival analysis, using Poisson regression.

Results: Unipolar depressive disorder, bipolar affective disorder, and schizoaffective disorder were associated with the same pattern of excess mortality. Schizophrenia had a lower mortality from unnatural causes of death and a higher mortality from natural causes compared to the 3 other disorders. Family history of psychiatric admission was associated with excess mortality.

Conclusion: Patients suffering from the 4 disorders all had an excess mortality, but the pattern of excess mortality was not the same. There was an excess mortality associated with mental disorder in a first-degree family member, but this only explained a small part of the general excess mortality associated with the 4 mental disorders examined.

(J Clin Psychiatry 2007;68:899–907)

Received July 4, 2006; accepted Oct. 10, 2006. From the National Centre for Register-Based Research, University of Aarhus, Aarhus (Drs. Laursen and Mortensen and Ms. Munk-Olsen); and the Department of Psychiatry, Bispebjerg Hospital, Copenhagen (Dr. Nordentoft), Denmark.

This study was supported by The Stanley Medical Research Institute, Chevy Chase, Md.

Psychiatric epidemiologic research at the National Centre for Register-Based Research is in part funded through a collaborative agreement with the Centre for Basic Psychiatric Research, Psychiatric Hospital in Aarhus, Denmark.

Dr. Laursen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

The authors report no additional financial or other relationships relevant to the subject of this article.

Corresponding author and reprints: Thomas Munk Laursen, M.Sc., Ph.D., National Centre for Register-Based Research, University of Aarhus, Taasingegade 1, DK-8000 Aarhus C, Denmark (e-mail: tml@ncrr.dk).

Patients with a mental disorder are subject to premature death from all causes compared to the general population.[1–3] Studies have reported mortality ratios for different categories of mental disorder, but to our knowledge a direct comparison of major psychiatric disorders based on current psychiatric classification, with respect to mortality, has never been made in a large population-based cohort. Admission with schizophrenia-like and affective disorders has a strong association with psychiatric admission of a family member.[4] Possibly, this association, which is most likely the mixture of genetic and environmental causes, could explain the excess mortality in persons admitted with a mental disorder. Our aim was to examine and compare mortality rates after admission with unipolar depressive disorder (from now on, unipolar disorder), bipolar affective disorder (from now on, bipolar disorder), schizoaffective disorder, and schizophrenia and to examine whether the impact of family history of psychiatric admission on mortality might explain some of the expected excess mortality.

METHOD

We used 3 Danish registers: the Danish Psychiatric Central Register,[5] the Civil Registration System,[6] and the Cause of Death register.[7] The unique personal identifica-

tion number, CPR, a Danish acronym, is used in all national registers, which ensures accurate linkage of information between registers. The Danish Psychiatric Central Register contains computerized data on all admissions to Danish psychiatric inpatient facilities since April 1, 1969, and is complete from April 1, 1970. The diagnostic system used until December 31, 1993, was ICD-8.[8] From January 1, 1994, the ICD-10[9] classification was used. There are no private psychiatric inpatient facilities in Denmark, ensuring that all psychiatric admissions are represented in the register. In the Civil Registration System, basic information on birthday, childbirth, day of death, etc., is available. Links to parents of persons born in the 1950s and forward in time are also available. The Cause of Death register is computerized from 1943 (from 1970 by the National Board of Health); the data used in this study are updated to December 31, 2000. The authorities handling the update of the register have updated the Cause of Death Register to 2000, and no newer results are available for the time being. In the follow-up period, the register contains causes of death according to the ICD-8 (up to 1994) and ICD-10 (from 1994 to 2000) classification. We used the underlying cause of death when examining cause-specific mortality.

Study Population

Using data from the Civil Registration System, we established 2 population-based cohorts. The first cohort comprised all persons born in Denmark who were alive on or born after January 1, 1973, and alive at their 15th birthday, in total 5,558,959 persons. We used this cohort to examine mortality rates after psychiatric admission in all deaths combined, natural/unnatural death, and cause-specific death. In this cohort, we had, however, only the opportunity to find the mothers and fathers, and hence siblings, of cohort members born in 1952 or later. We therefore made a subcohort comprising only persons born after 1952. This subcohort comprised all individuals born in Denmark from January 1, 1952, to January 1, 1986, who had a known mother in the register and were alive at their 15th birthday, a total of 2,152,357 persons. Of all persons in this cohort, 97.3% (2,093,442) had a registered link to a father. Siblings were identified through the link to the mother. Cohort members born in 1952 or later were at most 48 years old at the end of follow-up. We used this cohort to examine the impact of psychiatric admission in family members.

In both cohorts, follow-up started at the cohort members' 15th birthday or on January 1, 1973, whichever came later, and ended on the date of death, the date of emigration, or on January 1, 2001, whichever came first. We excluded persons admitted during the period from April 1, 1969, to December 31, 1972, thereby minimizing the risk of having a mixture of incident and prevalent cases at the start of follow-up.

Assessment of Cause of Death and Psychiatric Illness

Cause specific mortality was divided into 9 categories. All unnatural causes comprised suicide (ICD-10: X60–X84, Y87.0; ICD-8: 950–959), homicide (ICD-10: X85–Y09, Y87.l; ICD-8: 960–978), and accidents (ICD-10: V01–X59, Y10–Y86, Y87.2, Y88–Y89; ICD-8: 810–823, 800–807, 825–949). All natural causes comprised old age and apoplexy (ICD-10: F03.9, I60–I72, R54; ICD-8: 430–438, 794, 290–315, 440–448), malignant neoplasms (ICD-10: C00–D09; ICD-8: 140–209), cardiovascular diseases (ICD-10: I00–I25, I27, I30–I52; ICD-8: 390–429), respiratory diseases (ICD-10: J00–J99; ICD-8: 460–519), endocrine and metabolic conditions (ICD-10: E00–E07, E10–E90; ICD-8: 240–246, 250–279), and a group comprising the rest of the causes.

Cohort members and their parents and siblings were recorded by their diagnosis at discharge. They were categorized as suffering from the following disorders: schizoaffective disorder (ICD-8: 295.79 or 296.8; ICD-10: F25), schizophrenia (ICD-8: 295 [excluding 295.79]; ICD-10: F20), bipolar disorder (ICD-8: 296.19 or 296.39; ICD-10: F30 or F31), or unipolar disorder (ICD-8: 296.09, 296.29, 296.99, 298.09, 300.49, or 300.19; ICD-10: F32 or F33). Both main and auxiliary diagnoses were used. If cohortees were admitted with a psychiatric diagnosis, they were categorized as suffering from "any" psychiatric disorder. We allowed an overlap between the diagnostic groups, e.g., a person admitted with both bipolar disorder and schizophrenia was placed in both diagnostic groups. Separate analyses were then conducted on the 5 outcomes (any admission, unipolar disorder, bipolar disorder, schizoaffective disorder, and schizophrenia), ensuring that all statistical prerequisites for using survival analysis were met.

Statistical Analyses

Data were analyzed using the log-linear Poisson regression, with the logarithm to the person years as an offset variable,[10,11] in the SAS GENMOD version 8.2 (SAS Institute Inc., Cary, N.C.) procedures. All relative risks were adjusted for calendar period, age, and gender. Age, calendar year, and mother/father/sibling's history of diagnosis of mental disorder 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's test.

RESULTS

Numbers and Overlap

In the cohort comprising 5,558,959 persons, a total of 1,480,608 persons died during the follow-up period. A total of 261,887 persons had been admitted to a psychiatric hospital for the first time, and of these, 105,841 died. The numbers for unipolar disorders were 72,165 first ad-

Table 1. Mortality Rate Ratios of Persons Admitted to Danish Psychiatric Inpatient Facilities (N = 1,480,608) Stratified by Age

Age Groups by Type of Death	Mortality Rate Ratio (95% CI)[a]					
	Not Admitted, Reference[b]	Any Admission	Admitted With Unipolar Disorder	Admitted With Bipolar Disorder	Admitted With Schizoaffective Disorder	Admitted With Schizophrenia
Males						
All death						
≤ 24 y	1.00	7.95 (7.35 to 8.60)	14.73 (11.76 to 19.48)	10.09 (6.27 to 16.23)	**28.24 (17.29 to 46.13)**	13.35 (11.23 to 15.86)
25–39 y	1.00	10.68 (10.35 to 11.03)	12.12 (11.18 to 13.14)	9.70 (8.12 to 11.58)	**13.02 (10.34 to 16.38)**	11.18 (10.36 to 12.07)
40–54 y	1.00	5.51 (5.39 to 5.63)	4.66 (4.44 to 4.89)	5.09 (4.55 to 5.70)	**5.66 (4.71 to 6.79)**	4.91 (4.52 to 5.33)
55–79 y	1.00	2.60 (2.56 to 2.63)	1.88 (1.84 to 1.93)	1.88 (1.76 to 2.00)	1.92 (1.68 to 2.20)	**2.39 (2.23 to 2.58)**
80+ y	1.00	2.25 (2.21 to 2.30)	1.45 (1.39 to 1.52)	1.45 (1.28 to 1.65)	1.48 (1.11 to 1.96)	**1.73 (1.41 to 2.11)**
Natural death						
≤ 24 y	1.00	6.34 (5.44 to 7.40)	7.08 (3.68 to 13.62)	5.43 (1.75 to 16.86)	**10.73 (2.68 to 42.92)**	6.78 (4.45 to 10.31)
25–39 y	1.00	7.29 (6.94 to 7.65)	5.39 (4.62 to 6.29)	3.61 (2.48 to 5.27)	**6.04 (3.89 to 9.37)**	5.51 (4.78 to 6.35)
40–54 y	1.00	4.38 (4.27 to 4.49)	2.88 (2.70 to 3.07)	3.25 (2.80 to 3.79)	3.54 (2.76 to 4.54)	**3.93 (3.56 to 4.34)**
55–79 y	1.00	2.42 (2.39 to 2.45)	1.63 (1.59 to 1.67)	1.67 (1.56 to 1.79)	1.67 (1.45 to 1.94)	**2.28 (2.11 to 2.46)**
80+ y	1.00	2.22 (2.17 to 2.26)	1.39 (1.33 to 1.46)	1.42 (1.25 to 1.62)	1.47 (1.10 to 1.96)	**1.70 (1.38 to 2.08)**
Unnatural death						
≤ 24 y	1.00	8.75 (7.98 to 9.60)	18.59 (13.98 to 24.70)	11.73 (6.80 to 20.21)	**37.57 (22.23 to 63.49)**	16.60 (13.71 to 20.10)
25–39 y	1.00	15.56 (14.89 to 16.25)	22.34 (20.30 to 24.59)	18.48 (15.09 to 22.63)	**23.32 (17.80 to 30.57)**	18.88 (17.22 to 20.71)
40–54 y	1.00	12.83 (12.29 to 13.40)	16.81 (15.61 to 18.09)	17.30 (14.59 to 20.52)	**18.90 (14.42 to 24.76)**	10.57 (9.13 to 12.25)
55–79 y	1.00	7.92 (7.59 to 8.27)	**9.69 (9.10 to 10.32)**	8.08 (6.79 to 9.61)	9.38 (6.70 to 13.14)	5.54 (4.27 to 7.19)
80+ y	1.00	3.12 (2.85 to 3.41)	**3.03 (2.56 to 3.59)**	2.23 (1.29 to 3.84)	1.69 (0.42 to 6.75)	2.56 (1.07 to 6.16)
Females						
All death						
≤ 24 y	1.00	12.66 (11.26 to 14.24)	19.75 (14.75 to 26.45)	24.93 (15.00 to 41.43)	20.40 (7.65 to 54.38)	**29.70 (22.10 to 39.90)**
25–39 y	1.00	10.12 (9.65 to 10.61)	11.60 (10.64 to 12.64)	11.49 (9.42 to 14.03)	**16.34 (12.47 to 21.40)**	13.81 (12.09 to 15.78)
40–54 y	1.00	4.44 (4.32 to 4.56)	4.28 (4.09 to 4.48)	4.30 (3.81 to 4.85)	**5.17 (4.31 to 6.20)**	4.47 (3.98 to 5.02)
55–79 y	1.00	2.44 (2.41 to 2.47)	1.96 (1.92 to 2.00)	2.10 (1.98 to 2.23)	2.17 (1.97 to 2.39)	**2.36 (2.21 to 2.53)**
80+ y	1.00	1.77 (1.75 to 1.80)	1.31 (1.28 to 1.34)	1.34 (1.23 to 1.46)	1.34 (1.16 to 1.53)	**1.49 (1.34 to 1.66)**
Natural death						
≤ 24 y	1.00	6.27 (5.03 to 7.82)	4.61 (2.06 to 10.27)	**5.92 (1.48 to 23.69)**	…	3.53 (1.14 to 10.95)
25–39 y	1.00	5.18 (4.83 to 5.56)	4.20 (3.59 to 4.91)	4.55 (3.20 to 6.47)	3.84 (2.06 to 7.13)	**4.95 (3.86 to 6.34)**
40–54 y	1.00	3.14 (3.04 to 3.25)	2.54 (2.39 to 2.70)	2.54 (2.16 to 2.99)	3.07 (2.41 to 3.93)	**3.19 (2.77 to 3.68)**
55–79 y	1.00	2.24 (2.21 to 2.27)	1.72 (1.68 to 1.76)	1.87 (1.76 to 1.99)	1.85 (1.67 to 2.06)	**2.17 (2.02 to 2.33)**
80+ y	1.00	1.76 (1.73 to 1.78)	1.28 (1.25 to 1.32)	1.32 (1.21 to 1.44)	1.33 (1.15 to 1.53)	**1.47 (1.31 to 1.65)**
Unnatural death						
≤ 24 y	1.00	20.94 (18.14 to 24.18)	39.19 (28.56 to 53.77)	52.38 (30.29 to 90.58)	49.57 (18.56 to 132.39)	**66.88 (49.08 to 91.15)**
25–39 y	1.00	30.56 (28.38 to 32.92)	41.72 (37.35 to 46.60)	41.39 (32.40 to 52.86)	**71.34 (52.67 to 96.62)**	50.42 (42.84 to 59.35)
40–54 y	1.00	21.55 (20.32 to 22.87)	27.27 (25.26 to 29.44)	27.48 (22.84 to 33.06)	**32.26 (24.44 to 42.57)**	20.94 (17.09 to 25.65)
55–79 y	1.00	9.20 (8.81 to 9.61)	10.09 (9.55 to 10.66)	9.98 (8.50 to 11.72)	**13.16 (10.43 to 16.60)**	8.93 (7.27 to 10.97)
80+ y	1.00	2.08 (1.95 to 2.22)	1.95 (1.75 to 2.16)	1.79 (1.25 to 2.57)	1.56 (0.84 to 2.91)	**1.97 (1.24 to 3.14)**

[a]Bold = highest mortality rate ratio among the 4 illnesses.
[b]Reference: Persons NEVER admitted to a psychiatric hospital.

missions, of which 29,716 had died; for bipolar disorder, 11,648 first admissions and 3669 deceased; for schizophrenia, 17,660 first admissions and 3942 deceased; and for schizoaffective disorder, 4055 first admissions, with 1261 deaths.

There was an overlap between the diagnostic groups, particularly persons admitted with a schizoaffective disorder who had also been admitted with a unipolar disorder. Among the deceased patients in the schizoaffective disorder group, 58% had also had a unipolar disorder, 30% had also had a bipolar disorder, and 15% had also been admitted with a diagnosis of schizophrenia, emphasizing the instability of the group of persons with a schizoaffective disorder. Note that other admissions are not mutually exclusive, i.e., some of the patients suffering from schizoaffective disorder had 2 or more of the other diagnoses. In persons admitted with a bipolar disorder, 52% had also been admitted with a unipolar disorder. In the rest of the combinations between the 4 disorders, there was a 2% to 10% overlap between diagnoses.

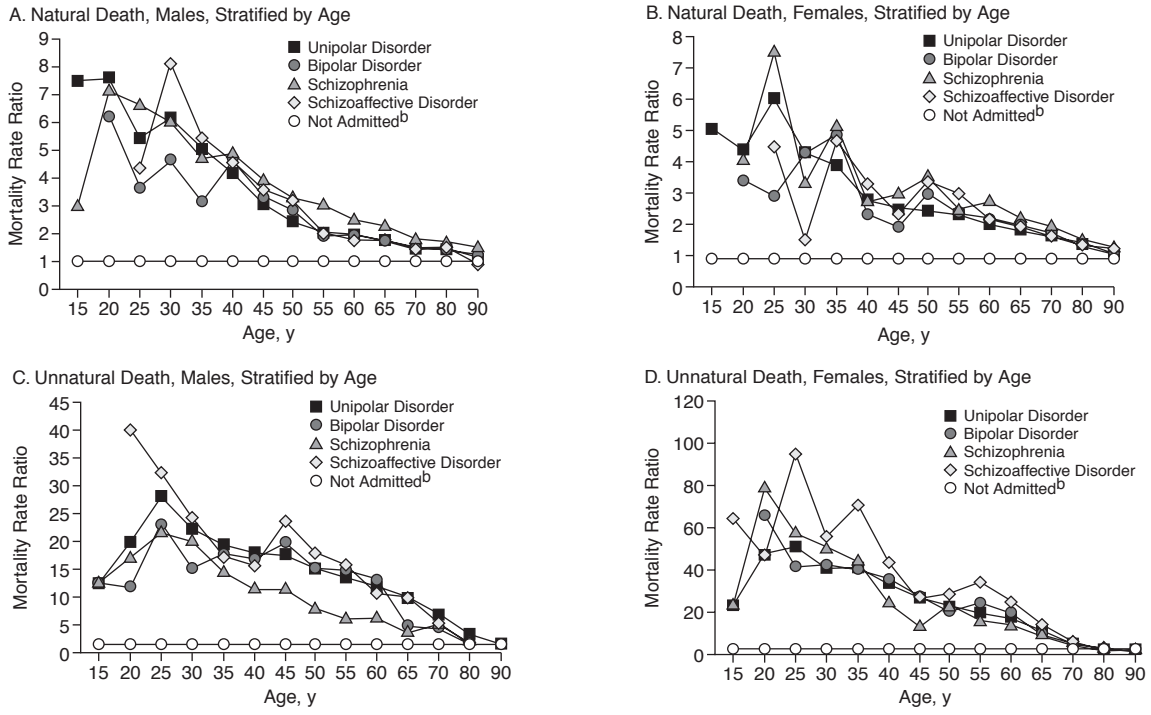
All Deaths Combined

Not surprisingly, cohort members had an increasing mortality rate with age, and males had a higher mortality rate than females. Both male and female cohortees, previously admitted, had an elevated mortality rate in all age groups (data not shown).

The mortality rate ratio was much higher in the younger age groups than in the older groups, when comparing cohort members who had been admitted with those who had not. It should be noted here that the baseline mortality rate in the younger age groups was much lower than in the older age groups. We accounted for this effect modification by age, by making age-stratified analyses.

For all deaths combined, in both males and females, the mortality rate ratios were highest in persons who had

Figure 1. Mortality Rate Ratio[a] According to Admission Status



[a]Adjusted for calendar time.
[b]Reference group; probands never admitted to a psychiatric hospital.

been admitted with schizophrenia and schizoaffective disorder (Table 1). Schizophrenia had the highest mortality rate ratio of the 4 illnesses in the age groups 55–79 and 80+.

Natural and Unnatural Death

A different pattern of mortality emerged when we examined natural and unnatural deaths. Both females and males admitted with a diagnosis of schizophrenia had a higher mortality rate ratio of natural causes of death, compared to persons admitted with unipolar, bipolar, and schizoaffective disorders. In males, the pattern of this higher mortality showed that the 2 lower age groups (≤ 24, 25–39) presented no significant differences (at a 5% level). The mortality rate was significantly higher in the 2 middle-aged groups (40–54, $p < .0001$; 55–79, $p < .0001$) and borderline significant in the oldest group (80+, $p = .07$; Table 1, Figure 1A). In females, the 2 lower age groups (≤ 24, 25–39) presented no significant differences, but a significantly higher mortality rate was present in the rest of the groups (40–54, $p = .005$; 55–79, $p < .0001$; 80+, $p = .02$; Table 1, Figure 1B).

Mortality from unnatural causes in males was lower among persons admitted with schizophrenia (although only significant in the age groups 40–54 and 55–79, $p < .0001$; Table 1, Figure 1C) and lower in females (significant in the age group 40–54, $p = .009$; Table 1, Figure 1D). In particular, persons suffering from a schizoaffective disorder had a higher mortality rate from unnatural death than persons suffering from schizophrenia. This tendency was statistically significant for males in the age groups ≤ 24 ($p = .01$), 40–54 ($p = .0005$), 55–79 ($p = .045$) and statistically significant for women in the age groups 40–54 ($p = .009$) and 55–79 ($p = .02$). After admission, females had a higher excess relative mortality from both natural and unnatural causes compared to males.

Cause-Specific Mortality

We found a significantly increased mortality rate ratio (compared to persons not admitted) for all causes of death examined in all of the 4 diagnostic groups (unipolar disorder, bipolar disorder, schizophrenia, and schizoaffective disorder), except for cancer in schizoaffective disorder and bipolar disorder (Table 2). Suicide was the cause of death with the highest increased mortality rate ratios following psychiatric admission. Among males admitted with a mental disorder, relative rates of death by suicide were lower than among females (although twice as common in absolute numbers).

Impact of Family History of Psychiatric Admission on Mortality Rates

When restricted to persons born after 1952, the cohort included 2,152,357 persons. In this cohort, we found a

Table 2. Cause-Specific Mortality Rate Ratios Following Psychiatric Admission,[a] According to Type of Admission (N = 1,480,608)

Cause of Death	Morality Rate Ratio (95% CI)					
	Not Admitted, Reference[b]	Any Admission	Admitted With Unipolar Disorder	Admitted With Bipolar Disorder	Admitted With Schizoaffective Disorder	Admitted With Schizophrenia
Males						
Natural death						
Cardiovascular diseases	1.00	2.07 (2.03 to 2.14)	1.59 (1.53 to 1.65)	1.58 (1.43 to 1.75)	1.60 (1.29 to 1.98)	2.07 (1.85 to 2.32)
Malignant neoplasms	1.00	1.49 (1.45 to 1.52)	1.15 (1.10 to 1.21)	1.02 (0.89 to 1.16)	1.13 (0.87 to 1.47)	1.24 (1.08 to 1.43)
Old age including apoplexy	1.00	3.77 (3.68 to 3.86)	1.95 (1.84 to 2.07)	1.90 (1.62 to 2.23)	3.10 (2.37 to 4.05)	2.81 (2.37 to 3.34)
Respiratory diseases	1.00	3.58 (3.47 to 3.69)	2.04 (1.91 to 2.18)	2.87 (2.46 to 3.34)	2.47 (1.74 to 3.51)	3.39 (2.81 to 4.09)
Endocrine and metabolic conditions	1.00	2.46 (2.29 to 2.64)	1.64 (1.40 to 1.91)	2.47 (1.79 to 3.42)	4.16 (2.51 to 6.90)	3.56 (2.68 to 4.73
Other	1.00	4.71 (4.62 to 4.80)	2.55 (2.43 to 2.67)	2.84 (2.54 to 3.18)	2.75 (2.18 to 3.46)	5.67 (5.23 to 6.15)
Unnatural death						
Suicide	1.00	17.26 (16.72 to 17.82)	25.91 (24.69 to 27.18)	23.98 (21.33 to 26.96)	34.51 (28.97 to 41.11)	25.38 (23.36 to 27.58)
Accidents	1.00	5.72 (5.52 to 5.92)	3.34 (3.05 to 3.65)	4.19 (3.43 to 5.11)	4.45 (3.09 to 6.41)	6.00 (5.28 to 6.82)
Homicide	1.00	10.41 (8.50 to 12.73)	1.95 (0.73 to 5.23)	5.09 (1.27 to 20.46)	…	12.47 (7.43 to 20.92)
Females						
Natural death						
Cardiovascular diseases	1.00	1.84 (1.80 to 1.87)	1.47 (1.43 to 1.52)	1.67 (1.52 to 1.83)	1.63 (1.40 to 1.90)	1.72 (1.53 to 1.93)
Malignant neoplasms	1.00	1.32 (1.29 to 1.35)	1.19 (1.15 to 1.23)	1.03 (0.92 to 1.15)	1.05 (0.88 to 1.26)	1.32 (1.18 to 1.48)
Old age including apoplexy	1.00	2.65 (2.60 to 2.71)	1.63 (1.57 to 1.70)	1.78 (1.58 to 2.01)	2.04 (1.70 to 2.46)	1.94 (1.67 to 2.25)
Respiratory diseases	1.00	2.96 (2.88 to 3.05)	2.11 (2.01 to 2.22)	2.17 (1.86 to 2.52)	2.18 (1.69 to 2.80)	3.24 (2.77 to 3.80)
Endocrine and metabolic conditions	1.00	1.89 (1.77 to 2.03)	1.50 (1.35 to 1.67)	2.01 (1.50 to 3.68)	2.35 (1.50 to 3.68)	1.69 (1.14 to 2.50)
Other	1.00	3.03 (2.97 to 3.10)	2.23 (2.16 to 2.31)	2.83 (2.58 to 3.12)	2.59 (2.20 to 3.06)	3.92 (3.55 to 4.33)
Unnatural death						
Suicide	1.00	29.08 (27.89 to 30.31)	37.22 (35.38 to 39.16)	43.22 (38.35 to 48.71)	58.81 (49.78 to 69.49)	45.59 (40.55 to 51.26)
Accidents	1.00	3.52 (3.38 to 3.67)	2.60 (2.43 to 2.79)	2.93 (2.38 to 3.60)	3.21 (2.32 to 4.43)	5.01 (4.14 to 6.05)
Homicide	1.00	6.32 (4.92 to 8.11)	3.77 (2.24 to 6.35)	5.86 (1.88 to 18.27)	…	…

[a]Adjusted for age and calendar period.
[b]Reference: persons NEVER admitted to a psychiatric hospital.

higher excess mortality rate ratio of approximately 10 times if a cohortee had had a psychiatric admission. Mortality from natural death was elevated approximately 6 times and for unnatural death approximately 15 times, compared to persons never admitted. These higher mortality rate ratios were expected, having Figures 1A–1D in mind, as this cohort was much younger than the unrestricted cohort.

When examining all deaths combined, a history of psychiatric admission in first-degree relatives was associated with an excess mortality rate ratio of 1.39 (95% CI = 1.34 to 1.44) for persons never admitted (Table 3A). Separating family history in psychiatric admission of fathers, mothers, and siblings revealed that there was an increased mortality rate ratio of 1.32 (95% CI = 1.25 to 1.40), 1.41 (95% CI = 1.35 to 1.47), and 1.44 (95% CI = 1.36 to 1.54), respectively. Overlapping confidence intervals between all 3 categories suggested little or no differences whether the psychiatric admission was among fathers, mothers, or siblings.

For persons who had both an admission with any psychiatric illness and a family history of psychiatric admission, the increased mortality rate ratio from all causes, over and above the excess mortality after the admission, was 1.10 (95% CI = 1.04 to 1.16). The corresponding numbers were 1.27 (95% CI = 1.09 to 1.48) for unipolar disorder and 1.13 (95% CI = 0.99 to 1.32) for schizophrenia. There were no significant effects of family history of admission after bipolar and schizoaffective disorder admissions (Table 3A).

We examined natural and unnatural death separately and found the same pattern, however, with a tendency to higher and more significantly increased mortality rate ratios after unnatural deaths (if there was an admission in the family). Especially mortality from unnatural causes in persons admitted with unipolar disorder was higher (mortality rate ratio = 1.33, 95% CI = 1.11 to 1.59) if there was also a family history of admission (Tables 3B and 3C).

Family history of psychiatric admission for persons who had never had a psychiatric admission was analyzed in more detail using the 4 categories. We found that family history of unipolar admission was associ-

Table 3. Mortality Rate Ratio Following Psychiatric Admission According to Type of Admission and Psychiatric Admission in the Family; Males and Females Combined[a]

	Mortality Rate Ratio (95% CI)		
Admission Reason, Probands	No Family Member Admitted	At Least 1 Family Member Admitted	Excess Risk Associated With Admission of Family Member[b]
A. All Death			
Not admitted	1.00 reference	1.39 (1.34 to 1.44)	1.39 (1.34 to 1.44)*
Unipolar disorder	10.23 (9.63 to 11.78)	12.94 (11.44 to 14.65)	1.27 (1.09 to 1.48)*
Bipolar disorder	10.24 (8.63 to 12.16)	8.72 (6.86 to 11.08)	0.85 (0.64 to 1.15)
Schizoaffective disorder	12.58 (9.96 to 15.89)	11.54 (8.39 to 15.86)	0.92 (0.62 to 1.36)
Schizophrenia	10.75 (9.92 to 11.65)	12.10 (10.85 to 13.49)	1.13 (0.99 to 1.29)
Any admission	9.44 (9.12 to 9.78)	10.37 (9.89 to 10.88)	1.10 (1.04 to 1.16)*
B. Natural Death			
Not admitted	1.00 reference	1.20 (1.14 to 1.26)	1.20 (1.14 to 1.26)*
Unipolar disorder	4.20 (3.54 to 4.98)	4.90 (3.88 to 6.18)	1.17 (0.88 to 1.55)
Bipolar disorder	3.37 (2.37 to 4.79)	2.97 (1.82 to 4.85)	0.88 (0.48 to 1.61)
Schizoaffective disorder	4.91 (3.16 to 7.61)	2.98 (1.42 to 6.26)	0.61 (0.26 to 1.44)
Schizophrenia	5.26 (4.56 to 6.06)	5.83 (4.81 to 7.08)	1.11 (0.87 to 1.41)
Any admission	6.24 (5.92 to 6.58)	6.31 (5.85 to 6.80)	1.01 (0.93 to 1.10)
C. Unnatural Death			
Not admitted	1.00 reference	1.62 (1.55 to 1.71)	1.62 (1.55 to 1.71)*
Unipolar disorder	22.74 (20.28 to 25.50)	30.19 (26.06 to 34.97)	1.33 (1.11 to 1.59)*
Bipolar disorder	23.80 (19.55 to 28.97)	19.81 (15.04 to 26.10)	0.83 (0.59 to 1.17)
Schizoaffective disorder	27.89 (21.17 to 36.75)	28.80 (20.24 to 41.00)	1.03 (0.66 to 1.61)
Schizophrenia	19.91 (18.05 to 21.96)	22.80 (19.98 to 26.01)	1.15 (0.98 to 1.34)
Any admission	14.52 (13.85 to 15.23)	16.90 (15.87 to 17.99)	1.16 (1.08 to 1.25)*

[a]Adjusted for gender, age (and their interaction), and calendar time.
[b]Reference no family member admitted (e.g., for unipolar disorder, all death, 12.94/10.23 = 1.27; for unipolar disorder, natural death, 4.90/4.20 = 1.17; and for unipolar disorder, unnatural death, 30.19/22.74 = 1.33).
*Indicates significant difference at a 5% level.

ated with an excess mortality of 1.30 for all causes (95% CI = 1.22 to 1.37), 1.18 for bipolar disorder (95% CI = 1.02 to 1.38), and 1.23 for schizophrenia (95% CI = 1.07 to 1.41) compared to persons with no psychiatric admission and no family history of psychiatric admission. When examining natural deaths, there were only borderline significant differences in unipolar disorder 1.09 (95% CI = 1.01 to 1.18) between the 2 groups, but when we examined unnatural deaths, we found the same pattern as in all causes: an excess mortality if family members had a history of psychiatric admission with unipolar disorder, bipolar disorder, or schizophrenia (see Table 4). No significant effect was associated with a family history of schizoaffective disorder.

DISCUSSION AND COMPARISON WITH OTHER RESULTS

Key Findings

Cohort members who had been admitted with unipolar disorder, bipolar disorder, schizoaffective disorder, or schizophrenia had an increased mortality by every cause of death, except for cancer in schizoaffective disorder and bipolar disorder. Females with a psychiatric admission had a higher relative excess mortality than males. Males and females who had been admitted with a diagnosis of schizophrenia had a higher mortality from natural death than after an admission with schizoaffective disorder, bipolar disorder, or unipolar disorder. On the other hand, schizophrenia was associated with a lower mortality from unnatural death compared to schizoaffective disorder, bipolar disorder, or unipolar disorder. Especially cohortees suffering from schizoaffective disorder had a higher mortality rate ratio from unnatural death than those suffering from schizophrenia.

Persons never admitted to a psychiatric hospital had an excess mortality if a first-degree relative had had a psychiatric admission. This excess mortality was highest if a family member had a unipolar disorder. If a person had been admitted, the impact of admission in the family was not as large, although persons admitted with unipolar disorder had a small but significant excess mortality if a family member had a mental disorder.

Comparison With Other Results

The generally increased mortality in patients suffering from a mental disorder was described in the extensive review by Harris & Barraclough.[12] They found an increased mortality in schizophrenia and affective disorder, especially by unnatural death. Population-based cohort studies concerning all-cause mortality among psychiatric patients have mostly originated in the Scandinavian countries. In a study from Sweden,[1] the standardized mortality ratio (SMR) for patients admitted with bipolar disorder was 2.5 for men and 2.7 for women, compared to the general population. The SMR for patients suffering from unipolar

Table 4. Mortality Rate Ratio[a] According to Family (mother, father, siblings) History of Psychiatric Admission[b]

	Mortality Rate Ratio (95% CI)				
Type of Death	No Family History of Psychiatric Admission (reference)	Family History of Unipolar Disorder	Family History of Bipolar Disorder	Family History of Schizoaffective Disorder	Family History of Schizophrenia
All death	1.00	1.30 (1.22 to 1.37)*	1.18 (1.02 to 1.38)*	1.09 (0.84 to 1.40)	1.23 (1.07 to 1.41)*
Natural	1.00	1.09 (1.01 to 1.18)*	1.02 (0.83 to 1.25)	0.86 (0.59 to 1.24)	1.05 (0.87 to 1.27)
Unnatural	1.00	1.56 (1.44 to 1.69)*	1.40 (1.13 to 1.73)*	1.40 (0.98 to 1.99)	1.45 (1.19 to 1.77)*

[a]Adjusted for gender, age (and their interaction), and calendar period.
[b]ONLY probands never admitted to a psychiatric hospital.
*Indicates significant difference at a 5% level.

disorder was 2.0 for both genders. In another study from Sweden,[2] the excess mortality in patients who had been admitted with schizophrenia was 2.8 for men and 2.4 for women. A further 30% significantly increased risk was associated with having a schizoaffective disorder compared to the whole group of schizophrenic patients. In a Finnish study,[13] the excess mortality in schizophrenic patients was 3.3 for men and 2.3 for women. In a population-based study from Denmark,[3] the SMR for patients admitted with schizophrenia was 4.7 for men and 2.3 for women, compared to the general population. In most studies, a strong and significant effect modification by age was present since the excess in mortality for persons admitted was higher in the younger age groups than in the older age groups. This was in line with our results, and we also found the same effect modification by age. Our finding regarding an increased mortality in patients suffering from unipolar disorder has previously been reported by Hoyer et al.[14]

No population-based studies, to our knowledge, have examined psychiatric admission of relatives as a risk factor for increased mortality and have compared schizophrenia, schizoaffective disorder, bipolar disorder, and unipolar disorder. Webb and colleagues[15] examined schizophrenia-related disorders or affective disorder in the parents as a risk factor for increased mortality in the offspring, in the age group 0–25 years. They found an increased mortality rate in the offspring if any of the disorders were present in the parents. Especially in the young age groups, a large excess risk of premature death was present. In a meta analysis by Webb et al.,[16] mortality in offspring of parents with psychotic disorders was examined, but in most of the studies the mortality outcome was infant death. Furthermore, most of the studies were not population based. In our study, we started follow-up at the 15-year birthday, excluding all deaths in early life. We found an excess mortality rate if a parent or sibling had been admitted. The excess in mortality rate was largest in persons never admitted, but even persons admitted had an increased mortality rate if any family member had been admitted with a mental disorder.

Psychiatric admission of family members has been shown to be associated with an increased risk of suicide.[17,18] In the Danish study,[18] an excess mortality rate of 27% was found, which was in line with the results presented here.

Why Is There an Excess Mortality?

We found that mental disorder was associated with excess mortality regardless of which mental disorder or which cause of death was examined. This could indicate that the disorders examined in this study had a set of factors leading to the excess mortality. One of these might be side effects of pharmacologic treatment. People admitted with the mental disorder examined here are often treated with antipsychotics, and a substantial weight gain could be associated with the use of this type of medication.[19] Obesity is well known to be associated with excess mortality. Another common risk factor is unhealthy lifestyle. Persons suffering from schizophrenia often have a more unhealthy lifestyle (e.g., unbalanced diets), which probably contributes to the excess mortality.[20] We found an excess mortality rate of endocrine and metabolic conditions, which could be an indication of unhealthy life style. Rates of cigarette smoking in persons suffering from schizophrenia and bipolar disorder are higher than in the general population.[21,22] Furthermore, patients with a psychiatric disorder tend to use medical services to a lesser degree, which could lead to an increased mortality.[23]

Negative social consequences, defined as living alone, receiving more social benefits, and otherwise being more outside the labor market, are frequent consequences of schizophrenia both before and after receiving a diagnosis.[24] A review of bipolar disorder and social background concluded that bipolar disorder is associated with unemployment, lower income, and single marital status, although no causal link was established.[25] In Denmark, these social indicators are well known to be associated with an excess mortality.[26]

The increased mortality rates in persons without psychiatric admission, but with psychiatric admission of a parent or a sibling, could be explained by unobserved mental disorder in the person or symptoms of a mental disorder not requiring admission. It could, however, also be a result of living in a family with a high level of stress due to the illness of the family member. Unipolar admission was associated with a high excess mortality from unnatural death, but the excess mortality was even higher if a family member had a history of psychiatric admission. Unipolar admission in the family was also associated with an excess mortality from unnatural causes. This could support the

theory of a suicidal transmission, either genetic or through an imitation model.[27] A genetic transmission could also be an explanation when focusing on natural death. If there is a genetic link to early death and psychiatric illness as hypothesized above, a consequence would be premature death in family members even though they have no psychiatric illness. The increased mortality in "healthy" relatives to psychiatric patients, on the other hand, could not be due to pharmacologic treatment, indicating that the treatment is not the entire reason for the increased mortality.

Despite similarities, we also found differences in the mortality. Persons admitted with schizophrenia had a different pattern of excess mortality. They had an even higher mortality from natural causes than unipolar, bipolar, and schizoaffective disorder. By definition and origin, schizophrenia has a poorer outcome than unipolar and bipolar disorder,[28] and this outcome also includes premature death, which was supported by our results. On the other hand, patients suffering from unipolar disorder, bipolar disorder, and schizoaffective disorder had a higher mortality from unnatural death. Depression has been shown to be a stronger risk factor for suicide (and hence all unnatural death) than schizophrenia.[29]

Remarks About the Design

Diagnoses used in the present study were register-based clinical diagnoses, which could be speculated to be less accurate than research criteria diagnoses. However, 2 studies 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 the diagnoses.[5,30] As we have only considered inpatients in the present study, we probably found the most severe cases. It is therefore not possible to generalize our results to all persons suffering from, e.g., depression.

In this study, we observed an overlap between the diagnostic groups. We chose not to censor patients shifting from one category to another, as we did not know which diagnosis was the more correct one. This could result in a mixing of the mortality rates, especially in patients suffering from schizoaffective disorder. However, unipolar disorder is considered "less severe" than the other disorders, and to censor cohortees if they were admitted with a unipolar disorder would underestimate the impact of the more severe diagnoses as they are often given later in the course of the illness.

CONCLUSION

Patients admitted with unipolar disorder, bipolar disorder, schizoaffective disorder, or schizophrenia have a highly increased mortality in almost every cause of death compared to persons never admitted with a mental disorder. There are some differences between the mortality rates of the 4 diagnostic groups. Especially a higher excess mortality rate from natural causes of death is seen in schizophrenia and a higher excess mortality from unnatural causes of death in unipolar, bipolar, and schizoaffective disorder, showing that the outcomes of the disorders are different and hence indicates differences between the disorders. These differences could derive from a partly different etiology of the disorders or a different pattern of medication and/or lifestyle.

Psychiatric disorders in the family are associated with excess mortality, even if the proband has never had a psychiatric admission. This could indicate either unobserved psychiatric disorder in the proband and thereby elevated mortality, or the proband having been brought up in an environment with a high level of stress or high occurrences of other risk factors associated with excess risk of death because of a psychiatric disorder in a family member.

The mortality is higher if there is a psychiatric disorder in first-degree family members, but is only a small part of the underlying causes of the excess mortality in patients suffering from 1 of the 4 disorders examined here.

REFERENCES

1. Osby U, Brandt L, Correia N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 2001;58:844–850
2. Osby U, Correia N, Brandt L, et al. Mortality and causes of death in schizophrenia in Stockholm County, Sweden. Schizophr Res 2000;45: 21–28
3. Mortensen PB, Juel K. Mortality and causes of death in first admitted schizophrenic patients. Br J Psychiatry 1993;163:183–189
4. Laursen TM, Labouriau R, Licht RW, et al. Family history of psychiatric illness as a risk factor for schizoaffective disorder: a Danish register-based cohort study. Arch Gen Psychiatry 2005;62:841–848
5. Munk-Jorgensen P, Mortensen PB. The Danish Psychiatric Central Register. Dan Med Bull 1997;44:82–84
6. Malig C. The civil registration system in Denmark. Tech Pap Int Vital Registr Stat 1996;66:1–6
7. Juel K, Helweg-Larsen K. The Danish registers of causes of death. Dan Med Bull 1999;46:354–357
8. World Health Organization. Klassifikation af sygdomme; Udvidet dansk-latinsk udgave af verdenssundhedsorganisationens internationale klassifikation af sygdomme. 8th revision, 1965. [Classification of diseases: Extended Danish-Latin version of the World Health Organization International Classification of Diseases. 8th revision, 1965]. 1st ed. Copenhagen, Denmark: Danish National Board of Health; 1971
9. World Health Organization. WHO ICD-10: Psykiske lidelser og adfærdsmæssige forstyrrelser. Klassifikation og diagnosekriterier [WHO ICD-10: Mental and Behavioural Disorders. Classification and Diagnostic Criteria]. Copenhagen, Denmark: Munksgaard Danmark; 1994
10. Andersen PK, Borgen Ø, Gill RD, et al. Statistical Models Based on Counting Processes. New York, NY: Springer-Verlag; 1993
11. Laird N, Olivier D. Covariance analysis of censored survival data using log-linear analysis techniques. J Am Stat Assoc 1981;76:231–240
12. Harris EC, Barraclough B. Excess mortality of mental disorder. Br J Psychiatry 1998;173:11–53
13. Joukamaa M, Heliovaara M, Knekt P, et al. Mental disorders and cause-specific mortality. Br J Psychiatry 2001;179:498–502
14. Hoyer EH, Mortensen PB, Olesen AV. Mortality and causes of death in a total national sample of patients with affective disorders admitted for the first time between 1973 and 1993. Br J Psychiatry 2000;176:76–82
15. Webb RT, Abel KM, Pickles AR, et al. Mortality risk among offspring of psychiatric inpatients: a population-based follow-up to early adulthood. Am J Psychiatry 2006;163:2170–2177

16. Webb R, Abel K, Pickles A, et al. Mortality in offspring of parents with psychotic disorders: a critical review and meta-analysis. Am J Psychiatry 2005;162:1045–1056
17. Gould MS, Fisher P, Parides M, et al. Psychosocial risk factors of child and adolescent completed suicide. Arch Gen Psychiatry 1996;53: 1155–1162
18. Qin P, Agerbo E, Mortensen PB. Suicide risk in relation to socioeconomic, demographic, psychiatric, and familial factors: a national register-based study of all suicides in Denmark, 1981–1997. Am J Psychiatry 2003;160:765–772
19. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156: 1686–1696
20. Brown S, Birtwistle J, Roe L, et al. The unhealthy lifestyle of people with schizophrenia. Psychol Med 1999;29:697–701
21. Itkin O, Nemets B, Einat H. Smoking habits in bipolar and schizophrenic outpatients in southern Israel. J Clin Psychiatry 2001;62:269–272
22. Dalack GW, Healy DJ, Meador-Woodruff JH. Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. Am J Psychiatry 1998;155:1490–1501
23. Cradock-O'Leary J, Young AS, Yano EM, et al. Use of general medical services by VA patients with psychiatric disorders. Psychiatr Serv 2002; 53:874–878
24. Agerbo E, Byrne M, Eaton WW, et al. Marital and labor market status in the long run in schizophrenia. Arch Gen Psychiatry 2004;61:28–33
25. Tsuchiya KJ, Byrne M, Mortensen PB. Risk factors in relation to an emergence of bipolar disorder: a systematic review. Bipolar Disord 2003;5:231–242
26. Andersen O, Laursen L, Petersen JK. Dødelighed og Erhverv (Occupational Mortality) 1981–1995. Copenhagen, Denmark: Danmarks Statistik; 2001
27. Qin P, Agerbo E, Mortensen PB. Suicide risk in relation to family history of completed suicide and psychiatric disorders: a nested case-control study based on longitudinal registers. Lancet 2002;360: 1126–1130
28. Angst J. Historical aspects of the dichotomy between manic-depressive disorders and schizophrenia. Schizophr Res 2002;57:5–13
29. Qin P, Nordentoft M. Suicide risk in relation to psychiatric hospitalization: evidence based on longitudinal registers. Arch Gen Psychiatry 2005;62:427–432
30. Kessing LV. Validity of diagnoses and other clinical register data in patients with affective disorder. Eur Psychiatry 1998;13:392–398