

Original Article

Sex differences in mortality among patients admitted with affective disorders in North Norway: a 33-year prospective register study

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Objective: Previous studies from North Norway showed significantly increased mortality in patients with schizophrenia and personality disorder. The aim of the present study was to investigate total and cause-specific mortality in inpatients with affective disorder in a 33-year follow-up cohort, with a specific focus on sex differences.

Methods: Based on a hospital case register covering all admissions to psychiatric hospital in the two northernmost counties in Norway from 1980 to 2012, 790 men and 866 women with major depressive disorder and 331 men and 514 women with bipolar disorder were included. The cohort was linked to the Norwegian Cause of Death Registry. The relative mortality in men compared to women was tested using Cox regression with attained age as the time variable. The standardized mortality ratio (SMR) of the patients when compared to the general population in Norway was calculated.

Results: Patients with affective disorders had twice the mortality of the general Norwegian population [SMR = 2.1, 95% confidence interval (CI): 1.9–2.3]. For major depressive disorder, the SMR for total mortality was higher among men (2.6, 95% CI: 2.2–3.0) than women (1.8, 95% CI: 1.5–2.1). For bipolar disorder, no difference was seen between men and women. The SMR for suicide among women showed an increasing trend throughout the period 1980–1990: 20.0 (95% CI: 10.4–38.4); 1991–2001: 27.0 (95% CI: 15.7–46.2); 2002–2012: 40.4 (95% CI: 23.0–71.2).

Conclusions: The substantially increased mortality in patients with affective disorders in Norway has been persistent over a period of 33 years, despite extensive reforms in psychiatric health care. Indications of increasing SMR for suicide in women call for further research.

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Patients with severe mental disorders have a significantly higher mortality than the general population, both from diseases and medical causes as well as external causes and injury (1–5), and have a 15–20-year reduction in life span. The difference in life expectancy is greatest for men (4). Substance abuse, schizophrenia, and personality disorders are associated with the highest risk of death due to

medical conditions, while affective disorders and personality disorders are associated with the highest risk for suicide (5).

The ratio of the observed to the expected number of deaths, the standardized mortality ratio (SMR), expresses the relative mortality of the patient group compared to that of the general population. When compared to the mortality in the

general population, patients with bipolar disorder have lower SMRs than patients with schizophrenia (5). Excess mortality due to cardiovascular diseases and other somatic diseases is higher than excess mortality due to suicides and other external causes for persons with bipolar disorders and schizophrenia, and diseases and medical causes contribute more than external causes of death and injury to the reduction in life span for both groups (6–9). A registry-based study from Sweden (1987–2006) published in 2012 demonstrated that suicides and other external causes accounted for 18% of deaths in individuals with bipolar disorders, whereas 38% were caused by cardiovascular diseases and 44% by other diseases (6). Mortality from cardiovascular diseases was equally increased for men and women.

In Norway, the mortality of individuals with severe mental illness has been reported infrequently since 1916 (10–16). Owing to a lack of relevant data, there has been no nationwide mortality study with long-term follow-up from Norway since 1970, but regional studies from North Norway show increasing SMRs for patients with schizophrenia, especially women (17). However, studies from Denmark and Finland between 1987 and 2006 have showed a slight decrease in the mortality gap between individuals with severe mental disorders and the general population, especially for women (4).

Individuals with bipolar disorders have been shown to have an up to 30 times higher risk of completing suicide than the general population, but the rates differ considerably across countries (18). Furthermore, episodes of depression and mixed states are probably associated with an increased suicide risk among people with bipolar disorder (19). Deaths by suicide in individuals with bipolar depression may be attributed to major depression episodes, and the SMR for patients with bipolar disorder may therefore be higher than previously shown (20). The study by Westman et al., from Sweden, demonstrated a 9.7 times higher mortality for suicide and other external causes for patients with bipolar disorder compared to the general population, slightly higher for women than for men (10.0 and 9.4, respectively) (6).

Regardless of some differences between the Nordic countries, there was, in general, an overall decline in suicide mortality in the Nordic countries between 1980 and 2009, of 25–50 to 20–36 per 100,000 for men, and 9–26 to 8–11 per 100,000 for women (21). The rates in Finland are consistently higher than in the other Nordic countries, and there has been a significant increase in suicides

among young women in Finland and Norway, and no change among young women in Sweden. Rural areas have the highest suicide rates, and in Finnmark, the northernmost county in Norway, the annual suicide rate for men at all ages is >35 per 100,000 inhabitants. For women, the rates in the northernmost counties are not markedly elevated compared to other regions of Norway. Nevertheless, studies from North Norway show an alarming increase in suicide mortality for patients with schizophrenia over a period of 27 years, from 1980 to 2006 (17), especially for women.

The aims of the present study were: first, to estimate the excess mortality due to deaths from diseases and deaths from external causes in men and women admitted with an affective disorder in North Norway during a 33-year period (1980–2012), and, second, to investigate whether the alarming increase in mortality observed in women admitted with schizophrenia also applies to women with affective disorders.

Materials and methods

The study cohort

The University Hospital of North Norway is the only psychiatric hospital covering the two northernmost counties in Norway – Troms and Finnmark. These counties comprise a vast area of approximately 75,000 km², with a total of 238,075 inhabitants in 2014. The development in relative age distribution in North Norway was more or less similar to that in Norway as a whole between 1986 and 2012 (22). Information about every admission to psychiatric departments has been collected since 1980, and this computerized register has been regularly validated against patient files. The data used in the present study were: date of admission, date of discharge, and diagnoses according to the International Classification of Diseases (ICD) at discharge. Between 1985 and 1997, the diagnostic system used in Norway was ICD-9 (23); since 1997, the ICD-10 has been used (24). ICD-8 (25) codes (used before 1985) were converted to ICD-9 codes.

The study population included all patients admitted from 1 January 1980 to 31 December 2012. The unique 11-digit personal identification number assigned to all Norwegian residents was used for linkage between the hospital register, the Norwegian Cause of Death Registry (26), and information regarding emigration held by Statistics Norway (27). The Cause of Death Registry covers data on all persons with residence in the country, independent of where they died. In Norway, all

death certificates are completed by a physician and coded in accordance with the current ICD system. The diagnoses recorded by the Cause of Death Registry as the underlying cause of death were grouped into cardiovascular causes (ICD-8 codes 390–459 and 782.4, ICD-9 codes 390–459, and ICD-10 codes I00–I99), cancer (ICD-8 codes 140–209, ICD-9 codes 140–208, and ICD-10 codes C00–C97), external causes and injury (ICD-8 codes and ICD-9 codes E800–999, ICD-10 codes V, W, X, Y), and suicide (ICD-8 and ICD-9 codes E950–959, ICD-10 codes X60–84). Diseases and medical causes were defined as all causes other than external causes and injury.

There were a total number of 32,150 admissions among 8,161 individuals in the study period. Of these, 283 were not included in the data file owing to missing discharge date ($n = 79$, 1.0%) or an invalid personal identification number, in most cases for refugees ($n = 204$, 2.5%). Thus, 4,217 men (53.5%) and 3,661 women (46.5%) were included. A total of 2,501 (1,121 men, 44.8%; 1,380 women, 55.2%) of these patients were diagnosed with an affective disorder (ICD-9 codes 296, 298.0, 311; and ICD-10 codes F30–F39) at discharge for at least one of their admissions. Patients with affective disorders were categorized into two groups: (i) major depressive disorder (ICD-9 296.2, 296.3, 298.0, 311; ICD-10 F32–F34, F38, F39) as the only main diagnosis and (ii) bipolar disorder (ICD-9 296.0, 296.1, 296.4–296.9, ICD-10 F30, F31) as the only main diagnosis or in combination with major depressive disorder at different admissions. The 2,501 patients were followed from the date of first admission after 1 January 1980 until death, moving abroad ($n = 30$), or 31 December 2012, for a total of 24,038 person-years. Twelve subjects who were in-hospital patients on 1 January 1980 were included in the cohort, with the start of follow-up on the same day. To investigate changes in mortality over time, we split the cohort into three time periods; the first group included

individuals admitted for the first time during 1980–1990, the second group included those with first admission during 1991–2001, and the third group included patients with first admission during 2002–2012.

Statistical analyses

Differences in the clinical characteristics of male and female patients were tested using Student's *t*-test, the Wilcoxon rank sum test (when the distributions were markedly positively skewed), or the chi-square test. We studied the differences in age-adjusted mortality rates between men and women with affective disorders in the study cohort, and sex differences in SMRs compared to the general population.

The relative mortality for men compared to women was tested using Cox regression, with attained age as the time variable. For comparison to the mortality of the general population of Norway, indirect age adjustment was used. The number of deaths to be expected among the patients, if the mortality rates were the same as in the general population in Norway according to age (five-year groups) and calendar year (five-year groups) during follow-up, was calculated. Confidence intervals (CIs) for the SMRs were computed. *p*-values < 0.05 were considered statistically significant. Statistical analyses were performed using SAS Enterprise Guide 6.1 (SAS Institute Inc., Cary, NC, USA).

Results

The cohort included 1,121 men and 1,380 women with an affective disorder diagnosis during the study period 1980–2012 (Table 1). Among these, 790 men (70.5%) and 866 women (62.8%) had major depressive disorder as their only main diagnosis, whereas 331 men (29.5%) and 514 women (37.3%) had bipolar disorder as the main

Table 1. Clinical characteristics of men and women with affective disorders

	Men ($n = 1121$)	Women ($n = 1380$)	<i>p</i> -value ^a
Major depressive disorder	790	866	
Bipolar disorder	331	514	
Number of deaths	235	266	
Number of admissions	4318	6,837	
Number of admissions, median (first and third quartiles)	2 (1, 4)	2 (1, 5)	0.002
Total number of days admitted, median (first and third quartiles)	30 (7, 88)	49 (12, 127.5)	0.002
Age at first admission, years, mean [median (SD)]	42.5 [39.8 (17.2)]	43.7 [40.8 (18.7)]	NS
Total length of follow-up (person-years)	9803	14,235	
Follow-up time, years, mean (SD)	8.7 (6.9)	10.4 (7.8)	<0.0001

NS = not significant; SD = standard deviation.

^aDifferences between men and women.

diagnosis, or bipolar disorder and major depressive disorder diagnoses at separate admissions. The difference between major depressive disorder and bipolar disorder was significantly higher among men than among women ($p < 0.0001$). Mean age at first admission was 42.5 years for men and 43.7 years for women; the difference between the sexes was not statistically significant. The mean length of follow-up was significantly longer among women (10.4 years) than men (8.7 years).

Sex differences in all-cause mortality among patients with affective disorders

A total of 501 patients (235 men and 266 women) died during the follow-up period from 1980 to 2012. Thus, the crude mortality rate was 20.8 per 1,000 person-years. A total of 392 deaths (78%) were due to diseases and 109 (22%) were due to external causes, of which 79 (16%) were suicides. The age-adjusted hazard ratio (HR) in men compared to women was 1.7 (95% CI: 1.4–2.1) (Table 2). Men had a higher mortality than women both for diseases (HR = 1.4, 95% CI: 1.1–1.7) and for external causes (HR = 1.8, 95% CI: 1.2–2.8), including suicide (HR = 1.7, 95% CI: 1.0–2.8). The relative mortality in men compared to women was highest in those with major depressive disorder only as the main diagnosis. The mortality rate was higher in men than in women in the period 1980–2001, while the mortality rate was similar in men and women admitted for the first time during 2002–2012. The diagnostic groups (major depressive disorder and bipolar disorder) did not differ in age- and sex-adjusted total and cause-specific mortality.

Mortality in patients with affective disorder compared to the general population (SMR)

Patients with affective disorders had twice the mortality of the general Norwegian population

(SMR = 2.1, 95% CI: 1.9–2.3). The mortality was elevated both for diseases (SMR = 1.7, 95% CI: 1.6–1.9) and for external causes of death (SMR = 8.2, 95% CI: 6.8–9.9). SMR was elevated for cardiovascular diseases (1.9, 95% CI: 1.6–2.2), but not for cancer (1.0, 95% CI: 0.8–1.3), and among the external causes, SMR was particularly elevated for suicide (23.4, 95% CI: 18.8–29.2). As displayed in Table 3, a similar pattern was found both in men and women. Among patients with major depressive disorder, the SMR for total mortality was higher among men (2.6, 95% CI: 2.2–3.0) than women (1.8, 95% CI: 1.5–2.1). For bipolar disorder, there was no significant difference between the sexes; SMR for men was 2.0 (95% CI: 1.6–2.5), and for women 2.1 (95% CI: 1.8–2.5) (Table 3).

All-cause mortality was elevated among patients with affective disorders compared to the general Norwegian population in all age groups, and highest in the younger age groups. However, for suicide, the SMRs for relatively young people did not differ much from SMR in older subjects (Table 4).

Time trends in mortality among patients with affective disorders

SMR was 1.9 (95% CI: 1.6–2.2) for patients with affective disorders and admitted for the first time during 1980–1990, 2.3 (95% CI: 2.0–2.6) for those admitted during 1991–2001, and 2.1 (95% CI: 1.8–2.6) for those admitted during 2002–2012. For men, the all-cause SMR was reasonably stable, at 2.3–2.4 throughout the study period (Table 5), while for women there was an increase in all-cause SMR, from 1.7 (95% CI: 1.4–2.1) for patients admitted during the first period, to 2.0 (95% CI: 1.6–2.6) for those admitted during the last period (Table 6). The SMR for cardiovascular disease mortality in women tended to increase, from 1.6 (95% CI: 1.2–2.2) to 2.2 (95% CI: 1.4–3.4), whereas in men there was a decrease from 2.4

Table 2. Relative mortality (hazard ratio) in men compared to women among patients with affective disorders

	Patients, n		Follow-up (person-years)		Deaths		Hazard ratio (95% CI)	p-value
	Men	Women	Men	Women	Men	Women		
All patients	1,121	1,380	9,803	14,235	235	266	1.7 (1.4–2.1)	<0.0001
Major depressive disorder	790	866	6,244	7,522	147	136	1.9 (1.5–2.4)	<0.0001
Bipolar disorder	331	514	3,559	6,713	88	130	1.6 (1.2–2.0)	0.002
Date of first admission								
1980–1990	120	218	2,443	4,790	68	100	2.1 (1.5–2.9)	<0.0001
1991–2001	337	440	3,954	5,714	107	109	1.7 (1.3–2.2)	<0.0002
2002–2012	664	722	3,406	3,730	60	57	1.4 (1.0–2.1)	0.10

CI = confidence interval.

Table 3. Standardized mortality ratio (SMR) among patients with affective disorder admitted to the University Hospital of North Norway, 1980 –2012, compared to the general Norwegian population

	All patients				Men			Women		
	Observed deaths (n)	Expected deaths, n	SMR (95% CI)		Observed deaths, n	Expected deaths, n	SMR (95% CI)	Observed deaths, n	Expected deaths, n	SMR (95% CI)
All patients										
Total mortality	501	238.0	2.1 (1.9–2.3)		235	101.0	2.3 (2.0–2.6)	266	137.0	1.9 (1.7–2.2)
Deaths from diseases	392	224.7	1.7 (1.6–1.9)		176	93.7	1.9 (1.6–2.2)	216	131.0	1.6 (1.4–1.9)
CVD	160	85.8	1.9 (1.6–2.2)		65	36.6	1.8 (1.4–2.3)	95	49.1	1.9 (1.6–2.4)
Cancer	68	68.4	1.0 (0.8–1.3)		33	29.5	1.1 (0.8–1.6)	35	38.9	0.9 (0.6–1.3)
External causes of death	109	13.3	8.2 (6.8–9.9)		59	7.3	8.1 (6.3–10.5)	50	6.0	8.3 (6.3–11.9)
Suicide	79	3.4	23.4 (18.8–29.2)		45	2.1	21.0 (15.7–28.2)	34	1.2	27.6 (19.8–38.7)
Major depressive disorder										
Total mortality	283	131.9	2.1 (1.9–2.4)		147	56.8	2.6 (2.2–3.0)	136	75.1	1.8 (1.5–2.1)
Deaths from diseases	224	124.0	1.8 (1.6–2.1)		108	52.3	2.1 (1.7–2.5)	116	71.7	1.6 (1.3–1.9)
CVD	88	47.0	1.9 (1.5–2.3)		38	19.7	1.9 (1.4–2.6)	50	27.3	1.8 (1.4–2.4)
Cancer	41	36.6	1.1 (0.8–1.5)		19	17.7	1.1 (0.7–1.8)	22	19.8	1.1 (0.7–1.7)
External causes of death	59	7.8	7.5 (5.8–9.7)		39	4.4	8.8 (6.4–12.0)	20	3.3	5.9 (3.8–9.2)
Suicide	47	2.0	23.9 (18.0–31.8)		32	1.3	24.0 (17.0–33.9)	15	0.6	23.7 (14.3–39.4)
Bipolar disorder										
Total mortality	218	106.1	2.1 (1.8–2.3)		88	44.2	2.0 (1.6–2.5)	130	61.9	2.1 (1.8–2.5)
Deaths from diseases	168	100.7	1.7 (1.4–1.9)		68	41.4	1.6 (1.3–2.1)	100	59.3	1.7 (1.4–2.1)
CVD	72	38.8	1.9 (1.5–2.3)		27	16.9	1.6 (1.1–2.3)	45	21.8	2.1 (1.5–2.8)
Cancer	27	31.9	0.8 (0.6–1.2)		14	12.8	1.1 (0.6–1.8)	13	19.1	0.7 (0.4–1.2)
External causes of death	50	5.5	9.2 (6.9–12.1)		20	2.8	7.1 (4.6–11.0)	30	2.6	11.3 (7.9–16.2)
Suicide	32	1.4	22.8 (16.1–32.2)		13	0.8	16.1 (9.4–27.8)	19	0.6	31.8 (20.3–49.8)

CI = confidence interval; CVD = cardiovascular disease.

Table 4. Standardized mortality ratio (SMR) according to age groups in patients with affective disorders admitted to the University Hospital of North Norway during 1980–2012, compared to the general Norwegian population

	Number of deaths	SMR total (95% CI)
All causes		
Age 15–39 years	42	7.5 (5.5–10.1)
Age 40–49 years	47	5.7 (4.3–7.6)
Age 50–59 years	51	2.9 (2.2–3.8)
Age 60–69 years	78	2.2 (1.8–2.8)
Age 70+ years	283	1.7 (1.5–1.9)
Total	501	2.1 (1.9–2.3)
Deaths from diseases		
Age 15–39 years	8	2.9 (1.4–5.6)
Age 40–49 years	23	3.6 (2.4–5.5)
Age 50–59 years	31	1.9 (1.4–2.7)
Age 60–69 years	61	1.8 (1.4–2.3)
Age 70+ years	269	1.6 (1.4–1.8)
Total	392	1.7 (1.6–1.9)
External causes of death		
Age 15–39 years	34	12.3 (8.8–17.2)
Age 40–49 years	24	12.9 (8.6–19.2)
Age 50–59 years	20	11.7 (7.5–18.1)
Age 60–69 years	17	12.4 (7.7–20.0)
Age 70+ years	14	2.5 (1.5–4.2)
Total	109	8.2 (6.8–9.9)
Suicide		
Age 15–39 years	27	24.4 (16.7–35.7)
Age 40–49 years	20	26.2 (16.9–40.1)
Age 50–59 years	13	19.7 (11.4–33.9)
Age 60–69 years	13	29.7 (17.3–51.2)
Age 70+ years	6	15.0 (6.7–33.4)
Total	79	23.4 (18.8–29.2)

CI = confidence interval.

(95% CI: 1.7–3.4) to 1.7 (95% CI: 1.0–2.8) (Table 5). SMR for suicide increased with year of first admission in both sexes, and the increase in women from 20.0 (95% CI: 10.4–38.4) during 1980–1990 to 40.4 (95% CI: 23.0–71.2) during 2002–2012 is substantial. However, none of the observed time trend differences in SMRs were statistically significant. Additional analyses restricted to subjects admitted during 1980–1990 showed that

all-cause SMR for men was 1.9 (95% CI: 1.1–3.3) with follow-up during 1980–1990, 1.7 (95% CI: 1.1–2.6) with follow-up during 1991–2001, and 3.2 (95% CI: 2.3–4.4) with follow-up during 2002–2012. For women, the corresponding figures were 2.4 (95% CI: 1.5–3.8), 1.3 (95% CI: 0.9–1.9), and 1.8 (95% CI: 1.4–2.4). Furthermore, all-cause SMR for men admitted and followed during 1991–2001 was 2.2 (95% CI: 1.5–3.2), and 2.3 (95% CI: 1.8–2.9) for men admitted and followed during 2002–2012. The corresponding figures for women were 2.2 (95% CI: 1.5–3.2) and 2.0 (95% CI: 1.6–2.6).

Discussion

Key findings

In the present study of all patients admitted to psychiatric hospital in North Norway during 1980–2012, we found 2–3 times higher all-cause mortality among patients with affective disorders compared to the general Norwegian population. Overall, there was no reduction in SMR due to diseases or external causes of death for patients with affective disorders over a period of 33 years. Among patients with major depression, men had significantly higher mortality both for diseases and for external causes. Among women there was a trend for increasing SMR due to suicide throughout the 33-year period.

Comparison to other countries

A meta-analysis by Walker et al. (28) states a relative mortality risk of 2.1 (95% CI: 1.9–2.3) for mood disorders. SMRs of 2.3 for all-cause mortality in men and 1.9 among women are thus in line with those found in a series of similar studies from other Nordic countries (2–7). A comprehensive registry-based study from Finland, Sweden, and

Table 5. Standardized mortality ratio (SMR) among men with affective disorders admitted to the University Hospital of North Norway during 1980–2012, compared to the general Norwegian population

	1980–1990		1991–2001		2002–2012	
	SMR (95% CI)	Deaths ^a	SMR (95% CI)	Deaths ^a	SMR (95% CI)	Deaths ^a
All causes	2.3 (1.8–2.9)	68 (29.9)	2.4 (2.0–2.9)	107 (44.5)	2.3 (1.8–2.9)	60 (26.6)
Deaths from diseases	2.1 (1.6–2.7)	58 (28.0)	1.9 (1.5–2.4)	78 (41.5)	1.7 (1.2–2.3)	40 (24.2)
CVD	2.4 (1.7–3.4)	29 (12.2)	1.4 (0.9–2.1)	22 (16.2)	1.7 (1.0–2.8)	14 (8.3)
Cancer	1.2 (0.7–2.3)	11 (8.8)	1.3 (0.8–2.1)	17 (13.9)	0.6 (0.3–1.6)	5 (7.8)
External causes of death	5.3 (2.8–9.8)	10 (1.9)	9.7 (6.7–13.9)	29 (3.0)	8.4 (5.4–13.1)	20 (2.4)
Suicide	11.8 (5.6–24.8)	7 (0.6)	29.6 (20.0–43.9)	25 (0.8)	18.4 (10.7–31.7)	13 (0.7)

CI = confidence interval; CVD = cardiovascular disease.

^aNumber of observed deaths (expected number of deaths).

Table 6. Standardized mortality ratio (SMR) among women with affective disorders admitted to the University Hospital of North Norway during 1980–2012, compared to the general Norwegian population

	1980–1990		1991–2000		2001–2012	
	SMR (95% CI)	Deaths ^a	SMR (95% CI)	Deaths ^a	SMR (95% CI)	Deaths ^a
All cause	1.7 (1.4–2.1)	100 (58.7)	2.2 (1.8–2.6)	109 (50.4)	2.0 (1.6–2.6)	57 (27.9)
Deaths from diseases	1.4 (1.2–1.8)	81 (56.4)	1.9 (1.6–2.3)	92 (48.1)	1.6 (1.2–2.2)	43 (26.5)
CVD	1.6 (1.2–2.2)	36 (22.5)	2.2 (1.6–3.1)	39 (16.5)	2.2 (1.4–3.4)	20 (9.1)
Cancer	0.8 (0.5–1.3)	13 (16.6)	1.0 (0.6–1.7)	15 (14.7)	0.9 (0.4–1.9)	7 (7.6)
External causes of death	8.1 (5.2–12.8)	19 (2.3)	7.5 (4.7–12.1)	17 (2.3)	9.9 (5.8–16.7)	14 (1.4)
Suicide	20.0 (10.4–38.4)	9 (0.5)	27.0 (15.7–46.4)	13 (0.5)	40.4 (23.0–71.2)	12 (0.3)

CI = confidence interval; CVD = cardiovascular disease.

^aNumber of observed deaths (expected number of deaths).

Denmark demonstrated a surprisingly consistent all-cause SMR for men (2.5 in Finland and Sweden, and 2.6 in Denmark) and women (2.1 in Finland, and 2.2 in Denmark and Sweden). SMR due to cardiovascular diseases in the present study was 1.8 for men (95% CI: 1.4–2.3). This is in line with that found in the other Nordic countries (1.8 in Sweden, and 2.0 in Finland and Denmark) (5), and also in studies from non-Nordic countries stating that bipolar disorder is associated with a near doubling of cardiovascular mortality risk compared to general population estimates (29). Women in the present study had a similar or slightly higher SMR due to cardiovascular diseases (1.9, 95% CI: 1.6–2.4) than women in Sweden (1.6), Denmark (1.7), and Finland (1.7) (5). In contrast to the Nordic and other countries, SMR due to cancer in the present study was 1.1 (95% CI 0.8–1.6) for men and 0.9 (95% CI 0.6–1.3) for women, which was no higher for patients with affective disorders than for the general Norwegian population. In all the other Nordic countries, the ratios were higher both for men (1.8 in Denmark, 1.4 in Finland, and 1.5 in Sweden) and women (1.7 in Denmark, 1.5 in Finland, and 1.6 in Sweden) (5), with similar findings from elsewhere, such as Australia (30, 31). SMRs due to suicide in the present study – 21.0 (95% CI: 15.7–28.2) for men and 27.6 (95% CI: 19.8–38.7) for women, are in line with data from Finland (18.3 for men and 26.3 for women), while the ratios were higher for both sexes in Denmark (36.6 for men, 50.5 for women) and Sweden (35.6 for men, 46.6 for women) (5).

For patients with a bipolar disorder, we found slightly higher SMR for cardiovascular causes of death in women than in the other Nordic countries: 2.1 (95% CI: 1.5–2.8) compared to 1.7 (95% CI: 1.5–1.9) in Denmark; 2.1 (95% CI: 1.7–2.4) in Finland; and 1.8 (95% CI: 1.7–1.9) in Sweden (7). SMR for external causes of death (including suicide) in bipolar women was also somewhat higher

in the present study than in a Swedish study: 11.3 (95% CI: 7.9–16.2) compared to 10.2 (95% CI: 9.0–11.1) (6). However, the differences are not statistically significant.

As in the other Nordic countries, SMRs for persons with affective disorders in North Norway were lower compared to SMRs for schizophrenia [3.5 for men (95% CI: 3.1–4.1) and 2.6 for women (95% CI: 2.1–3.2)] (17). The denominator for SMRs in the present study are based on the entire Norwegian population, and because North Norway had slightly higher mortality rates for men than in the rest of Norway during most of the follow-up period (32), this might have resulted in higher SMRs for men in the present study. However, a comparison to the population in North Norway would nevertheless have led to biased (low) SMRs because the suicide deaths of the patients in the cohort contribute to the total number of deaths in the population of North Norway.

Age at first admission

The median age at onset for all mood disorders ranges between the late 20s and the early 40s worldwide (33), and approximately half of those with bipolar I disorder or subthreshold bipolar disorder reported an onset before the age of 25 years (34). The median age at first admission in the present study cohort was 39.8 years [standard deviation (SD) = 17.2, range: 16–89 years] for men and 40.8 (SD = 18.7, range: 15–93 years) for women, indicating that many patients may be admitted to specialist health care facilities at a late stage during the disease course owing to a crisis or exacerbation of symptoms. The high age at first admission could also be explained by a number of patients being admitted before 1980, but it is highly unlikely that there were many patients admitted before 1980 who did not have their next admission before, for example, 1990. Hence, the

inpatient population with affective disorders is probably highly selected and biased towards more severe cases, and the increased mortality may thus indicate a strong association with symptom severity both for major depressive disorder and bipolar disorder. There are long travelling distances to specialist health care facilities in North Norway, and many patients may have had several contacts with primary health care before their first admission to hospital. Unfortunately, we have no information on treatment outside hospital. Nevertheless, we found the highest SMR values in the younger age groups (<50 years) both in men and women both for diseases and for external causes of death. Munk Laursen et al. (7) stated that life expectancy in Finland is lower in men with bipolar disorder than in men with schizophrenia owing to the high mortality in younger age groups. Owing to the high age at first admission in our cohort compared to age at onset reported in prevalence studies (33, 34), there may be an actual underestimation of mortality in individuals in younger age groups.

Changes in mortality over time

With regard to the other Nordic countries, Norway has undergone a reform within psychiatric health care over the last two decades. There has been a strengthening of decentralized psychiatric services and development of community-based mental health services, and a decrease in hospital beds and inpatient care. As demonstrated in Table 2, more patients were admitted for the first time during 1991–2000 than during 1981–1990. This reflects that inpatient care has changed toward treating a higher number of patients, with admissions of shorter duration. Wahlbeck et al. concluded that there is a slight trend for reduced total mortality risk for patients with all mental disorders between 1987 and 2006 (4). In the present study, we found that SMRs both for diseases and for external causes of death for men and women with affective disorders were essentially unchanged, or at least not reduced, during the period 1980–2012.

The mortality risk may be higher in the first years after first admission, and thus the SMR differences between the three time cohorts could be affected by changes in the length of follow-up and average age of the cohorts over time. However, additional analyses of subjects admitted during 1980–1990 showed no such effect. Furthermore, there was little evidence for a significant improvement in prognosis with regard to mortality in patients admitted in the 2000s than in the 1980s.

The difference in mortality between men and women admitted for the first time during 2002–2012 was not statistically significant (Table 2), indicating that the mortality for women is increasing relative to that in men. In our previous study of mortality in schizophrenia, based on the same inpatient population (admitted and followed up during 1980–2006), albeit with a shorter follow-up period, we found higher SMRs for patients admitted for the first time during 1993–2006 than for patients admitted during 1980–1992 (17). The SMR for suicide was particularly high for women admitted in the 2000s. In the present study, we found a trend for increasing SMRs for suicide in women with affective disorders as well.

Strengths and limitations

A strength of the present study was the long follow-up and the completeness of data on admitted patients, with regular quality control against patient files. In addition, there was virtually no loss to follow-up as the Norwegian Cause of Death Registry has a near-complete degree of coverage and completeness (35, 36). In two international quality assessments, the Norwegian Cause of Death Registry was assessed in the second-best groups (37, 38) owing to an excessively high rate of unspecified diagnoses; in a third assessment it was ranked in the best group (39). The rate of unspecified diagnoses are higher for cardiovascular diagnoses than for cancer diagnoses (40), so there might have been an overestimation of cardiovascular mortality in the present study (both for the patients and the national mortality rates we used for comparison). There are no private psychiatric hospitals in Norway. Being the only regional psychiatric hospital, all residents from the two northernmost counties admitted to any psychiatric hospital in Norway will be transferred to the University Hospital of North Norway. The mental health services in these counties are almost exclusively public, with established structures for cooperation on admission and follow-up. Hence, few admissions for subjects who are resident in these two counties have taken place elsewhere without eventually being included in the database. However, we have no information on whether such patients are treated or have not been in primary health care facilities before admission.

Diagnoses are registered on the day of discharge by the treating clinician, usually derived by a team discussion, but diagnostic reliability is not known. This may have affected the validity of the diagnosis.

The study comprised only the two northernmost counties in Norway. These counties are sparsely

populated, with long travelling distances and only one hospital covering both counties. In line with the other Nordic countries, Norway has a long tradition of egalitarian health and welfare policies. There may still be regional inequity in health care delivery or a lack of socioeconomic protective factors affecting risk factor prevention, follow-up after discharge from hospital, or continuous support from decentralized psychiatric health care and community-based services. The present study may therefore not be fully representative of Norway at a national level, and further studies are needed to compare the northern regions to the rest of the country, as well as to similar regions in other countries. Furthermore, we have no information on potential confounders such as severity of psychiatric symptoms, smoking, or alcohol or substance abuse. The study was underpowered for time-trend analysis of specific causes of mortality.

Conclusions

The present study demonstrated a persistent mortality gap between patients with affective disorders and the general population in Norway over a period of 33 years. Our findings support the assumption that the reforms in psychiatric health care that have been implemented in Norway over the last two decades have not reduced mortality among patients with severe mental disorders relative to the mortality in the general population. Mortality is affected by prevention of lifestyle risk factors, equal access to quality health care, and strategies to reduce suicide risk. High mortality compared to the general population is thus a proxy indicator of the effectiveness of policy on health care, social services, and access to meaningful work and activities. Our findings should therefore prompt a change in clinical prevention and treatment strategies, to reduce the mortality gap between patients with affective disorders and the general population. The importance of preventing deaths from somatic diseases in this group of patients is underscored, as 64% of the excess mortality in the present study was due to diseases and medical causes. Furthermore, the indications of increasing mortality due to suicide in women with affective disorders compared to the general population call for further research.

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Disclosures

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

References

1. Eaton W, Martins S, Nestadt G et al. The burden of mental disorders. *Epidemiol Rev* 2008; 30: 1–14.
2. Laursen TM, Munk-Olsen T, Nordentoft M et al. 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. *J Clin Psychiatry* 2007; 68: 899–907.
3. Lawrence D, Kisely S, Pais J. The epidemiology of excess mortality in people with mental illness. *Can J Psychiatry* 2010; 55: 752–760.
4. Wahlbeck K, Westman J, Nordentoft M et al. Outcomes of Nordic mental health systems: life expectancy among people with mental disorders. *Br J Psychiatry* 2011; 199: 453–458.
5. Nordentoft M, Wahlbeck K, Hallgren J et al. Excess mortality, causes of death and life expectancy in 270 770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. *PlosOne* 2013; 8: e55176.
6. Westman J, Hällgren J, Wahlbeck K et al. Cardiovascular mortality in bipolar disorder: a population-based cohort study in Sweden. *BMJ Open* 2013; 3: e002373.
7. Munk LT, Wahlbeck K, Hällgren J et al. Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries. *PLoS ONE* 2013; 8: e67133.
8. Hayes JF, Miles J, Walters K et al. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. *Acta Psychiatr Scand* 2015; 131: 417–425.
9. Laursen TM, Munk-Olsen T, Gasse C. Chronic somatic comorbidity and excess mortality due to natural causes in persons with schizophrenia or bipolar affective disorder. *PLoS ONE* 2011; 6: e24597.
10. Ødegård Ø. Mortality in Norwegian mental hospitals from 1916–1933. *Acta Psychiatr Nevrl Scand* 1936; II: 323–356.
11. Ødegård Ø. Mortality in Norwegian hospitals 1926–1941. *Acta Genet Stat Med* 1951; 2: 141–173.
12. Ødegård Ø. The excess mortality of the insane. *Acta Psychiatr Nevrl Scand* 1952; 27: 353–367.
13. Ødegård Ø. Mortality in Norwegian mental hospitals 1950–1962. *Acta Genet Stat Med* 1967; 17: 137–153.
14. Saugstad L, Ødegård Ø. Mortality in psychiatric hospitals in Norway 1950–74. *Acta Psychiatr Scand* 1985; 59: 431–447.
15. Hansen V, Arnesen E, Jacobsen BK. Cause-specific mortality in psychiatric patients after deinstitutionalization. *Br J Psychiatry* 1997; 170: 186–190.
16. Hansen V, Arnesen E, Jacobsen BK. Total mortality in people admitted to a psychiatric hospital. *Br J Psychiatry* 2001; 179: 438–443.
17. Høye A, Jacobsen BK, Hansen V. Increasing mortality in schizophrenia: are women at particular risk? A follow-up of 1111 patients admitted during 1980–2006 in Northern Norway. *Schizophr Res* 2011; 132: 228–232.
18. Pompili M, Gonda X, Serafini G et al. Epidemiology of suicide in bipolar disorders: a systematic review of the literature. *Bipolar Disord* 2013; 15: 457–490.

19. Gonda X, Pompili M, Serafini G et al. Suicidal behaviour in bipolar disorder: epidemiology, characteristics and major risk factors. *J Affect Disord* 2012; 143: 16–26.
20. Miller C, Bauer MS. Excess mortality in bipolar disorders. *Curr Psychiatry Rep* 2014; 16: 499.
21. Titelman D, Oskarsson H, Wahkbeck K et al. Suicide mortality trends in the Nordic countries 1980–2009. *Nord J Psychiatry* 2013; 67: 414–423.
22. Sund E, Hansen FH. Demography and living conditions in North Norway (in Norwegian). Report, Regional Health Authority of North Norway, 2012.
23. World Health Organization. International Classification of Diseases, Ninth Revision. Geneva: World Health Organization, 1978.
24. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization, 1992.
25. World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-8). Geneva: World Health Organization, 1967.
26. The Norwegian Institute of Public Health. The Cause of Death Registry, 2015. Available from: <http://www.fhi.no/helseregistre/dodsarsaksregisteret>.
27. Statistics Norway Population (2015). Available from: <https://www.ssb.no/> (Accessed 15 December 2013).
28. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry* 2015; 7: 334–341.
29. Weiner M, Warren L, Fiederowicz JG. Cardiovascular morbidity and mortality in bipolar disorder. *Ann Clin Psychiatry* 2011; 23: 40–47.
30. Kisely S, Crowe E, Lawrence D. Cancer-related mortality in people with mental illness. *JAMA Psychiatry* 2013; 70: 209–217.
31. Kisely S, Forsyth S, Lawrence D. Why do psychiatric patients have higher cancer mortality rates when cancer incidence is the same or lower? *Aust N Z J Psychiatry* 2016; 50: 254–263.
32. Norwegian Institute of Public Health. Report 1: Social disparities in health (In Norwegian), 2007. Available from: <http://www.fhi.no/artikler/?id=63144>.
33. Kessler RC, Angermeyer M, Anthony JC. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry* 2007; 6: 168–176.
34. Merikangas KR, Jin R, He J-P et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. *Arch Gen Psychiatry* 2011; 68: 241–251.
35. Gjertsen F. The Cause of Death Registry – an important source in medical research (in Norwegian). *Tidsskr Nor Legeforen* 2002; 122: 2551–2554.
36. Pedersen AG, Ellingsen CL. Data quality in the cause of death registry. *Tidsskr Nor Legeforen* 2015; 135: 678–770.
37. Mathers CD, Fat DM, Inoue M et al. Counting the dead and what they die from: an assessment of the global status of cause of death data. *Bull World Health Organ* 2005; 83: 171–177.
38. Mahapatra P, Shibuya K, Lopez AD. Civil registration systems and vital statistics: successes and missed opportunities. *Lancet* 2007; 370: 1653–1663.
39. Phillips DE, Lozano R, Naghavi M. A composite metric for assessing data on mortality and causes of death: the vital statistics performance index. *Popul Health Metr* 2014; 12: 14.
40. Bakken IJ, Ellingsen CL, Pedersen AG et al. Comparison of data from the Cause of Death Registry and the Norwegian Patient Register. *Tidsskr Nor Legeforen* 2015; 135: 1949–1953.