

Increasing mortality in schizophrenia: Are women at particular risk? A follow-up of 1111 patients admitted during 1980-2006 in Northern Norway.

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Abstract

A study of mortality for all patients with schizophrenia admitted to the University Hospital of North Norway during 1980 – 2006 was performed, with a special focus on gender differences and changes in mortality during a period of transition from hospital-based to community-based care.

A total of 1111 patients with schizophrenia were included, and the cohort was linked to the Causes of Death Register of Norway. Males and females had 3.5 and 2.6 times, respectively, higher mortality than the general population. The standardized mortality ratios were higher during the last nine years than the first nine years, and for women admitted after 1992, we found evidence for an increasing difference in mortality compared to the general female population as well as an increase in absolute mortality. In the subgroup of patients who had always been admitted voluntarily, women tended to have higher mortality, and a particularly high standardized mortality rate (SMR) was found in this group of female schizophrenic patients. Our results confirmed a persisting mortality gap between patients with schizophrenia and the general population over a period of 27 years, with a tendency of increasing standardized mortality ratios over time. The SMR for total mortality of women with schizophrenia is rising and becoming just as high as for men, both for unnatural and natural causes of death.

Keywords: Schizophrenia, Schizophrenia/mortality, Schizophrenia/gender differences; Standardized mortality ratios

1. Introduction

In Norway, mortality of patients with mental illness has been reported regularly since 1916 (Hansen et al., 1997 and 2001, Saugstad and Ødegård, 1979,1985, Ødegård, 1936, 1951, 1952, 1957) Already in the period 1963 – 1974, an increase in standardized mortality ratios (SMRs) was evident (Saugstad and Ødegård, 1985). In a study from 2001 based on the case register of the University Hospital of North Norway with follow-up 1980-1992 (Hansen et al) a 62 % rise in mortality rates was seen for male psychiatric patients compared to the period 1963-1974. Several studies show a significantly higher risk of premature death in persons with schizophrenia than in the general population (Brown et al., 2000 and 2010, Eaton et al., 2008, Harris and Barraclough, 1998, McGrath et al., 2008, Saha et al., 2007), but it is unclear whether this excess mortality has increased during the last decades as results from different studies are conflicting (Heilä et al., 2005, Mortensen and Juel, 1993, Ösby et al., 2000). A review by Saha et al. (2007) concludes with increased standardized mortality ratios for all-cause mortality. However, SMRs from different countries are difficult to compare, due to large differences in mortality in the general population.

The present study is a follow-up of patients with schizophrenia admitted to the University Hospital of North Norway, now covering the 27-years period from January 1st 1980 to December 31st 2006. The aim of the study was to investigate the mortality of schizophrenia, with the main emphasis on sex differences as well as changes in mortality over the entire period.

2. Materials and methods

2.1 *The study cohort*

The University Hospital of North Norway is the only psychiatric hospital covering the two northern-most counties in Norway; Troms and Finnmark. These counties comprise a vast area of approximately 26 000 km², with a total of 224 407 inhabitants in 2000. Information about each admission has been collected

since the late 1970s, and this computerized register has been regularly checked for validity against patient files. The information used in this study was the unique 11-digit person number assigned to every resident of Norway; date of admission; commitment status; date of discharge and diagnoses at discharge. The present study includes all admissions from January 1st 1980 to December 31st 2006. During this period of 27 years there was a stable bed-to-population ratio of approximately 4 per 10 000 inhabitants.

The personal identification number was used for linkage of the admission register with the national Cause of Death Register and the information concerning emigration from Norway held by Statistics Norway (2000).

In the study period there were 22434 admissions. A total of 5840 persons were admitted, 2724 females and 3116 males. 1111 patients, 426 women (38 %) and 685 men (62 %), received a schizophrenia diagnosis at discharge at some point. Schizophrenia was defined according to the International Coding of Diseases (ICD-9: 295, ICD-10: F20, F21 and F25). Before 1985, ICD-8 was used, and the diagnoses in this period were converted retrospectively to ICD-9 codes (World Health Organization, 1967, 1978, 1992).

The 1111 patients were observed from the date of first admission after January 1st 1980 until death, moving abroad or the end of 2006, for a total of 16129 person years. Subjects who were in-hospital patients at January 1st 1980 were included, with start of follow-up the same day. In Norway, all death certificates are coded according to the current ICD-system based on the information given by a physician. The diagnoses recorded by the Cause of Death Register as the underlying cause of death were used in this study.

2.2 *Statistical analyses*

We studied the differences in age-adjusted mortality rates between men and women in the study cohort, and gender differences in standardized mortality ratios (SMR) for patients with schizophrenia compared to the general population. These analyses were also performed in several subgroups of the cohort, including attained age, commitment status, follow-up period (1980-1988, 1989-1997 and 1998-2006) and year of first admission (1980 – 1992 and 1993 – 2006).

We performed analyses according to follow-up period and years of first admission. Many of the patients were under follow-up in two or three of these periods. The first hypothesis tested was whether the relationship between gender and mortality, within the cohort or compared to the mortality in the general population, differs between follow-up periods characterized by changes in treatment regimens. The second hypothesis tested was related to differences between patients who have their first diagnosis before or after 1992. When stratifying according to age at first admission, we investigated more specifically whether relationship between gender and mortality, within the cohort or compared to the mortality in the general population, depended on when the patients had their first diagnosis. The year 1992 was chosen partly for analytical reasons (the inclusion of enough deaths for a meaningful analysis in the last period) and partly because we have previously published a follow-up ending in 1992 (Hansen et al., 1997, 2001).

Differences in the characteristics of male and female patients (table 1) were tested with t-test, Wilcoxon rank sum test (when the distributions were markedly positively skewed) or chi-square test. Age adjustments of the mortality rates were carried out applying a Poisson regression model. Statistical testing of differences between mortality rates was done with Poisson regression, including gender, person-years, age (1-year interval) and number of deaths in the analyses. The relative mortality in men compared to women was tested with Cox regression with attained age as the time variable. For comparison with 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 of the general population in Norway according to age (5-year groups) and calendar year (5-year groups) during follow-up had prevailed, was calculated. 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. Confidence intervals for the SMRs, which were only dependent on the number of observed deaths, were computed.

P-values < 0.05 were considered statistically significant. Statistical analyses were performed with SAS 9.2 (2007).

3. Results

3.1 Mortality in the cohort

Table 1 gives baseline data according to gender. The women were significantly older at first admission and they were followed for a longer period. The genders did not differ much with regard to total number of admissions, total days admitted or degree of coercion, but the women had longer median length of stay when admitted.

A total of 192 men and 103 women died during 1980-2006. Table 2 gives the number of deaths according to gender and cause of death. Twenty-seven percent of the patients died and approximately 3 out of 4 deaths were due to natural causes. The proportion that died of unnatural causes was higher in men than in women.

The crude rates of all cause mortality were 15.6 and 20.1 per 1000 person years in women and men, respectively. The corresponding age-adjusted mortality rates were 11.7 and 21.7 per 1000 person-years, respectively ($p < 0.001$). In accordance with this, table 3 demonstrates that male patients with schizophrenia had nearly twice the mortality of female patients; the age-adjusted hazard ratio was 1.9 (95 % CI: 1.5, 2.4) higher in men than in women.

Age at first admission was significantly lower in men than in women. We adjusted for this in a separate set of analyses, but this did not influence our results (results not shown).

A total of 121 patients were already admitted to the hospital at the first day of follow-up (January 1st 1980). These patients were in our analyses registered as admitted at this date and 71 of them died before December 31st 2006. They contributed to the higher number of person-years and deaths in patients admitted for the first time during 1980 – 1992 (table 3). Exclusions of these patients from the follow-up did not, however, influence the results (Hazard ratio (HR) 1.9 (95 % CI: 1.4, 2.5)) (results not shown).

The higher mortality in men than in women was a very consistent finding in the different strata of this cohort. The main exception was the lack of association in subjects admitted for the first time after 1992 (p-value for interaction = 0.02). The reason was a 1.7 (95 % CI: 1.0-2.8) times higher age-adjusted total mortality rate in women who were admitted for the first time after 1992 than in the previous years. In men, the opposite was the case (HR=0.7, 95 % CI: 0.5, 1.2). However, in the group of patients admitted for the first time before 1993, but followed during 1993-2006, we found the same relationship between gender and mortality as found in the main analyses.

There was also a significant interaction (p= 0.02) with regard to commitment status as no increased mortality was found in men compared to women in the group of patients who always had been voluntarily admitted. There were 25 and 16 deaths among the 74 men and 47 women, respectively, who always had been admitted voluntarily.

The higher mortality in men than in women was found for both natural and unnatural death as well as for cardiovascular disease and suicide. The difference was not statistically significant for cancer, however (table 4).

3.2 *Mortality in patients with schizophrenia compared to the general population (SMR)*

The mortality of the patients compared to the general Norwegian population is displayed in table 5. Male and female schizophrenic patients had 3.5 (95 % CI: 3.1 to 4.1) and 2.6 (95 % CI: 2.1 to 3.2) times higher mortality, respectively ($p=0.01$ for the difference between the genders). The differences between men and women for each of the examined causes of death were not statistically significant. Still, we note that SMRs were higher for men than for women for both natural and unnatural death. The SMR for cancer was lower than for all natural causes combined for both men and women, and was for women not significantly different from the cancer mortality in the general population. As expected, very high SMRs were found for suicides. If the mortality of the patients had been the same as in the general Norwegian population, we would have expected 85.5 and 8.5 deaths due to natural and unnatural causes (suicide and accidents combined), respectively. Consequently, there were 141.5 and 59.5 excess deaths due to natural and unnatural causes. The excess mortality for cardiovascular mortality alone (64.7 deaths) was approximately the same as for all unnatural deaths (59.5 deaths).

Whereas the SMR for men who always had been admitted voluntarily was relatively low, the opposite was found in women with a statistically significant ($p=0.005$) inverse relationship between use of coercion during admission and SMR.

We also examined the SMRs according to time period of follow-up and date of first admission. The SMR was higher for the 1980-1988 period than for the 1998-2006 period. This was the case for both men and women.

When classifying the patients according to first admission in 1980-1992 or 1993-2006, we found that female patients admitted to the hospital for the first time after 1992 had significantly higher SMRs (4.6, 95 % CI: 2.9 to 7.2) than women who were admitted earlier (SMR=2.4, 95 % CI: 1.9 to 2.9) ($p=0.009$). As detailed above, the major reason for this was that the age-adjusted mortality rates in female

schizophrenic patients admitted for the first time after 1992 was considerably (70 %) higher than the mortality in women admitted previously. Thus, there was not only an increasing difference in mortality compared to the general female population; the absolute mortality had also increased. The SMRs for women admitted after 1992 were higher than for men for both natural and unnatural causes of death (table 6).

4. Discussion

A major strength of this study is the long follow-up and the completeness of data. There is virtually no loss to follow-up as the Norwegian Cause of Death Register must be considered complete with regard to mortality.

There are no private psychiatric hospitals in Norway. Being the only regional psychiatric hospital, all residents from these counties admitted to any psychiatric hospital in Norway will be transferred to the University Hospital of North Norway. The health services in the counties are almost exclusively public with established structures for cooperation on admission and follow-up. In addition, all involuntary treatment has to be initiated in a hospital according to Norwegian legislation. Hence, very few admissions have taken place elsewhere without eventually being included in our database.

The cohort of 1111 patients with schizophrenia is based on diagnoses registered on the day of discharge after at least one admission. All diagnoses are made by clinical consensus and not by standardized diagnostic procedures. This may have affected the validity of the diagnosis and probably resulted in non-differential misclassification and attenuation of the reported relationships.

It is possible that some patients with schizophrenia are not included because they are not admitted or because they do not get the correct diagnosis. This is particularly likely in the last part of the 27 year period because of more extensive out-patient care of patients. A study of the diagnostic process in the same cohort (Høye et al., 2000) showed a considerable delay between first admission and first

diagnosis of schizophrenia, significantly longer for women than for men. We do not find it likely that missed patients have influenced our main findings. In order to explain the higher SMR for women admitted for the first time after 1992, these missed patients must have been relatively many and have had a particularly low, and gender correlated, mortality.

4.1 *Gender differences in standardized mortality ratio*

The two-to three-fold higher mortality of patients with schizophrenia compared to the general population confirms results from recent studies from other countries (Saha et al., 2007), as does the higher SMR in men compared to women in all the three follow-up periods (Mortensen and Juel, 1990, Ösby et al., 2000). Both Mortensen and Juel, Ösby and Brown et al. (2000, 2010) show higher SMR due to unnatural deaths for women than for men. In our study, SMR for unnatural causes of death did not differ significantly between the genders. The SMR for cancer for both sexes is lower than for cardiovascular diseases, which is also in accordance with Saha (2007) and others (Joukamaa et al 2001, Saku et al., 1995, Tran et al., 2009).

The patients with schizophrenia have approximately 8 times increased risk of dying due to unnatural causes. However, the mortality by natural causes is higher than that by unnatural causes also in this group of psychiatric patients. Therefore, there are many more deaths of natural causes in excess of what would be expected based on the mortality in the Norwegian general population, than there are excess deaths of unnatural causes (141.5 and 59.5 deaths, respectively). As has been pointed out by others (Amaddeo et al., 2007, Brown et al., 1999, Räsänen et al 2005), the lifestyle of many patients with schizophrenia includes heavy cigarette smoking, unhealthy diet, obesity and little exercise. As shown by Lawrence et al. (2003), patients with schizophrenia are also less likely to receive appropriate treatment for cardiovascular diseases. The impact of second-generation antipsychotic drugs on mortality has yet to be determined (Kelly et al., 2010), even if Tiihonen et al.(2009) found that the use of antipsychotic drugs reduces mortality.

4.2 *Commitment status*

Previous studies (Honkonen et al., 2008, Crisanti and Love, 1999) indicate that involuntarily admitted patients have higher SMR values than those voluntarily admitted. Different legislation and variation in application of coercion between countries make comparisons of mortality and commitment status difficult. We find that men who have always been admitted voluntarily have non-significantly lower mortality than women in the same situation (table 3). This could be partly explained by the assumption that these men represent a subgroup with less symptoms and a higher degree of compliance that could, theoretically, affect mortality. The lower SMR value for always voluntarily admitted men (table 5) may give some support to this interpretation. In women, there was a different pattern: the highest SMR was found with less use of coercion. None of the 16 deaths in always voluntarily admitted women were caused by suicide or other unnatural cause of death.

4.3 *Deinstitutionalization and time trends in standardized mortality ratio*

From 1998 - 2008 the Norwegian authorities implemented a nationwide plan to strengthen decentralized psychiatric services. At the University Hospital of North Norway, the total number of days admitted in the hospital for patients with diagnosed schizophrenia has decreased by 63 % when comparing the period 1993-2006 with 1980-1992. An evaluation made by The Research Council of Norway (2009) concludes with improved availability and better quality of services. With our finding of higher SMRs for both men and women in the 2000s than in the 1980ies, and particularly of higher SMRs for women admitted for the first time after 1992 than from 1980-1992, it seems that the changes in services have not been able to protect these patients from increased risk of premature death.

4.4 *Conclusion*

Our study confirms the persisting mortality gap between patients with schizophrenia and the general population over a period of 27 years, with a tendency of increasing standardized mortality ratios. Some

of the excess mortality may be difficult to prevent due to the nature of the disease, nevertheless should prevention of somatic diseases be considered just as important as prevention of suicides in this group of patients.

There are indications in our study that the standardized mortality ratio for total mortality of women with schizophrenia is rising and becoming just as high as for men. In addition, the highest SMR was found for women with less use of coercion. Because of the paucity of deaths in these patients, one must be careful to draw any firm conclusions. The findings combined may nevertheless lead to the speculation that there is a subgroup of relatively well functioning, but vulnerable women who need better follow-up than given in the existing, deinstitutionalized health care system.

Contributors:

AH has the main responsibility for drafting and revision of the manuscript. VH and BKJ contributed to design of the study, critical revision of the manuscript, data analysis and discussion of the results. All authors have read and approved the manuscript. It is not under consideration for publication in any other journal.

Ethics committee approval:

The project has been approved by Regional Ethical Committee of Health Research, North Norway

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Conflict of interests:

None

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Table 1 Unadjusted characteristics (mean (standard deviation), median (1 & 3 quartile) or number of subjects (percentages)) according to gender of patients with schizophrenia, University Hospital of North Norway, 1980-2006

	Men	Women	p-value
Number of patients	685	426	
Age at first admission in years (SD)	33.2 (12.8)	38.4 (15.6)	< 0.001
Mean follow-up time in years (SD)	13.9 (8.2)	15.5 (8.2)	0.003
Median total number of days admitted (1 & 3 quartile)	178 (60, 615)	199.5 (79, 723)	0.11
Median length of stay (1 & 3 quartile)	29.5 (16.9, 60.5)	34.7 (21.0, 68.3)	0.005
Median number of admissions (1 & 3 quartile)	5 (2, 10)	5 (2, 12)	0.67
Commitment status			
Always voluntarily admitted (%)	74 (10.8)	47 (11.0)	
Sometimes committed (%)	516 (75.3)	310 (72.8)	0.5
Always committed (%)	95 (13.9)	69 (16.2)	

Table 2 Number of patients with schizophrenia, person-years and deaths according to gender. University Hospital of North Norway, 1980-2006

	Men	Women
Number of patients	685	426
Total number of person-years	9545	6584
Total number of deaths (% of patients)	192 (28.0)	103 (24.2)
Dead during first year of follow-up (% of patients)	15 (2.1)	8 (1.9)
Cause of death		
Natural deaths (% of patients)	140 (20.4)	87 (20.4)
<i>Cancer (% of patients)</i>	28 (4.1)	16 (3.8)
<i>Cardiovascular diseases (% of patients)</i>	62 (9.1)	38 (8.9)
Unnatural deaths (total) (% of patients)	52 (7.6)	16 (3.8)
<i>Suicide (% of patients)</i>	40 (5.8)	9 (2.1)

Table 3 Mortality in men compared to women in the cohort of patients with schizophrenia according to follow-up period, date of first admission, attained age, commitment status and number of admissions. University Hospital of North Norway, 1980-2006. Figures are hazard ratio (HR) (95 % confidence intervals).

	Person-years	Deaths	HR	p-value
All subjects	16129	295	1.9 (1.5, 2.4)	< 0.001
Follow-up period				
1980-1988	3386	50	1.9 (1.0, 3.5)	0.04
1989-1997	5663	110	2.2 (1.5, 3.4)	< 0.001
1998-2006	7077	135	1.7 (1.2, 2.5)	0.003
Date of first admission				
1980-1992	13255	257	2.1 (1.6, 2.7)	< 0.001
1980-1992, follow-up 1980-1992	5700	102	2.0 (1.3, 3.1)	0.002
1980-1992, follow-up 1993-2006	7554	155	2.2 (1.6, 3.1)	< 0.001
1993-2006	2873	38	1.0 (0.5,1.9)	0.89
Attained age (years)				
< 50	11145	92	3.1 (1.8, 5.4)	< 0.001
50-59	2630	54	1.9 (1.1, 3.4)	0.03
60-69	1476	69	1.1 (0.7, 1.8)	0.62
≥ 70	876	80	2.1 (1.3, 3.3)	0.001
Commitment status				
Always voluntarily admitted	1417	41	0.8 (0.4, 1.5)	0.43
Sometimes committed	12598	168	2.4 (1.7, 3.4)	< 0.001
Always committed	2113	86	1.5 (0.9, 2.4)	0.10
Number of admissions				
1	2402	108	1.5 (1.0, 2.3)	0.04
2-5	5368	104	2.6 (1.7, 4.0)	< 0.001
> 5	8359	83	1.6 (1.0, 2.6)	0.03
Table 3 continues..				

Total time of admission				
< 60 days	2736	72	1.9 (1.1, 3.2)	0.02
61-180 days	3942	72	1.9 (1.2, 3.1)	0.01
181-365 days	2468	33	3.9 (1.7, 9.4)	0.002
More than 365 days	6982	118	1.6 (1.1, 2.3)	0.03

Table 4 Cause-specific mortality in men compared to women in a cohort of patients with schizophrenia. University Hospital of North Norway, 1980-2006. Figures are hazard ratios (HR) (95 % confidence intervals)

	Deaths	HR	p-value
All deaths	295	1.9 (1.5, 2.4)	< 0.001
Natural deaths	227	1.8 (1.4, 2.4)	< 0.001
<i>Cardiovascular deaths</i>	100	2.0 (1.3, 3.0)	0.002
<i>Cancer</i>	44	1.7 (0.9,3.2)	0.08
Unnatural deaths	68	2.3 (1.3, 4.1)	0.005
<i>Suicides</i>	49	2.8 (1.3, 5.8)	0.006

Table 5 Standardised mortality ratio (SMR) for men and women in patients with schizophrenia. University Hospital of North Norway, 1980-2006. Figures are SMR (95 % confidence interval)

	Men		Women		<i>p</i> -value*
	<i>Deaths</i>	<i>SMR</i>	<i>Deaths</i>	<i>SMR</i>	
Total mortality	192	3.5 (3.1, 4.1)	103	2.6 (2.1, 3.2)	0.01
Natural causes	140	2.9 (2.5, 3.5)	87	2.3 (1.9, 2.9)	0.09
<i>Cardiovascular diseases</i>	62	3.0 (2.4, 3.9)	38	2.6 (1.9, 3.6)	0.46
<i>Cancer</i>	28	1.9 (1.3, 2.8)	16	1.3 (0.8, 2.1)	0.21
Unnatural causes	52	8.1 (6.2, 10.6)	16	7.8 (4.8, 12.7)	0.9
<i>Suicide</i>	40	17.5 (12.8, 23.8)	9	15.0 (7.8, 28.7)	0.7
Total mortality					
Commitment status					
<i>Always voluntarily admitted</i>	25	2.5 (1.71, 3.74)	16	6.1 (3.7, 9.9)	0.006
<i>Sometimes committed</i>	118	4.0 (3.34, 4.79)	50	2.4 (1.8, 3.2)	0.003
<i>Always committed</i>	49	3.3 (2.47, 4.33)	37	2.3 (1.7, 3.1)	0.10
Follow-up period					
1980-1988	35	2.6 (1.9, 3.7)	15	2.1 (1.2, 4.4)	0.45
1989-1997	77	3.9 (3.1, 4.9)	33	2.6 (1.9, 3.7)	0.06
1998-2006	80	3.8 (3.0, 4.7)	55	2.8 (2.1, 3.6)	0.08
Date of first admission					
1980-1992	173	3.5 (3.0, 4.1)	84	2.4 (1.9, 2.9)	0.003
1993-2006	19	3.6 (2.3, 5.6)	19	4.6 (2.9, 7.2)	0.43

* *p*-value for difference in SMR between the genders

Table 6 Standardised mortality ratio (SMR) according to gender and date of first admission and cause of death in patients with schizophrenia. University Hospital of North Norway, 1980-2006. Figures are SMR (95 % confidence interval) (number of observed deaths)

	1980-1992		1993-2006	
	Men	Women	Men	Women
Total mortality	3.5 (3.0, 4.1) (173)	2.4 (1.9, 2.9) (84)	3.6 (2.3-5.6) (19)	4.6 (2.9-7.2) (19)
<i>Natural causes</i>	2.9 (2.5-3.5) (129)	2.1 (1.7-2.7) (72)	2.6 (1.5-4.7) (11)	3.9 (2.3-6.4) (15)
<i>Cardiovascular</i>	3.0 (2.3-3.9) (57)	2.4 (1.7-3.4) (32)	3.6 (1.5-8.6) (5)	4.4 (2.0-9.8) (6)
Unnatural	8.3 (6.2-11.1) (44)	6.6 (3.8-11.7) (12)	7.1 (3.6-14.3) (8)	16.0 (6.0-42.7) (4)
<i>Suicide</i>	17.6 (12.5-24.8) (33)	9.6 (4.0-23.0) (5)	16.7 (8.0-35.1) (7)	50.2 (18.8-133.6) (4)