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

Anne Høye [a,*], Bjarne K. Jacobsen [c], Vidje Hansen [b]

[a] Centre for Clinical Documentation and Evaluation Regional Health Authority of North Norway Mailbox 6, University Hospital of North Norway 9037 Tromsø, Norway
[b] Institute of Clinical Medicine Faculty of Health Sciences University of Tromsø and University Hospital of North Norway 9037 Tromsø, Norway
[c] Centre for Clinical Documentation and Evaluation and Department of Community Medicine Faculty of Health Sciences University of Tromsø 9037 Tromsø, Norway

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.

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1. Introduction

Several studies show a significantly higher risk of premature death in persons with schizophrenia than in the general population (Harris and Barraclough, 1998; Brown et al., 2000, 2010; Eaton et al., 2008; McGrath et al., 2008). A review by Saha et al. (2007) based on standardized mortality ratios from 25 different nations concludes with an increasing mortality gap between persons with schizophrenia and the general population, affecting men and women equally. Male patients have been shown to have higher SMRs than female (Mortensen and Juel, 1993; Ösby et al., 2000), but higher SMR due to unnatural deaths are found for female patients (Ösby et al., 2000 and Brown et al., 2010).

Many patients with schizophrenia are admitted to hospital by use of coercion. Previous studies (Crisanti and Love, 1999; Honkonen et al., 2008) indicate that involuntarily admitted patients have higher SMRs. There are, however, few studies concerning the importance of coercion on mortality, and different legislation and variation in application of coercion between countries make comparisons of mortality and commitment status difficult.

In Norway, mortality of patients with mental illness has been reported regularly since 1916 (Ødegård, 1936, 1951, 1952; Ødegård, 1967; Saugstad and Ødegård, 1979,1985; Hansen et al., 1997). A previous study based on the case register of the University Hospital of North Norway with follow-up 1980–1992 (Hansen et al., 2001) documented increase in SMRs compared to earlier periods, especially high for men. The focus on deinstitutionalization was from 1998–2008 augmented with a nationwide plan for decentralized follow-up of psychiatric patients, in our cohort illustrated by a significant reduction in length of stay.

The aim of the present study was to investigate the differences in age-adjusted mortality rates between men and women with schizophrenia, and standardized mortality ratios (SMR) compared to the general population over a follow-up period of 27 years. We also wanted to investigate the relationship between use of coercion and mortality in this group of patients.

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 26 000 km², with a total of 224 407 inhabitants (2000). Information about each admission has been collected since 1980, and this computerized register has been regularly checked for validity against patient files. The information used was the unique 11-digit person number assigned to every Norwegian

* Corresponding author. Tel.: +47 777 55803, +47 908 49334.
E-mail addresses: anne.hoye@unn.no (A. Høye), bjarne.koster.jacobsen@uit.no (B.K. Jacobsen), vidje.hansen@unn.no (V. Hansen).

resident; date of admission; commitment status; date of discharge and diagnoses at discharge. All admissions from January 1st 1980 to December 31st 2006 are included. During this 27 years period there was a stable bed-to-population ratio of approximately 4 per 10 000 inhabitants.

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

In the study period there were 22 434 admissions; 5840 persons were admitted, 2724 females and 3116 males. A total of 1111 patients, 426 women (38%) and 685 men (62%), received at some point a schizophrenia diagnosis. Schizophrenia was defined according to the International Classification 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 16 129 person years. In-hospital patients at January 1st 1980 were included, with start of follow-up the same day. All death certificates are coded by a physician according to the current ICD-system, The diagnoses recorded by the Cause of Death Register as the underlying cause of death were used.

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 (SMRs) 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).

Thus, we performed analyses according both to follow-up period and years of first admission. Many of the patients were under follow-up in two or three of the follow-up 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 an increasing degree of deinstitutionalization. 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 admission. 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).

Based on the total number of days admitted and the number of stays, we computed the mean length of each stay in the ward. The distribution of the length of stay variable was positively skewed as some patients had admissions of very long duration.

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 (SMR) expresses the relative mortality of the patient group compared to that of the general population. Confidence intervals for the SMRs were computed.

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

3. Results

3.1. Gender differences

Twenty-seven percent of the patients, 192 men and 103 women, died during 1980–2006. Table 1 shows characteristics of the patient population according to gender, Table 2 gives the number of deaths according to gender and cause of death. 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 age-adjusted mortality rates were 21.7 and 11.7 per 1000 person-years in men and women, respectively (p<0.001); male patients in the cohort had nearly twice the mortality of female patients (Hazard ratio (HR) 1.9 (95% CI: 1.5, 2.4)) (Table 3).

Age at first admission was significantly lower in men than in women (Table 1). We adjusted for this in a separate set of analyses, but this did not influence our results (results not shown). Median length of stay was significantly (p<0.001) higher for patients admitted for the first time during 1980–1992 (37 days) than for patients admitted for the first time during 1993–2006 (25 days). Adjusting for length of stay did not, however, influence the relationship between gender and mortality.

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 influence the results (HR 1.9 (95% CI: 1.4, 2.5)) (results not shown in the table). Table 4 demonstrates that the higher mortality in male than female patients was a consistent finding for all main causes of deaths.

The SMRs compared to the general Norwegian population is displayed in Table 5. Male and female 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, than the general population (p = 0.01 for the difference between the genders). The gender differences for each of the examined causes of death were not statistically significant, but the SMRs were higher for men than for women for both natural (2.9 vs. 2.3) and unnatural (8.1 vs. 7.8) deaths. The SMR for cancer was lower than for all natural causes combined, and was for women not significantly different from the cancer mortality in the general population. As expected, very high SMRs (17.0 (95% CI: 12.8 to 22.4) for men and women combined) 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).

3.2. Changes in mortality over time

The higher mortality in men than in women was a consistent finding in the different strata (Table 3). The main exception was that the association with gender was statistically significantly stronger in patients admitted during the first period (1980–1992) than in patients admitted for the first time after 1993 (p = 0.02). The reason was a 1.7 (95% CI: 1.0–2.8) times higher age-adjusted total mortality

Table 1
Unadjusted characteristics 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 (mean, SD)	33.2 (12.8)	38.4 (15.6)	<0.001
Follow-up time in years (mean, SD)	13.9 (8.2)	15.5 (8.2)	0.003
Total number of days admitted (Median, 1 and 3 quartile)	178 (60, 615)	199.5 (79, 723)	0.11
Length of stay (median, 1 & 3 quartile)	29.5 (16.9, 60.5)	34.7 (21.0, 68.3)	0.005
Number of admissions (median, 1 and 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)	

Figures are mean (standard deviations), median (1 and 3 quartile) or number of subjects (percentages).

rate in women who were admitted for the first time after 1992 than in the previous period, while the opposite was the case in men (HR = 0.7, 95% CI: 0.5, 1.2). In accordance with this, we found that

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)
Cancer (% of patients)	28 (4.1)	16 (3.8)
Cardiovascular diseases (% of patients)	62 (9.1)	38 (8.9)
Unnatural deaths (total) (% of patients)	52 (7.6)	16 (3.8)
Suicide (% of patients)	40 (5.8)	9 (2.1)

Table 3
Mortality in men compared to women in the cohort of patients with schizophrenia. University Hospital of North Norway, 1980–2006.

	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
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

Figures are hazard ratio (HR) (95% confidence intervals).

female patients admitted for the first time after 1992 had significantly higher SMRs (4.6, 95% CI: 2.9 to 7.2) than women admitted earlier (SMR = 2.4, 95% CI: 1.9 to 2.9) (p = 0.009) (Table 5). Thus, there was not only an increasing difference in mortality compared to the general female population; but an increase in absolute mortality. The SMRs for women admitted after 1992 were higher than for men for both natural and unnatural causes of death (Table 6). Adjusting for length of stay had no impact on the relationship between gender and mortality in analyses stratified for year of first admission (1980–1992 or 1993–2006, respectively). When examining the SMRs according to 3 time periods of follow-up, the SMRs for both men and women were higher during the 1998–2006 period than during the 1980–1988 period, (Table 5).

3.3. Commitment status

No increased mortality was found in men compared to women in the group of patients who always had been voluntarily admitted (Table 3) (p-value for interaction between gender and commitment status = 0.02). There were 25 and 16 deaths among the 74 men and 47 women, respectively, who always had been admitted voluntarily. Whereas the SMR for men, if anything, was positively associated with degree of coercion, the opposite was found in women with a statistically significant (p = 0.005) inverse relationship between use of coercion during admission and SMR (Table 5).

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.

Being the only regional psychiatric hospital, all residents from these counties admitted to any psychiatric hospital in Norway are transferred to the University Hospital of North Norway. It is possible that some patients with schizophrenia are not included because they are not admitted at all. This is particularly likely in the last part of the 27 year period because of more extensive out-patient care. In order to explain the higher SMR for women admitted after 1992, these missed

Table 4
Cause-specific mortality in men compared to women in a cohort of patients with schizophrenia. University Hospital of North Norway, 1980–2006.

	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
Cardiovascular deaths	100	2.0 (1.3, 3.0)	0.002
Cancer	44	1.7 (0.9,3.2)	0.08
Unnatural deaths	68	2.3 (1.3, 4.1)	0.005
Suicides	49	2.8 (1.3, 5.8)	0.006

Figures are hazard ratios (HR) (95% confidence intervals).

Table 5

Standardized mortality ratio (SMR) for men and women in patients with schizophrenia. University Hospital of North Norway, 1980–2006.

	Men			Women			
	Number of deaths	Expected number of deaths	SMR	Number of deaths	Expected number of deaths	SMR	p-value[*]
Total mortality	192	54.4	3.5 (3.1, 4.1)	103	39.6	2.6 (2.1, 3.2)	0.01
Natural causes	140	47.9	2.9 (2.5, 3.5)	87	37.6	2.3 (1.9, 2.9)	0.09
Cardiovascular diseases	62	20.6	3.0 (2.4, 3.9)	38	14.7	2.6 (1.9, 3.6)	0.46
Cancer	28	14.6	1.9 (1.3, 2.8)	16	12.4	1.3 (0.8, 2.1)	0.21
Unnatural causes	52	6.4	8.1 (6.2, 10.6)	16	2.1	7.8 (4.8, 12.7)	0.9
Suicide	40	2.3	17.5 (12.8, 23.8)	9	0.6	15.0 (7.8, 28.7)	0.7
Commitment status							
Always voluntarily admitted	25	9.9	2.5 (1.7, 3.7)	16	2.6	6.1 (3.7, 9.9)	0.006
Sometimes committed	118	29.5	4.0 (3.3, 4.8)	50	20.7	2.4 (1.8, 3.2)	0.003
Always committed	49	15.0	3.3 (2.5, 4.3)	37	16.3	2.3 (1.7, 3.1)	0.10
Follow-up period							
1980–1988	35	13.4	2.6 (1.9, 3.7)	15	7.3	2.1 (1.2, 4.4)	0.45
1989–1997	77	19.8	3.9 (3.1, 4.9)	33	12.6	2.6 (1.9, 3.7)	0.06
1998–2006	80	21.2	3.8 (3.0, 4.7)	55	19.8	2.8 (2.1, 3.6)	0.08
Date of first admission							
1980–1992	173	49.1	3.5 (3.0, 4.1)	84	35.6	2.4 (1.9, 2.9)	0.003
1993–2006	19	5.3	3.6 (2.3, 5.6)	19	4.1	4.6 (2.9, 7.2)	0.43

Figures are SMR (95% confidence interval).

[*] p-value for difference in SMR between the genders.

patients must have been relatively many and have had a particularly low, and gender correlated, mortality. There are no private psychiatric hospitals in Norway, and in the area there are well established structures for cooperation on admission and follow-up. In addition, all involuntary treatment must be initiated in a hospital according to Norwegian legislation. Hence, we assume that very few admissions have taken place elsewhere without eventually being included in our database, but we cannot fully exclude that during the more recent time period, the more severely ill were admitted.

All diagnoses are made by clinical consensus. This may have affected diagnostic validity and thereby introduced a non-differential misclassification and attenuation of the reported relationships. A study of the diagnostic process in the same cohort (Høye et al., 2000) showed a delay of 2.6 years for women and 1.6 years for men between first admission and first schizophrenia diagnosis, it might therefore be that some patients are not included because they have not had enough in-hospital time to be correctly diagnosed.

4.1. Gender differences

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). Unlike Mortensen and Juel (1993), Ösby et al. (2000) and Brown et al. (2010) who show higher SMR due to unnatural deaths for women than for men, we find that 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 et al. (2007) and others (Saku et al., 1995; Joukamaa et al., 2001; Tran et al., 2009).

The patients with schizophrenia have approximately 8 times increased risk of dying due to unnatural causes. However, as the mortality by natural causes is higher than that by unnatural causes also in these patients, 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 (Brown et al., 1999; Räsänen et al., 2005; Amaddeo et al., 2007; Hiroeh et al., 2008), many patients with schizophrenia have a high-risk lifestyle. 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. Changes in mortality over time

The main issue of the national escalation plan for mental health was to strengthen decentralized psychiatric services. A consequence of a more decentralized system is less in-patient contact, shown by a significantly shorter median length of stay. As Saha et al. (2007) points out, an increasing SMR suggests that people with schizophrenia do not fully benefit from the general improvements in health outcomes. It is possible that in-patient treatment may have a protective effect; a Norwegian study by Hanssen-Bauer et al. (2011) points at the relative strengthening of services to adolescents, and concludes that use of in-patient units effectively meet the challenge of suicidal risk and other severe problems. Our findings of higher SMRs for both men and women in the 2000s than in the 1980s, and particularly of higher SMRs for

Table 6

Standardized 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.

	1980–1992		1993–2006	
	Men	Women	Men	Women
Total mortality	3.5 (3.0, 4.1) (173, 49.1)	2.4 (1.9, 2.9) (84, 35.5)	3.6 (2.3–5.6) (19, 5.3)	4.6 (2.9–7.2) (19, 4.1)
Natural causes	2.9 (2.5–3.5) (129, 43.8)	2.1 (1.7–2.7) (72, 33.7)	2.6 (1.5–4.7) (11, 4.2)	3.9 (2.3–6.4) (15, 3.9)
Cardiovascular	3.0 (2.3–3.9) (57, 19.2)	2.4 (1.7–3.4) (32, 13.3)	3.6 (1.5–8.6) (5, 1.4)	4.4 (2.0–9.8) (6, 1.4)
Unnatural	8.3 (6.2–11.1) (44, 5.3)	6.6 (3.8–11.7) (12, 1.8)	7.1 (3.6–14.3) (8, 1.1)	16.0 (6.0–42.7) (4, 0.2)
Suicide	17.6 (12.5–24.8) (33, 1.9)	9.6 (4.0–23.0) (5, 0.5)	16.7 (8.0–35.1) (7, 0.4)	50.2 (18.8–133.6) (4, 0.1)

Figures are SMR (95% confidence interval) (number of observed deaths, expected number of deaths).

women admitted for the first time after 1992 than from 1980–1992, indicate that the changes in services have not decreased the risk of premature death. The increase in the SMRs for suicide for women, from 9.6 to 50.2, was particularly worrying. However, as this finding was based on relatively few deaths and because of the many comparisons conducted, caution should be exercised in the interpretation.

4.3. Commitment status

Always voluntarily admitted men have non-significantly lower mortality than women (Table 3), and there are lower SMR value for always voluntarily admitted men (Table 5). Our finding could mean that these men represent a subgroup with less symptoms and a higher degree of compliance that could, theoretically, affect mortality. This is in line with studies implying a correlation between use of coercion and higher mortality (Crisanti and Love, 1999; Honkonen et al., 2008). In women, however, we found a different pattern: the highest SMR was found with less use of coercion. Hunt et al. (2007) conclude that use of coercion may reduce risk of suicide, but in our study none of the 16 deaths in women who had never been involuntarily admitted were caused by suicide or other unnatural cause of death. It may be that the somatic problems of these relatively compliant women are systematically overlooked, but it may also be a chance finding and further studies are required.

5. 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 SMRs. 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 alarming indications that the SMRs for 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.

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