Schizophrenia: A Life-Shortening Disease

by Peter Allebeck

Abstract

The author reviews a number of studies which have shown that the overall mortality among patients with schizophrenia is about twice that in the general population. The highest excess mortality is found in suicide and violent death, but there seems to be an increased mortality also in cardiovascular disorders. Whether there is an increased mortality in cancer among schizophrenic patients remains a controversial issue. A reduced mortality, and particularly a reduced suicide rate, must be an important aim for any treatment policy or therapeutic program. The use of computerized patient data bases, linked to cause-of-death registers, is recommended to permit regular followup studies of large patient populations and facilitate the access to medical records and death records for more detailed analyses. A 10-year followup of 1,190 patients with schizophrenia, selected from the Stockholm County inpatient register is described. The overall mortality was more than twice that in the general population, and the mortality in suicide was more than 10 times higher. The inpatient register was used to identify hospital episodes. Medical records were then obtained for studies on the validity of diagnoses and causes of death and for analyses of risk factors for suicide.

It is now about 50 years since the first studies were published in which patients with schizophrenia were systematically followed by methods for mortality analysis and were found to have a shortened lifespan compared with the general population (Malzberg 1934; Ødegård 1936; Alström 1942). For a long time, however, these and later studies did not seem to have a substantial impact on clinicians' and the general public's view of schizophrenia. It was not until the last one or two decades that the survival aspect of schizophrenia attracted more widespread interest, and research activities in this field have since grown rapidly.

The fact that schizophrenia belongs to the category of "chronic diseases" and that the disease, at least until relatively recently, has been associated with very long, sometimes lifelong, periods of confinement in mental hospitals, asylums or other types of sheltered living probably contributes to making the idea of schizophrenia as a life-shortening disease incredible or uninteresting. Not only did the patients live long with their disease, but it was also a life of remarkably poor quality. However, the advent of neuroleptics and other psychotropic drugs, as well as the development of sociotherapy and other forms of active treatment, has profoundly altered our way of thinking about this disease. To prevent early death, especially suicide and other forms of violent death, has become an important part of the rehabilitation process, and the need for more knowledge about factors predisposing to early death is widely recognized.

Another impetus for research in mortality among schizophrenic patients is the clues this knowledge could give about the etiology of schizophrenic disorders. The question of whether patients with schizophrenia have an increased

(Herrman et al. 1983; Nakane and Ohta 1986) or decreased (Rassidakis et al. 1973; Fox and Howell 1974; Dupont et al. 1986) cancer mortality has been the subject of debate, since this could shed light on the biological mechanisms behind the two types of diseases.

In this article, I review some of the previous research on mortality in schizophrenia and discuss the prospects for further research in this area, with special focus on the use of computerized patient registers. Data from the Stockholm County patient data base are presented and discussed.

Overall Mortality—Consistent Results With Different Methods

A problem in comparing the various studies performed is that different authors have used different ways of selecting their samples, and they also applied the diagnosis of schizophrenia differently. It is only during the last 15 years or so that well-specified diagnostic criteria have become more widely used. Most followup studies have been composed of patients with psychiatric disorders treated at a given hospital or living in a defined area without focus on a specific diagnosis. In some studies, patients with schizophrenia as well as other patient categories have been identified as a part of the ordinary routine of psychiatric care, whereas in others, the selection of patients with schizophrenia has involved a more rigorous application of criteria for research purposes (Tsuang and Woolson 1977; Black et al. 1985).

In table 1, I have listed the studies in which patients with schizophrenia have been followed for a period of at least 5 years and their mortality compared with that in the general population. Only studies with a sufficient number of person years of observation to yield at least 30 deaths are included. The overall excess mortality has in most studies been found to be about twice that in the general population. Given the heterogeneity of the studies, the differences found are less remarkable than the similarities. An indication of what this means in terms of years of life lost was offered by Tsuang et al. (1980). By applying survival curves, they estimated the survival time was shortened by 10 years for males and 9 years for females.

The overall results in table 1 do not indicate a change in mortality over the time period. A more detailed analysis of mortality pattern over time would be interesting, in order to assess the effects of the introduction of psychotropic drugs and the general changes in treatment policy. There is, as yet, no study that has addressed this problem analyzing comparable groups of patients with schizophrenia (i.e., classified according to similar diagnostic criteria and applying similar criteria for study entry). Saugstad and Ødegård (1979) followed patients identified at three different time periods and found a substantial decline in the excess mortality. Craig and Lin (1981) also found a decline in the mortality among psychiatric patients, although not analyzed by psychiatric diagnosis. They pointed out that comparison over time is difficult because of changes in admission criteria, length of stay, etc. The main conclusion of Craig and Lin (1981) was that the mortality among psychiatric patients had not increased after the introduction of psychotropic drugs and that a decline in mortality may

Table 1. Mortality studies in which schizophrenic patients have been followed for at least 5 years and with at least 30 deaths

Authors	Period of entry to study	Number of patients	Number of deaths	O/E males-females
Alström (1942)	1924–36	30,828 p – y[1]	774	1.9–2.3
Babigian & Odoroff (1969)	1960–66	8,672	541	1.6–1.9
Black et al. (1985)	1972–81	688	32	2.4–2.8
Herrman et al. (1983)	1971–73	592	57	2.0–1.9
Kendler (1986)	1958–59	590	128	1.8
Lindelius & Kay (1973)	1947–58	355	32	2.5
Saugstad & Ødegård (1979)	1950, 1960, 1970	14,336	2,757	1.8–2.3
Tsuang & Woolson (1977)	1934–44	192	80	1.8–2.0
Ødegård (1952)	1926–41	1,327	1,327	3.2–4.8

Note.—O/E = observed/expected number of deaths when compared with the mortality in the general population, males and females separately when available.
[1] In this study only person years (p–y) of observation were provided.

have occurred. The possible decline in mortality might be explained by such factors as medication, deinstitutionalization, and quality of inpatient care.

So far, the general conclusion must be that there is still a substantial excess mortality among patients with schizophrenia, though the profound changes in treatment policy that have taken place during recent decades may have had some minor effect on the overall mortality. Far more important changes have taken place in the cause-of-death pattern.

Causes of Death

In the earlier investigations on mortality in schizophrenia, tuberculosis was found to be an important cause of death (Alström 1942; Ødegård 1952). This is of historical interest, since it reflects the conditions of pharmacologically untreated patients, sometimes malnourished, and for long times confined in mental hospitals with a high risk of infection. Lindelius and Kay (1973) described and discussed the causes of the shift in the cause-of-death pattern during recent decades. Suicide is now the main cause of the increased mortality among schizophrenic patients. A similar change in the cause-of-death pattern was later found in the time series of Saugstad and Ødegård (1979).

It is a well-known fact that patients with schizophrenia have an increased risk for suicide. The current knowledge in this field has been comprehensively reviewed by Drake et al. (1985) and Roy (1986). Both articles appropriately quoted Bleuler (1911/1950, p. 188): "The suicidal drive is the most serious of schizophrenic symptoms." A number of predictors for suicide have been identified; being young and male, having a relapsing illness,

having been depressed in the past or being currently depressed, and being socially isolated are factors that often have been identified as being strongly associated with suicide. Shaffer et al. (1974) showed, however, that such predictors often are of limited value in the long-range prediction of eventual suicide.

The question of whether suicides and accidental deaths are the sole causes for the excess mortality in schizophrenia was addressed by Tsuang and Woolson (1978), who concluded that a significant excess mortality remained after excluding these causes of death in the analysis. Among recent studies, Saugstad and Ødegård (1979) and Herrman et al. (1983) also found an increased mortality in "natural" deaths (cardiovascular disorders) among schizophrenic patients. Black et al. (1985), although their study was based on small numbers of patients, did not find any excess mortality in natural deaths. The issue of cancer mortality among schizophrenic patients is controversial. Reviews by Baldwin (1979), Dupont et al. (1986), and Harris (1988) have indicated the problems involved in the study of this issue. Suffice it to say here that large cohorts must be followed in well-designed studies, in order to approach the question of whether cancer or any other somatic disease occurs to a higher or lower extent among schizophrenic patients. Phenothiazine treatment may be an environmental factor that protects against malignant neoplasia (Mortensen 1986).

Prospects for Further Research

The question of whether there is still a need for mortality studies in

psychiatry was addressed by Tsuang and Simpson (1985), who concluded that there is ample justification for further research to assess risks associated with specific disorders and to monitor the effects of changing patterns of treatment and aftercare. A similar conclusion was reached by Drake et al. (1984), who recommended future research in this field take the form of a prospective followup of a large sample of schizophrenic patients in which risk factors would be assessed at regular intervals.

Tsuang and Simpson (1985) discussed different strategies for future research and pointed out that the record-linkage approach is an efficient way to obtain an adequate sample size (e.g., to analyze specific causes of death) and that it enables the determination of mortality status at any time during the followup period. These advantages, enhanced by the development of powerful statistical methods for survival analysis, should be balanced against the lack of precision and diagnostic inaccuracies inherent in comprehensive patient record files that have not been set up for specific research purposes. Tsuang and Simpson suggested measures to be taken to improve the quality of mortality studies based on record-linkage systems, several of which were met in the design of the project described in the next section based on the Stockholm County inpatient register (Allebeck et al. 1986; Allebeck and Wistedt 1986).

Methods

The Stockholm County Inpatient Register. A computerized information system covering all hospitals in Stockholm County was set up at the end of the 1960's and was in

full operation by 1971. It is linked to the general population register that covers all residents in Stockholm County, and it thus provides a useful denominator for epidemiological studies. The key to the person-based data is the 10-digit person number unique for every citizen. The person number enables record linkage with other registers using the number, provided that permission has been obtained from the faculty Ethical Review Committee and the National Data Inspection Board. For every hospitalization, the patient is registered with dates of admission and discharge, diagnosis according to the Swedish version of the International Classification of Diseases (ICD-8; World Health Organization 1967) (in use throughout the followup period), and certain medical procedures performed.

Selection of Patients and Followup. From the inpatient register, we selected all patients discharged with a diagnosis of schizophrenia (ICD-code 295.00–295.99) from any hospital in Stockholm County during 1971. Except for a smaller number of patients treated at mental hospitals outside the county, this selection covered patients at all psychiatric clinics and mental hospitals within the county, virtually all of them residents in the county (i.e., no selective referral to Stockholm hospitals). A total of 1,190 patients were selected in this way. Table 2 shows the distribution of age and sex in the sample.

All deaths in the cohort were identified by a linkage with the national cause-of-death register. This register records deaths among Swedish citizens and is more than 99 percent complete. The only loss to followup would be persons who had emigrated, a number which in

Table 2. Age and sex distribution of patients in the cohort at the beginning of followup

Age (years)	Males	Females	Total
0– 9	0	2	2
10–19	5	8	13
20–29	156	91	247
30–39	127	119	246
40–49	119	123	242
50–59	93	124	217
60–69	40	89	129
70–79	24	39	63
80–	8	23	31
Total	572	618	1,190

this patient group must be considered negligible. Causes of death are recorded at the Central Bureau of Statistics on the basis of death certificates issued by physicians. Autopsies were performed in 79 percent of the deaths in this group.

To obtain an age- and sex-standardized measure of the excess mortality in the cohort of schizophrenic patients compared with the general Stockholm County population, the expected number of deaths was computed on the basis of official death rates. The number of person years of observation in the cohort was calculated for each stratum of age (in 10-year intervals), sex, and calendar year of the followup. These were multiplied by the general population death rates for the corresponding strata and summed to obtain the expected number of deaths. Estimates of standard mortality ratios (SMR) were thus obtained by dividing observed and expected number of deaths. The method described by Rothman and Boice (1982), based on the Poisson distribution, was used to compute 95 percent confidence intervals around the SMR estimates.

Analysis of Suicides and Violent Deaths. An indepth analysis was performed on suicide and violent deaths by scrutinizing medical records and death certificates for those deceased in the ICD chapter XVII, "injuries" (Allebeck et al. 1986). Death certificates were obtained from the Central Bureau of Statistics for all 68 deaths in this category, and medical records were obtained for 63 of these cases (93 percent). Information could thus be obtained on whether the patient was hospitalized by the time of death or immediately before death, as well as communication of suicidal thoughts, physician's assessment of suicidality, and other data that could be used to validate the cause of death.

Results

In the cohort of 1,190 patients, 231 patients (19 percent) died during the 10-year followup, giving an SMR of 2.4 (2.1–2.7). The death rate was virtually the same in males, (SMR = 2.3; 1.9–2.8) as in females (SMR = 2.5; 2.0–2.9). The excess mortality was constant during the followup period—that is, with no

Table 3. Observed and expected number of deaths in the cohort distributed by underlying cause of death

ICD chapter	Underlying cause of death	Number of deaths		SMR
		Observed	Expected	
I	Infections	3	0.7	4.4 (0.9–12.8)
II	Cancer	34	24.8	1.4 (0.9–1.9)
III	Endocrine disorders	5	1.9	2.6 (0.9–6.2)
V	Mental disorders	3	0.8	3.9 (0.8–11.6)
VI	Nervous system	3	1.3	2.3 (0.5–6.9)
VII	Circulatory disorders	86	48.0	1.8 (1.5–2.2)
VIII	Respiratory disorders	11	4.6	2.4 (1.2–4.2)
IX	Gastrointestinal disorders	10	4.2	2.4 (1.2–4.4)
X	Urogenital disorders	6	1.4	4.2 (1.5–9.1)
XVII	Injuries	68	8.1	8.4 (6.5–10.6)
All causes		231	96.5	2.4 (2.1–2.7)

Note.—SMR (standardized mortality ratio) with 95% confidence interval. In 2 patients the cause of death was undetermined.

Table 4. Observed and expected number of deaths in the cause-of-death categories "suicide" and "undetermined"

Cause-of-death category (ICD codes)	Sex	Number of deaths		SMR
		Observed	Expected	
Suicide	Males	18	1.8	9.9 (5.9–15.6)
(E950–959)	Females	15	0.9	17.5 (9.8–28.9)
	All	33	2.7	12.3 (9.1–15.6)
Undetermined	Males	6	0.7	8.9 (3.3–19.4)
(E980–989)	Females	8	0.3	26.2 (11.3–51.7)
	All	14	1.0	14.3 (9.6–21.3)

Note.—SMR = standardized mortality ratio.

clustering of the deaths in time. It was, however, strongly concentrated to the younger ages (up to the fifties).

Table 3 shows the observed and expected number of deaths due to various causes. As could be expected, the ICD chapter XVII, "injuries," had the highest excess mortality and accounted for 29 percent of the deaths. There was also a significant excess mortality in cardiovascular diseases, which accounted for 37 percent of the

deaths. Other categories of "natural" causes of death also had a significant excess mortality, with SMR estimates about 2–4. There was a moderate excess mortality in cancer, but it was not statistically significant.

Table 4 shows the observed and expected number of deaths in the categories "suicide" (ICD-codes 950–959) and "undetermined" (ICD-codes 980–989). Especially in women, the excess mortality in these causes of death was extremely

high. The analysis of medical records of those deceased from "injuries" (ICD chapter XVII) showed that 44 percent (14/32) of the definite suicides occurred during hospital care and that half of these patients were under compulsory care. Fully 54 percent (34/63) of the deaths in the category XVII occurred during or shortly after hospital care (table 5). Information in medical records and death certificates revealed that four of the deaths classified as undeter-

Table 5. Number of patients deceased from "injuries" (ICD chapter XVII) who were hospitalized or had outpatient contact with psychiatric care by the time of or within 1 week before death

	Suicide (n = 32)	Undetermined (n = 13)	Accident (n = 18)	All (n = 63)
Hospitalized psychiatric care	14	2	7	23
Voluntary treatment	7	1	3	11
Compulsory treatment	7	1	4	12
Discharged "on trial"	2	3	1	6
Discharged <1 week before death	—	—	1	1
Outpatient contact <1 week before death	3	—	1	4

mined and three of those classified as accidents were in reality definite suicides.

Discussion

Our results are in agreement with previous findings of an overall excess mortality of about twice the general population mortality. Although the highest excess mortality was found in the ICD chapter XVII, "injuries," the mortality in "natural" causes of death was also significantly increased. Circulatory disorders accounted for a majority of these deaths.

Increased Mortality in "Natural" Causes of Death. Since several studies have found an increased cardiovascular mortality among patients with schizophrenia, hypotheses about the mechanisms behind this phenomenon are worth considering. Genetic factors, lifestyle, and masking of other causes of death are relevant to consider. Schizophrenia has a strong hereditary component (Gottesman et al. 1987), with evidence for an HLA (human leukocyte antigen) association (Minayaga et al. 1984). There

are, however, no immediate explanations for an association between the genetic components of schizophrenia and those of cardiovascular disorder. Recent findings on a susceptibility to cardiac disorders among patients with HLA-associated disorders (Bergfeldt and Möller 1983) may be relevant in this context.

Regarding lifestyle factors, the sedentary life associated with confinement in mental hospitals and asylums could indeed have predisposed to cardiovascular disease 25 years ago. Although patients now are more mobile and socially active, the sedative effects of neuroleptics nevertheless have an immobilizing and slowing-down effect that might predispose patients to cardiovascular disorders. Furthermore, neuroleptics do have direct effects on the circulatory system, but whether and to what extent this may affect the mortality rate is unclear. Smoking is a potential confounder when considering risk factors for cardiovascular deaths, but we have not found any hard data on smoking habits among schizophrenic patients.

Cardiovascular disease is a cause

of death sometimes given in the absence of more solid evidence for the underlying cause of death and is sometimes misleading. In a recent validation of death certificates, Ågren and Jakobsson (1987) found a number of deaths in the category "ischemic heart disease" that in reality were alcohol-related cardiomyopathies. Such a misclassification could be present in our sample, but the number of chronic alcoholics among patients with schizophrenia could hardly be high enough to alter our findings substantially. Regarding the more general problem of classification of "natural" causes of death, there is no reason to believe that patients with schizophrenia are more subject to such misclassification than the general population of deceased persons.

The slightly increased cancer mortality does not contribute much to the controversy over whether there is any relation between schizophrenia and cancer. We also analyzed mortality rates for cancer at specific sites, but we found no significant increase in mortality.

Increased Mortality in Suicide. As could be expected, the highest excess mortality was found in the categories "suicide" and "undetermined." The "true" number of definite suicides in ICD chapter XVII, "injuries," cannot be inferred from retrospective record data. The analysis of medical records and death certificates did, however, reveal a number of "undetermined" and "accidental" deaths that in reality were suicides, which shows that a careful scrutiny of record data can give at least an indication of the quality of the cause-of-death register.

The problem of unreliable cause-of-death certification in regard to

self-inflicted injury is one reason for being careful when comparing suicide rates in different studies. Another reason is that suicide rates among patients identified from hospital case registers depend very much on the selection of patients for inpatient care. Thus, if the admission policy is restrictive, suicide risk will be one reason for hospitalizing a patient who otherwise would remain in outpatient care, and the general suicide rate is thereby increased. Contrariwise, if most patients with schizophrenia are hospitalized at some stage of the disease, a larger proportion of nonsuicidal patients will be admitted, and the suicide rate among these patients is thus lower. These effects could very well explain the facts that our suicide rates were higher than in other studies (Lindelius and Kay 1973; Tsuang and Woolson 1978; Herrman et al. 1983) but lower than those of Black et al. (1985).

Although selection factors and problems relating to the cause-of-death classification, as outlined earlier, may contribute to some of the twofold difference in suicide rate between men and women (table 4), there are probably important real differences between men and women in regard to mortality. Seeman (1986) has recently reviewed gender differences in schizophrenia outcome and pointed out that contrary to what is found in the general population, where the suicide rate is much higher in men than in women, among schizophrenic patients, women have suicide rates similar to men or even higher than men.

In a separate study of risk factors for suicide in this cohort (Allebeck et al. 1987), we found that women who were unmarried, single, or divorced had a significantly

increased risk for suicide compared with married patients (RR = 9.6; 1.5–62), whereas this association did not exist among men (RR = 0.5; 0.1–4.0). The females also had significantly higher rates of previous suicide attempts and documented suicidal thoughts compared with males. A history of alcohol abuse, however, was related to suicide in males but not in females.

Although we identified some predictors of suicide, most of the variables under study did not discriminate those who completed suicide from those who did not. Our general conclusion was that suicidal acts among schizophrenic patients often are impulsive and difficult to predict. This is in agreement with the statement of Drake et al. (1985) that "traditional suicide risk scales are ineffective predictors for schizophrenics" (p. 90) and that "few guidelines are available to help the clinician in the difficult task of assessing suicide risk among these patients" (p. 90). This statement indeed indicates a need for further knowledge in the problem

of suicide in schizophrenia, probably the most important aspect of mortality in schizophrenia.

Validity of the Diagnosis of Schizophrenia. As pointed out by Tsuang and Simpson (1985), the quality of the register, and especially the validity of the diagnosis, is a central matter of concern in followup studies based on computerized case registers. In a separate study of medical records, we assessed the validity of the diagnosis of schizophrenia in the cohort used in this study (Kristjansson et al. 1987). Table 6 shows that among a random sample of 102 patients registered with an ICD-8 diagnosis of schizophrenia, 76 percent met strictly applied DSM-III (American Psychiatric Association 1980) criteria. However, taking into account a lack of documentation in medical records as to age at onset and duration of the disease, we estimated that 80 to 85 percent of the patients actually met DSM-III criteria for schizophrenia.

Table 6 shows that those with an ICD-8 diagnosis of schizoaffective

Table 6. Validity of the ICD–8 diagnosis (Swedish version with 5-digit codes) recorded in the inpatient register when compared with DSM–III assessment of medical records

Recorded ICD–8 diagnosis	Number of patients	Patients who met DSM–III criteria	
		Number	%
Schizophrenia			
Simple 295.00	11	9	82
Hebephrenic 295.10	5	4	80
Paranoid 295.30	14	9	64
Residual 295.40	1	1	100
Schizoaffective 295.70	7	1	14
Unspecified 295.99	60	50	83
Other in 295-series	4	4	100
Total	102	78	76

schizophrenia to a large extent did not meet *DSM-III* criteria for schizophrenia. Whether or not the diagnosis of schizoaffective disorder should be classified together with the schizophrenic disorders is a controversial issue (Pope et al. 1980), and more than just a question of register quality. In this sample, the proportion of patients with a schizoaffective diagnosis was only 7 percent, so the problem was of minor importance. This is in agreement with observations made previously that Swedish psychiatrists, by tradition and through influence of Germany and other central European countries, have narrowly applied the diagnosis of schizophrenia (Leff 1977).

Mortality Studies to Monitor Psychiatric Care. In spite of profound changes in the treatment of patients with schizophrenia, the mortality—and particularly the suicide mortality—among these patients remains in significant excess when compared with the general population mortality. A possibly improved survival among schizophrenic patients in general may not be detected in studies based on hospitalized populations, because of changes in admission policy to inpatient care. Furthermore, the deinstitutionalization and the trend toward greater accessibility of psychiatric care—inpatient as well as outpatient—has led to more people coming in contact with psychiatric care. With more people being treated, patients at a high risk for suicide may be admitted to hospitals to a larger extent, thus increasing the suicide mortality among hospitalized patients. This phenomenon has actually been described in a nationwide Swedish study on suicide in inpatient care (Socialstyrelsen 1985).

Even if selection factors for hospital care do affect mortality trends as described above, the fact that patients with schizophrenia have a twofold increased overall mortality and a manyfold increased suicide mortality poses a challenge to the psychiatric community. As long as a reduced mortality, and particularly a reduced suicide rate, is an important aim for the development of new treatment policies and therapeutic programs, there will be a need to find different ways to monitor and assess the mortality in psychiatric populations.

The use of computerized patient data bases linked to comprehensive cause-of-death registers opens up possibilities for regular monitoring of mortality among psychiatric patients (Socialstyrelsen 1985) as well as specific analyses of cohorts like the one described in this article. The quality of the data recorded is a major issue for concern, but again, the patient data base is a valuable "key" for identification of hospital episodes, which enables access to medical records for further analyses of the case records.

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