

## Excess Mortality by Natural Causes of Italian Schizophrenic Patients

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**Summary.** The risk of mortality over a 5- to 8-year period for a total 1-year prevalence cohort of schizophrenic patients extracted by means of the South-Verona Psychiatric Case Register (Italy) was assessed using three methods: (1) case control with both non-psychotic patients and the general population matched for sex and age; (2) indirect standardization using mortality tables; (3) a recently described method using survival tables. All methods yielded an excess mortality associated with schizophrenia, close to the two-fold increase described in other studies, while the survival tables method produced a higher standardized mortality ratio (SMR). The increased SMR did not appear solely attributable to suicide. Most deaths were attributable to natural causes. This is a departure from other recently reported mortality studies. The possible reasons are discussed.

**Key words:** Schizophrenia – Mortality – Psychiatric case register

### Introduction

Numerous mortality studies have been made in psychiatry, but Tsuang and Simpson (1985) stressed that more are still needed to define the risks associated with specific disorders and to monitor the effects of changing patterns of treatment and after-care.

Most studies of mortality in schizophrenia have yielded an approximately doubled risk (Babigian and Odoroff 1969; Tsuang et al. 1980; Black et al. 1985). Suicide has been repeatedly emphasized as an important cofactor to this increased risk (Allebeck and Wistedt 1987). In Italy, however, reports from Trieste (Giannichedda 1986) and analysis of national trends (Williams et al. 1987a, b) do not support a relative increase of suicides amongst psychiatric patients. However, these reports did not include a separate analysis for patients with schizophrenia.

The Italian psychiatric reform has attracted much attention (Mosher 1982; Mollica 1985). Its intent, to develop a community-based system of care rather than hospital-based services, follows a trend already in development in Europe and North America (Mechanic 1974). However, its closure of admissions to mental hospital was radical. The reform has been criticized on the basis of reports on areas where it has not been properly implemented (Smythies 1985; Jones and Poletti 1986). The main issue remains: whether or not the new pattern of psychiatric care delivery is effective where it is fully applied.

South-Verona is one such area of full implementation (Jablensky and Henderson 1983). Its care delivery is comprehensive and is based on staff intensive domiciliary visits and day-care to avoid hospitalization as much as possible (Burti et al. 1986). The area has been monitored since 1979 by a Psychiatric Case Register and an epidemiological/evaluative research team. It has started to yield some of the quantitative evidence that has been lacking to evaluate the reform (Tansella et al. 1987). So far, there have been very few Italian patient studies (Bollini et al. 1986; De Girolamo and Tumminello 1986; Muscettola et al. 1987), and only one has examined comprehensive area-based service cohorts from the case register data (Balestrieri et al. 1987).

The evaluation of the new pattern of services delivery in Italian areas calls for more outcome studies, especially for individuals with severe mental disorders, since these patients' needs for psychiatric care are great. Because the reform is under way, it is now impossible to set up a comparison between the effects of hospital-based services and community-based services. In 1986, our research team in Verona conducted a follow up of all but one of the 61 individuals from South-Verona who made contacts with the psychiatric services in 1979 and received a diagnosis of schizophrenia. Multi-dimensional standardized measurements appropriate to outcome studies were conducted: psychiatric symptoms, social functioning, and needs for care. These results will be published elsewhere (Lesage et al. 1990; Mignolli et al. 1990). Briefly,

we found that the patients remaining in the mental hospital experienced more symptoms, more social disabilities and more needs for care than patients in contact with the community-based services. Five individuals were found out of contact with psychiatric services and were showing less disabilities than patients in contact. No single case of severe social abandonment was found, nor of "drift" to large cities: most patients were living with their families (Lesage 1989). Most of their medical needs for physical conditions were judged as met. Mortality risks were also determined and were found to be increased, warranting this separate publication.

## Methods

The South-Verona Psychiatric Case Register (Tansella et al. 1985) provided the sampling base. The case register records the contacts with psychiatric services (psychiatrists, psychologists, psychiatric nurses and social workers) of all South-Verona adult residents (population 75,000). The reporting agencies included all public and private inpatient facilities of Verona, the South-Verona Mental Health Centre (which provides day-care, outpatient care and domiciliary visits), and other outpatients agencies (for drug addicts, child and adolescents etc.). The 1-year prevalence of schizophrenia in 1979 was 823:100000 or 0.82%. In 1979, 61 patients who made at least one contact with the reporting services received a diagnosis of schizophrenia or paranoid states (group  $S_{79}$ ). The diagnosis was based on the register director's ICD-9 diagnosis. Using the Present State Examination Syndrome Check-list (Wing et al. 1974), two independent research team members reviewed the casenotes of 60 of 61 cases: 44 patients had an ICD-9 diagnosis of schizophrenic psychoses, 8 had a diagnosis of paranoid states and 8 a diagnosis of other psychoses. No case of manic-affective disorder was identified (Mignolli et al. 1990). The case register incidence of schizophrenia in South-Verona was similar to British Case Register areas (Tansella et al. 1984), suggesting uniform diagnostic practices amongst case register directors. In 1979, 12 of 61 patients were admitted to a mental hospital, 2 to private clinics and the rest were in contact with the Mental Health Centre. Of the 234 patients who made contact with the services in 1979 and received a diagnosis of neurotic depression, anxiety states or personality disorder, 61 were matched for sex and age to the  $S_{79}$  group ( $C_{79}$ ).

The City of Verona's residents are all registered by law in the City Register. The City Register is based both on families and individuals, and includes basic socio-demographic information (sex, age, site of birth, address, site and date of death). The register goes back to the last century, but it has been computerized only in the 1980s. Information prior to that period has not been automated. Unfortunately, the 1979 list of residents was destroyed and the oldest available list of patients was of 31 December, 1981. This forced us to draw from the Psychiatric Case Register the 1982 cohort of schizophrenics ( $S_{82}$ ,  $n = 68$ ) and a non-psychotic group  $C_{82}$ ,  $n = 68$ ) matched as above, in order to perform a case control design with the general population. The City Register provided us with a random sample of 410 South-Verona residents, from which 68 ( $P_{82}$ ) were matched for sex and age to the  $S_{82}$  cohort. The City Register officials estimated that less than 1% of the population may fail to report changes of status. Indeed, as part of the evaluative study, all  $S_{79}$  patients were sought for interview in 1986. All cases reported alive according to the City Register were seen by the interviewers.

Three methods of assessing the risk of death were used. First, the method of indirect standardization was used, since it has become a standard procedure in mortality studies. We used the last available ISTAT (Italy's National Vital Statistics Bureau) mortality tables by sex and 5-year age-group in 1978. The method was

applied to all subgroups of the study. The analysis required the calculation of the standardized mortality ratio (SMR) and the assessment of the 95% confidence intervals using the Poisson distribution assumption (Harland 1983).

The second method consisted of indirect standardization with survival tables. It was hoped that this would provide a more refined assessment. ISTAT survival tables for 1977–1979, by sex and age, were used. The method is an extension of the formula described by Sturt (1983):

$$p(x, a) = \frac{(e_x - a/2)}{(e_{x+a} + a/2)}$$

where  $e_x$  = life expectancy in years at age  $x$ ;  $a$  = period of follow-up;  $p(x, a)$  = probability of surviving for the follow-up period at age  $x$ .

The SMR and analysis for the 95% confidence intervals were determined as above.

The third method was a case control design where the  $S_{82}$  group was compared with the non-psychotic group ( $C_{82}$ ). The aim here was to check that any excess mortality was not related simply to status as a psychiatric patient. Comparison was also made with a general population ( $P_{82}$ , control group). The 95% confidence intervals were measured according to the procedure described by Armitage (1971). The follow-up period extended from 1979 for  $S_{79}$  and  $C_{79}$ , and from 1982 for  $S_{82}$ ,  $C_{82}$  and  $P_{82}$ , until 31 December, 1986.

## Results

The sociodemographic characteristics of all the subgroups were examined. The suitability of the matching was confirmed. The mean age was comparable but the schizophrenic group and the non-psychotic groups had a lower representation than the general population in the over 65 age-group, 6.5%–8.8% vs 13.9%. The schizophrenic groups were more likely to be single, as were the non-psychotic patient groups.

The estimates for the relative risk of mortality for the mortality tables and survival tables method and the SMRs are shown on Table 1. Both methods show that the increased mortality risk is significant for the schizophrenic groups but not the non-psychotic  $C_{82}$  group when the figures for men and women were taken together. The increase was also significant with both methods for men, but only with the survival tables method for women. The case control method could only be applied to the  $S_{82}$  and  $C_{82}$  groups. Only one death was observed in the general population sample. The relative risk for  $S_{82}$  was 10.2 with a 95% confidence interval of 1.3–83.1, that is statistically significant at a 5% level; the respective figure for  $C_{82}$  was 4.2 (0.5–38.5).

The three methods indicate a significant increased mortality risk for the schizophrenic cohorts followed over a maximum of 8 ( $S_{79}$ ) and 5 years ( $S_{82}$ ). The difference was also significant between the schizophrenic groups and the non-psychotic groups, using chi-square statistics or MacNemar test. The estimated relative risk and SMRs varied according to the method used. The case-control method yielded the less precise estimates, varying from 1.3 to 83.1, since it relied on the comparison of two small groups of about 60 patients. The other two methods compared one group with the whole population, increasing the precision of estimates. The survival table method

**Table 1.** Observed number of patient deaths, expected number of deaths according to mortality tables and survival table methods, and standardized mortality ratio (SMR) with 95% confidence intervals in parenthesis

	Schizophrenia and paranoid states (S <sub>79</sub> )			Schizophrenia and paranoid states (S <sub>82</sub> )			Non-psychotic psychiatric patients (C <sub>82</sub> )		
	Males	Females	Both	Males	Females	Both	Males	Females	Both
No. in series	31	30	61	32	36	68	32	36	68
No. of deaths observed	8	4	12	5	4	9	3	1	4
Expected no. of deaths (mortality tables method)	1.7	1.7	3.3	1.3	1.1	2.5	1.4	1.1	2.4
SMR (mortality tables method)	4.8 (2.1–9.4) <sup>a</sup>	2.4 (0.6–6.2)	3.6 (1.9–6.3) <sup>a</sup>	3.7 (1.2–8.7) <sup>a</sup>	3.4 (0.9–8.7) <sup>a</sup>	3.6 (1.6–6.8) <sup>a</sup>	2.2 (0.5–6.5)	0.9 (0–5.2)	1.7 (0.5–4.2)
Expected no. of death (survival tables method)	1.3	1.1	2.5	0.9	0.8	1.7	1.0	0.8	1.8
SMR (survival tables method)	6.0 (2.6–11.9) <sup>a</sup>	3.6 (1.0–9.3) <sup>a</sup>	4.9 (2.5–8.6) <sup>a</sup>	5.4 (1.7–12.7) <sup>a</sup>	4.9 (1.3–12.6) <sup>a</sup>	5.2 (2.4–4.9) <sup>a</sup>	3.1 (0.6–9.0)	1.2 (0–6.8)	2.2 (0.6–5.7)

<sup>a</sup> Statistically significant at 5% level

**Table 2.** Sociodemographic, treatment status and details of death of the 12 deaths of the 1979 cohort of schizophrenic patients in South-Verona (1979–1986, *n* = 12/61)

Age (years)	Sex	Status	Year of death	Cause of death
20	M	General hospital	1979	Choked on beefsteak
20	M	General hospital	1979	Atypical broncho-pneumonia (aspiration?)
29	M	Mental hospital	1985	Suicide
36	F	Day patient	1986	Suicide
37	M	Day patient	1984	Gastric haemorrhage (alcoholism)
48	M	Outpatient	1979	Heart attack
54	M	Outpatient	1984	Heart attack, diabetes
61	M	Mental hospital	1980	Heart attack
63	F	Mental hospital	1986	Cancer
64	M	Outpatient	1985	Cancer
69	F	Nursing home	1980	Cancer
73	F	Mental hospital	1985	Heart attack (?)

did produce lower expected number of deaths than the mortality tables method. This is probably due to the fact that standard indirect standardization is based on 5-year intervals, therefore using average risk of death for the period rather than a more exact risk based on survival tables which give estimates of risk year by year and even allow estimates of risk between each year. However, all methods yielded confidence intervals compatible with a two-fold increase of mortality in both the schizophrenic cohorts 1979 and 1982.

Table 2 illustrates the causes and details surrounding the 12 deaths recorded for the S<sub>79</sub> cohort. It was obtained from the case notes and confirmed if necessary by the treating psychiatrist. An excessive number of deaths occurred in both the first 2 years and in the last 3, but numbers were too small to test the significance of this. Four deaths occurred in the State Mental Hospital or nursing home, 3 in the general hospital and 5 of 12

deaths occurred in the community. There were two suicides, one at the Mental Hospital, the other of a 36-year-old woman who killed herself shortly after discharge from hospital. Three patients died of heart attack and 3 elderly patients of cancer. The two early deaths of young men require details. They both occurred during admission on the university ward. One patient choked on his steak while dining with other patients and in front of staff: the resuscitation team called at once was unsuccessful. A young man in a confused, catatonic state died 3 weeks following transfer from the military barracks. It was impossible to assess the exact nature of his atypical broncho-pneumonitis that was refractory to all treatments.

## Discussion

Because of the small numbers involved, it was not appropriate to analyse the SMR for suicide alone. It cannot be disregarded that the two suicide cases represented a significant increase of suicide. There was one accidental death (the young man who choked on his steak). However, the excess mortality found in these schizophrenic cohorts cannot be solely attributed to suicide, but mainly, in 9 of 12 deaths, to natural causes. This represents a major departure from other reports in the literature where excess mortality in both outpatient and inpatient schizophrenics was not related to "natural deaths" (Black et al. 1985; Martin et al. 1985) but entirely or mainly to suicides or accidental deaths (Allebeck and Wistedt 1987). There are many possible explanations for these findings. First, there is a risk of misdiagnosis. For example, manic-depressive illnesses misdiagnosed as schizophrenia may have been responsible for some of the excess mortality previously found. We were careful to have independent raters check the diagnosis, especially for major affective disorders.

A second explanation relates to the health care available for these patients. Certainly one young man's death on a beefsteak in front of nursing staff should not occur

in a ward. Otherwise, Verona is known to be one of the best equipped areas of Italy with hospitals and specialists. The review of the casenotes of the deaths and the assessment of the medical needs for care of the survivors in 1986 did not allow us to identify clear cases of neglect and as far as our assessments go, medical needs for physical conditions were met. Thirdly, since heart diseases and cancer were identified as common causes of death, the possibility cannot be excluded that these patients were exposing themselves more to certain risk factors like heavy smoking.

A fourth factor to consider is a selection process. All Italian Case Registers have a 1-year prevalence of about half of the British Case Register areas (Lesage 1989). As mentioned before, the incidence of schizophrenia is similar in South-Verona and Great Britain; a lower prevalence means that less patients with schizophrenic psychoses keep contact with Italian Psychiatric Services. One may hypothesize that the patient who remain in contact with psychiatric services may be those more socially handicapped and those with less social support. Such social skills and support are instrumental in helping individuals to seek and to implement proper care for physical diseases. Therefore these patients may be more at risk of dying from underlying diseases or neglecting their health.

This study supports the often reported excess mortality found in patients with a diagnosis of schizophrenic psychoses, using three different methods. Because of the small numbers involved, the confidence intervals were particularly large around the relative risk of SMRs, and may have prevented the mortality tables method from showing a significant increased risk for women. Overall, the methods yielded SMRs from 3.6 to 5.2, but with confidence intervals from 1.6 to 9.9. The hypothesis of two-fold or so increased mortality risk found in previous studies cannot be rejected.

The difference found between the methods based respectively on mortality and survival methods may be surprising at first, since they are based on the same data in Italy. However, the mortality method was based on 5-year group mortality tables, and this may inflate the estimated risk of death for each individual. Confirmation of the validity of the survival tables method would be necessary from other research units using both methods.

This is the first patient study report from Italy based on the following population-based methods: case registers, City Register and national vital statistics. The use of a case register's 1-year prevalence as a sampling frame provided a comprehensive picture of the psychiatric services offered to the patients of the area, whether mental hospital or community-based services. It does allow us to state that in South-Verona the excess mortality risk found is within the limits monitored in North American, British and Scandinavian mental health services. Mortality is but one index needed to monitor new mental health services. It needs to be considered together with the results of the outcome study conducted on the survivors of the cohort.

Further studies are required to confirm our findings of excess mortality by natural causes for patients with

non-affective psychoses. The other Italian Case Register areas (Lomest and Portogruaro) cover together 0.5% of the Italian population (Torre 1985; Tansella and De Salvia 1986). They would provide a greater pool of schizophrenic patients and population base. Care should be taken to ensure diagnostic reliability. However, if the SMRs of 3.5 or more were also found there, this would call for detailed studies of the medical care received by these patients and the health risks factors to which they may be exposed.

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## References

- Allebeck P, Wistedt B (1987) Mortality in schizophrenia. A ten-year follow-up based on the Stockholm County Inpatient Register. *Arch Gen Psychiatry* 43:650–653
- Armitage P (1971) *Statistical methods in medical research*. Blackwell, London
- Babigian HM, Odoroff CL (1969) The mortality experience of a population with psychiatric illness. *Am J Psychiatry* 126:470–480
- Balestrieri M, Micciolo R, Tansella M (1987) Long-stay and long-term psychiatric patients in an area with a community-based system of care. A register follow-up study. *Int J Soc Psychiatry* 33:251–262
- Black DW, Warrack G, Winokur G (1985) The Iowa record-linkage study. I–III. *Arch Gen Psychiatry* 42:71–88
- Bollini P, Muscettola G, Piazza A, Puca M, Tognoni G (1986) Mental health care in Southern Italy: application of case-control methodology for the evaluation of the impact of the 1978 psychiatric reform. *Psychol Med* 16:701–707
- Burti L, Garzotto N, Siciliani O, Siciliani O, Zimmermann-Tansella Ch, Tansella M (1986) South-Verona's psychiatric service: an integrated system of community care. *Hosp Community Psychiatry* 37:809–813
- De Girolamo B, Tumminello B (1986) *Psichiatria italiana e riforma nella letteratura internazionale*. Fogli Inform 120:1–36
- Giannichedda MG (1986) Preliminary report of Trieste for the WHO Regional Bureau for Europe's pilot study in mental health areas. Trieste
- Harland A (1983) An efficient procedure for computerising exact confidence limits for a SMR. *Comput Biomed Res* 16:40–43
- Jablensky A, Henderson J (1983) Report on a visit to the South-Verona Community Psychiatric Service. World Health Organization Assignment Report. WHO, Geneva
- Jones K, Poletti A (1986) The Italian experience in mental health care. *Hosp Community Psychiatry* 37:795–801
- Lesage AD (1989) Sociological factors affecting clinical caseload in Italian good practice areas. *Int J Soc Psychiatry* 35:54–61
- Lesage AD, Mignolli G, Faccincani C, Tansella M (1990) Standardized assessment of the needs for care in a cohort of patients with schizophrenic psychoses. *Psychol Med* (in press)
- Martin RL, Cloninger CR, Guze SB, Clayton PJ (1985) Mortality in a follow-up of 500 psychiatric outpatients. I–II. *Arch Gen Psychiatry* 42:47–66
- Mechanic D (1974) *Politics, medicine and social sciences*. Wiley, London
- Mignolli G, Faccincani C, Platt S (1990) Psychopathology and social performance in a cohort of patients with schizophrenic psychoses. A 7-year follow-up. *Psychol Med* (in press)

- Mollica RF (1985) The unfinished revolution in Italian psychiatry. An international perspective. *Int J Ment Health* 14:1-2
- Mosher LR (1982) Italy's revolutionary mental health: an assessment. *Am J Psychiatry* 139:199-203
- Muscettola G, Casielle M, Bollini P, Sebastiani G, Pampallona S, Tognoni G (1987) Pattern of therapeutic intervention and role of psychiatric setting: a survey in two regions of Italy. *Acta Psychiatr Scand* 75:55-61
- Smythies JR (1985) On the current state of psychiatry in Northern Italy. *Bull R Coll Psychiatr* 14:149-154
- Sturt E (1983) Mortality in a cohort of long-term users of community psychiatric services. *Psychol Med* 13:441-446
- Tansella M, De Salvia D (1986) Case registers in comprehensive community psychiatric service areas in Italy. In: Horn GHMM ten, Giel R, Gulbinat WH, Henderson GH (eds) *Psychiatric case registers in public health*. Elsevier, Amsterdam, pp 140-145
- Tansella M, Faccincani C, Fiorio R, Mignolli G (1984) Epidemiologia e aspetti di terapia delle psicosi schizofreniche a Verona Sud. In: Faccincani C, Fiorio R, Mignolli G, Tansella M (eds) *Le psicosi schizofreniche, dalla ricerca alla pratica clinica*. Pàtron, Bologna, pp 65-106
- Tansella M, Faccincani C, Mignolli G, Balestrieri M, Zimmermann-Tansella Ch (1985) Il registro psichiatrico di Verona-Sud. Epidemiologia per la valutazione dei nuovi servizi territoriali. In: Tansella M (ed) *L'approccio epidemiologico in psichiatria*. Boringhieri, Turin, pp 225-259
- Tansella M, De Salvia D, Williams P (1987) The Italian psychiatric reform: some quantitative evidence. *Soc Psychiatry* 22:37-48
- Torre E (1985) Planning and evaluation of mental health services in Italy. In: Pichot P, Berner P, Wolf R, Thau K (eds) *Psychiatry*. Plenum Press, London, pp 71-77
- Tsuang MT, Simpson JC (1985) Mortality studies in psychiatry: should they stop or proceed? *Arch Gen Psychiatry* 42:98-103
- Tsuang MT, Woolson RF, Fleming JA (1980) Premature deaths in schizophrenia and affective disorders. *Arch Gen Psychiatry* 37:979-983
- Williams P, De Salvia D, Tansella M (1987a) Suicide, psychiatric reform and the provision of psychiatric services in Italy. *Soc Psychiatry* 21:89-95
- Williams P, De Salvia D, Tansella M (1987b) Suicide and the Italian psychiatric reform: an appraisal of two data collection systems. *Eur Arch Psychiatr Neurol Sci* 236:237-240
- Wing JK, Cooper JE, Sartorius N (1974) *The measurement and classification of psychiatric symptoms*. Cambridge University Press, Cambridge