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# Prospective analysis of premature mortality in schizophrenia in relation to health service engagement: a 7.5-year study within an epidemiologically complete, homogeneous population in rural Ireland

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## Abstract

While premature death in schizophrenia is well recognised, mortality risk has received little longitudinal study in relation to population representativeness and patient engagement with health services. Within a rural Irish catchment area of socioeconomic, ethnic and geographical homogeneity and low residential mobility, an epidemiologically complete population of 72 patients with schizophrenia was followed up over 7.5 years in order to quantify mortality prospectively. Information was obtained in relation to 99% of the cohort, with 94% of those surviving retained in engagement with psychiatric care. There were 25 deaths (35% of cohort). A relative risk of 2.06 (95% CI, 1.40–2.80;  $P < 0.001$ ) among this epidemiologically complete population may constitute an estimate of risk for mortality inherent to schizophrenia when disengagement from health services, residential mobility and socioeconomic, ethnic and geographical diversity are minimised. On long-term prospective evaluation, risk for death in schizophrenia was doubled on a background of enduring engagement in psychiatric care with increasing provision of community-based services and introduction of second-generation antipsychotics.

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**Keywords:** Survival; Health service provision; Longitudinal study; Psychosis; Antipsychotic polypharmacy

## 1. Introduction

Among the breadth of studies now available on all aspects of schizophrenia, premature loss of life

is one of the most consistent and accepted epidemiological findings. A relative mortality that is of the order of twice that of the general population remains poorly understood. It is recognised that though up to 10% of patients with schizophrenia complete suicide, this high rate appears unable to account fully for the excess burden of mortality

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and directs attention to increased risk for physical disease; for example, there is evidence for an over-representation of respiratory and other non-circulatory diseases, an under-representation of certain forms of malignant disease, and an increased risk for unexplained sudden death (Caldwell and Gottesman, 1990; Jablensky, 1995; Simpson and Tsuang, 1996; Jeste et al., 1996; Brown, 1997; Waddington et al., 1998; Reilly et al., 2002).

These issues can be addressed from several perspectives and using a variety of experimental approaches. The commonly utilised resources of large health service databases can have inherent and sometimes serious limitations, which often include one or more of retrospective design, epidemiological non-representativeness, uncertainty regarding psychiatric service diagnoses by diverse diagnosticians and lack of information as to individual patient circumstances at death; furthermore, such large datasets can generate spurious associations based on inadequate or inaccurate information over which the investigator has no control (Kuller, 1995).

It has been argued that understanding would be advanced by integrating the study of mortality in psychiatric illness into longitudinal studies of psychiatric populations, so that such mortality might be related to other dimensions of illness and care (Tsuang and Simpson, 1985), but it has proved difficult to translate this ideal into practice. For example, continuity of patient engagement underpins the effectiveness of psychiatric service provision for a given population (Möller and von Zerssen, 1995; Lang, 1999), and ongoing medical care may be one of several factors that influence mortality in psychiatric illness (Druss et al., 2001). However, mortality in schizophrenia has received little study in relation to engagement and to representativeness of the population engaged. Also, there has been concern that increased risk for unexplained sudden death may be related in part to treatment with particular antipsychotic drugs, and that polypharmacy, with antipsychotics and other psychopharmaceuticals, as well as non-psychotropic medications, may be associated with adverse, and sometimes fatal, consequences for patients (Jeste et al., 1996; Waddington et al., 1998; Reilly et al., 2002). Thus, there is a need

for prospective study of these issues among an epidemiologically complete, socioeconomically and ethnically homogeneous population over an extended period of time.

In 1992, we identified 'all' prevalent cases of DSM-III-R schizophrenia within a rural Irish catchment area (Youssef et al., 1999). This cohort, identified initially to investigate geographical variations in rate of schizophrenia, has been utilised to quantify mortality over the subsequent 7.5-year period, on a background of the trajectory and demographics of engagement with the area psychiatric service.

## **2. Methods**

### *2.1. Study region*

The study region is the South Monaghan catchment area, population 21 520, of Cavan–Monaghan psychiatric service. Situated within Co. Monaghan, a northeastern border county of the Republic of Ireland, this region has a substantial agricultural economy with little major industry; the largest town within the 32 constituent District Electoral Divisions (DEDs) has a population of 2029 (Central Statistics Office, 1993, 1994), illustrating the overwhelmingly rural nature of the region. Among all persons currently resident in Co. Monaghan, 77% were born in the county, while in the year before the most recent census only 4% of the usually resident population changed address, with over half of these moving within the county; equivalent percentages of 11% for Dublin city (Central Statistics Office, 1997) and 18% for an inner city area of London (Harvey et al., 1996) attest to the very low social mobility of the region. Of the resident population, 96% were born in Ireland (the Republic of Ireland or Northern Ireland), 3% in Britain and 0.3% in the USA (the vast majority of whom had at least one Irish parent), 0.1% in continental Europe, 0.1% in Africa, 0.1% in Asia and 0.1% elsewhere; this attests to the overwhelming ethnic homogeneity of the study region. Among households, 96% occupied a private house, of which 82% were owner-occupied, 84% had four or more rooms, 83% were occupied by five or fewer persons and 70% had

at least one car. Furthermore, on a national 'Deprivation index' score of 1–5, with '5' indicating greatest deprivation, 84% of DEDs score in the middle categories thereof; these data show the substantial socioeconomic homogeneity of the region.

## 2.2. Case ascertainment

The index population was ascertained in 1992 through multiple sources of information, using methods that have been described previously in detail (Youssef et al., 1991, 1999; Scully et al., 2000). In brief, potential cases of schizophrenia-like psychosis who were born in and/or became ill in the study region, under the strict catchment area policy of the North Eastern Health Board in accordance with Irish mental health legislation, were identified through inpatient and outpatient records, community psychiatric nurses, other persons active in the community, and field work with cases and their families by a psychiatrist having extensive personal knowledge of the area and its services. After giving informed consent, all persons ascertained as having a putative schizophrenia-like psychosis, including both inpatients and those living in the community, were interviewed by one investigator and diagnosed in accordance with DSM-III-R criteria (American Psychiatric Association, 1987) by the same diagnostic team. Demographics and details on current prescription of antipsychotics, together with any other psychotropic medications, were recorded.

## 2.3. Case follow-up

In 1999, some 7.5 years after case ascertainment, and under continuing approval from the Ethics (Research) Committee of the North Eastern Health Board, the current disposition of each case was sought by the same investigatory team, again using multiple sources of information: admission registers, inpatient and outpatient records, community psychiatric nurses, field work with cases, families and local clergy by a psychiatrist having personal knowledge of the area and its services, and death certificates. Disposition categories were defined as follows: (i) deceased, subdivided into

death through natural causes, accident, or suicide; (ii) inpatient, receiving care in St. Davnet's Hospital, Monaghan, which has the only admission unit in the catchment area; (iii) outpatient, subdivided into those living in staffed hostels/group homes, who were by definition in regular contact with the psychiatric services, or living independently in the community. Cases living independently were subdivided further into those in 'regular' contact with psychiatric services, and those in 'irregular' contact therewith; 'regular' contact was defined as interaction with a mental health professional as often as deemed clinically necessary, while 'irregular' contact was defined as any continuing pattern of interaction that fell outside those limits; (iv) defaulters, lost to contact with psychiatric services. Additionally, details on the most recent prescription of antipsychotics, together with any other psychotropic medications, were recorded.

## 2.4. Data analysis

Mortality data for this patient cohort, using the primary end point of age at death from any cause, were analysed actuarially by the life table method using the 1992 Statistical Release from the Central Statistics Office, Government Information Service, Ireland (Waddington et al., 1998); relative risk was determined as the observed number of deaths divided by the expected number of deaths, adjusting for age and gender, together with 95% confidence interval (CI) and two-tailed probability values as calculated using exact methods (Stat-Exact 4).

Survival data for this patient population, as individual times from initial evaluation in 1992 to death and with those still alive 7.5 years later treated as censored values, were analysed by Cox proportional hazards modelling (BMDP). Among variables recorded at study entry in 1992 (as means (S.D.) with range, or prevalence (% of population); Table 1), those which made significant independent prediction of hazard ratio were identified in terms of their model coefficients and associated relative risk, together with 95% CI and two-tailed probability values (Waddington et al., 1998); some clinical variables in the dataset, such

Table 1

Demographics of the 72 patients (40 men, 32 women) at entry into the prospective study

Variable	
Age, years [mean (S.D.) range]	56.8 (14.6) 20–83
Current antipsychotic dose, mg CPZeq <sup>a</sup> [mean (S.D.) range]	466 (734) 0–4150
Number of concurrent antipsychotics [mean (S.D.) range]	1.3 (0.7) 0–3
Current anticholinergic [prevalence (%)]	46/72 (64%)
Current mood stabiliser [prevalence (%)]	5/72 (7%)
Current antidepressant [prevalence (%)]	9/72 (13%)
Current anxiolytic/hypnotic [prevalence (%)]	8/72 (11%)

<sup>a</sup> CPZeq, chlorpromazine equivalents.

as family history status (Youssef et al., 1999), were not included in these analyses to limit the range of putative predictor variables vis-à-vis the limited number of deaths in the absence of a priori hypotheses.

### 3. Results

#### 3.1. Demographics at ascertainment

In 1992, 72 cases of DSM-III-R schizophrenia (40 male, 32 female; Table 1) were identified within the catchment area of 21 520, giving a 1-year prevalence of 3.4 (S.E.M. 0.4)/1000 and a lifetime morbid risk of 6.6 (S.E.M. 0.8)/1000 (see Youssef et al., 1999). Of these 72 cases, 22 (31%) were inpatients while 50 (69%) were outpatients; of these 50, 13 (26%; 18% of total) were living in staffed hostels/group homes while 37 (74%; 51% of total) were living independently in the community. Their mean age was in the mid-50s, by virtue of the epidemiological completeness of the population, which encompassed the whole spectrum of schizophrenia: from first-episode cases in their second decade, through the diversity of adult patients resident in the community, to elderly inpatients in their ninth decade.

Current antipsychotic and adjunctive treatment at ascertainment is detailed in Table 1; of these 72 patients, 6 (8%) were not currently receiving an antipsychotic, 45 (63%) were receiving one antipsychotic, 16 (22%) were receiving two antipsychotics, and 5 (7%) were receiving three antipsychotics. No patient was receiving a second-

generation ('atypical') antipsychotic as currently conceptualised (Waddington et al., 1997; Waddington et al., in press), though two patients (3%) were receiving treatment with sulpiride.

#### 3.2. Demographics at follow-up

Some 7.5 years later, information was obtained in relation to all but one (99%) of the original 72 cases ascertained. Of these 72 cases, 25 (35%) were found to be deceased. Certification of death from local or central registry offices was obtained for 21 of these, though for four deceased patients, no death certificate could be located; in these instances, collateral information was obtained from a reliable family member and/or local clergy. Of the surviving 47 cases, only eight (17%) remained as inpatients, there being one surviving person returned to the community from long-term inpatient care and no instances of new inductions into such care. The remaining 39 of these 47 (83%) were living outside of a hospital setting, among whom 11 (23% of those surviving) were living in staffed hostels/group homes and 28 (60% of those surviving) were living independently in the community; of these 28, 14 (30% of those surviving) remained in 'regular' contact with psychiatric services, 11 (23% of those surviving) were in 'irregular' contact, one male resided in the community but had defaulted from care, while one male had defaulted from care and was currently of no fixed abode within the community. Only for the remaining male could no information be obtained, i.e. there was no record of service contact over the

Table 2  
Predictors of reduced survival over 7.5 years by Cox proportional hazards modelling

Variable	$\beta$	S.E. $\beta$	<i>P</i>	Relative risk	95% CI
Age	0.07	0.02	<0.001	1.07	1.03–1.12
Sex	−0.15	0.42	NS	0.86	0.38–1.96
Current antipsychotic dose, mg CPZeq	0.00	0.00	NS	1.00	0.99–1.01
Number of concurrent antipsychotics	−0.08	0.41	NS	0.92	0.41–2.06
Current anticholinergic	0.65	0.52	NS	1.91	0.68–5.36
Current mood stabiliser	−0.44	1.04	NS	0.65	0.08–5.02
Current antidepressant	−0.40	0.65	NS	0.67	0.19–2.43
Current anxiolytic/hypnotic	1.44	0.66	<0.05	4.26	1.18–15.39

follow-up period, and no information from persons active in the community or from any other source; in the absence of any death certificate or other indication of demise, this case was deemed to have defaulted from care. Thus, three cases (4% of initial population; 6% of those surviving) were deemed to have defaulted on a long-term basis.

Among the 44 patients not deceased or defaulted over this 7.5-year prospective period, five patients were not currently receiving an antipsychotic [11% (7% at initial assessment)], 28 [64% (59%)] were receiving one antipsychotic, nine [20% (25%)] were receiving two antipsychotics, and two [5% (9%)] were receiving three antipsychotics. In relation to the introduction of second-generation antipsychotics: four patients had been started on clozapine (three as monotherapy; one with an anticholinergic and an antidepressant); six had been started on risperidone (one as monotherapy; three with another antipsychotic, two of whom were also receiving an anticholinergic; one with a mood stabiliser; one with an anticholinergic); three had been started (two as monotherapy; one with a mood stabiliser and an anticholinergic); and one had been started on amisulpride as monotherapy. The two patients who were receiving sulpiride at initial assessment continued to do so at follow-up (one with two other antipsychotics and an anticholinergic; one with an anticholinergic). Overall, anticholinergic usage among those surviving had declined from 29 (66%) to 16 (36%) patients; 16 patients had an anticholinergic withdrawn, while three had an anticholinergic introduced.

### 3.3. Mortality

Over this 7.5-year period, the death of 25 of 72 patients [15 male, 10 female; mean age at death 69.7 (S.D. 11.4), range 49–85] and an expected value of 12.14 indicated a relative risk of 2.06 (95% CI 1.40–2.80;  $P < 0.001$ ). Twenty-two of 25 deaths (88%) were from natural causes: six circulatory; five neoplastic; four respiratory; two gastrointestinal; one endocrine; one genitourinary; three were recorded as ‘natural causes—old age’ without further details. There were also two accidental deaths (8%: a 60-year-old male outpatient by drowning; a 76-year-old female outpatient in a road traffic accident) and one suicide (4%: a 50-year-old male outpatient by hanging). All deceased patients had been engaged with the psychiatric service following ascertainment; one elderly patient with malignant disease had relocated to her family in the UK, where she received care prior to her death.

A Cox proportional hazards model indicated that two variables, increasing age and current receipt of an anxiolytic or hypnotic, were predictors of reduced survival over 7.5 years among these 72 patients (Table 2). To examine whether instances of unnatural death might be exerting a disproportionate influence on findings which were derived primarily from natural causes (Waddington et al., 1998), this analysis was repeated: firstly, with exclusion of the one instance of suicide; secondly, with exclusion of the one instance of suicide and the two instances of accidental death.

On exclusion of the instance of suicide, the association of reduced survival with age remained significant while that with receipt of an anxiolytic or hypnotic lost its statistical significance. An unaltered survival model on excluding also accidental death complements our previous finding of an unaltered survival model on excluding death following assault (Waddington et al., 1998).

## 4. Discussion

### 4.1. Study strengths and limitations

This study design and patient population present both advantages and disadvantages: (i) the cohort is epidemiologically complete, and as such encompasses the totality of schizophrenia, from young, first episode cases, through a majority of cases receiving care in the community, to a minority of elderly cases who continue to receive long-term inpatient care; (ii) potential confounding factors such as residential mobility and socioeconomic, ethnic and geographical diversity are either substantially reduced or eliminated; (iii) all cases were ascertained, interviewed in person and diagnosed using contemporary operational criteria by the same investigatory team; (iv) mortality or long-term engagement in care was assessed prospectively over a prolonged period (7.5 years) by that same investigatory team, with field work in the community aided by hospital staff living in close association with the population studied; and (v) it was possible to obtain information on all but one case (99%) in the cohort; this is particularly important in the present context as patients lost to follow-up may include a higher proportion of early deaths relative to those traced more easily (Sims, 1973). However, as for the majority of such studies, little information was available on factors such as diet, smoking habits and exercise. Also, the logistical demands of ascertaining such an epidemiologically complete population mean that the above advantages are offset by a modest sample size, giving reduced statistical power relative to large health service databases such that individual causes of death could not be analysed separately; yet the greater statistical power of such databases is itself offset by material limitations

such as: retrospective design; epidemiological non-representativeness; uncertainty regarding psychiatric service diagnoses by diverse diagnosticians; and lack of information as to individual patient circumstances at death (see Section 1).

### 4.2. Patient engagement

Over the 7.5-year prospective period following index evaluation, it was possible to retain 94% of the initial study population surviving in some form of engagement with psychiatric care. At one level, it might be argued that such a low default rate (6%) is unrepresentative of day-to-day experience elsewhere, particularly in urban settings. For example, findings among recent studies of continuity of care and clinic attendance for schizophrenia and related disorders include the following: among first-episode patients, 19% had defaulted after 2 years (Salokangas, 1997); after discharge, 9 and 11% of patients had defaulted after 2 or 4 years (Sytema et al., 1997; Sytema and Burgess, 1999); among inner city outpatients selected for study entry and diagnosed from case notes, 8% could not be traced and 34% declined to participate, with 29% of those attending an outpatient clinic at study entry not attending 1 year later (Killaspy et al., 2000); among studies comparing community mental health team management with other standard approaches, these were associated with losses to follow-up of 33 and 45%, respectively, over periods from 3 months to 2 years (Simmonds et al., 2001). Thus, in this rural psychiatric service, low residential mobility and socioeconomic, ethnic and geographical stability, together with investment in community-based care that emphasises domiciliary visits and homebase treatment (Scully et al., 2002), could be seen as a confluence of unusually favourable circumstances.

### 4.3. Mortality

However, as a chastening counterpoint, increased risk for death was evident in spite of these otherwise favourable circumstances. Among this cohort, mortality was increased more than twofold. The present relative risk [2.06 (95% CI 1.40–2.80)] can be compared with that which we

have reported among older inpatients within the Cavan–Monaghan psychiatric service [1.33 (95% CI 1.01–1.65); Waddington et al., 1998], and that deriving from a meta-analysis of diverse study populations undertaken previously [1.56 (95% CI 1.51–1.62), natural causes 1.37 (95% CI 1.34–1.41); Harris and Barraclough, 1998]. These differences might reflect, at least in part, reduced risk for accidental death and suicide (Fenton et al., 1997) and greater access to medical attention within hospital settings (Druss et al., 2001), from which much of the previous data have been derived, together with aspects of experimental design. More specifically, we are not aware of any previous study that has quantified increased risk among an epidemiologically complete population, all of whom had been interviewed and diagnosed by operational criteria in life and then followed prospectively over a prolonged period within the same psychiatric service by the same investigatory team. Thus, the present value may estimate risk for mortality inherent to schizophrenia when social mobility and socioeconomic, ethnic and geographical diversity are minimised.

As would be expected in any population, the primary predictor of reduced survival was increasing age; this emphasises that the limited sample size is adequate for resolving such aspects of mortality. One finding in our previous study (Waddington et al., 1998) was an independent association between reduced survival and an index of antipsychotic polypharmacy, i.e. the maximum number of antipsychotics prescribed concurrently at any time over each patient's treatment history up to and including ascertainment, as determined by detailed review of lifetime medical records in a long-term inpatient population. Among the present cohort, the great majority were outpatients for whom no such lifetime records of treatment were available; hence it was not possible to determine that same index, and an alternative index, number of antipsychotics prescribed concurrently at ascertainment, was recorded. The present cohort, due to its epidemiological completeness, is appreciably younger than the older inpatients studied previously; thus, it remains possible that the association at issue is specific not only for the index of antipsychotic polypharmacy utilised but also for patient

demography. Among the survivors, 7.5 years later, it was noteworthy that antipsychotic polypharmacy was still common, with second-generation antipsychotics introduced sparingly and often as adjuncts to continuing treatment with first-generation antipsychotics and other agents. The association of reduced survival with receipt of an anxiolytic or hypnotic, deriving from suicide, echoes the recent finding of an association between suicide and extent of exposure to psychosedatives (Salokangas et al., 2002). More data are needed to clarify this association.

Increased risk for premature death endured despite continuing engagement in psychiatric care, with increasing investment in community service provisions and introduction of second-generation antipsychotics, with minimal social mobility and socioeconomic, ethnic and geographical diversity. It remains possible that the low rate of suicide or other forms of unnatural death reflects the high level of engagement with mental health services; the high level of mortality due to natural causes could then raise questions as to how well physical, as opposed to psychiatric, illness was treated in such populations. More speculatively (Waddington et al., 1998), it should be noted that across primate species, including humans, lifespan is proportional to overall brain size and regional brain volumes (Allman et al., 1993a,b). Thus, reduced overall brain size and regional brain volumes in schizophrenia (Ward et al., 1996; Waddington et al., 1999) may contribute to some component of increased mortality in this disorder. The extent to which premature mortality in schizophrenia might be reduced in the future through further improvements in service provision, engagement and treatment remains to be determined and requires urgent study.

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