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Mortality in Schizophrenia and Related Psychoses: Data from Two Cohorts, 1875-1924 & 1994-2010

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Abstract

Objective: To investigate mortality rates in schizophrenia and related psychoses.

Design: Data from two epidemiologically complete cohorts of patients presenting for the first time to mental health services in North Wales for whom there are at least 1, and up to 10 year follow up data have been used to calculate survival rates and standardized mortality rates for schizophrenia and related psychoses.

Setting: The North Wales Asylum Denbigh (archived patient case notes) and the North West Wales District General Hospital psychiatric unit.

Population: Cohort 1: The North Wales Asylum Denbigh (archived patient case notes). Of 3168 patients admitted to the North Wales Asylum Denbigh 1875-1924, 1074 had a schizophrenic or related psychosis. Cohort 2: Patients admitted between 1994 and 2010 to the North West Wales District General Hospital psychiatric unit, of whom 355 had first admissions for schizophrenia or related psychoses.

Results: This study reports a 4-fold increased mortality rate in schizophrenia and related psychoses in the historical period compared to population norms then and in the contemporary period compared to population norms now. Suicide is the commonest cause of death in schizophrenia in the contemporary period (SMR 35), while tuberculosis was the commonest cause historically (SMR 9). In the contemporary data, deaths from cardiovascular causes and from suicide arise at different illness stages and at different ages.

Conclusions: Contemporary mortality rates in schizophrenia and related psychoses are high but there are particular hazards and windows of risk that enable interventions. The data point to a clear intervention in the incident year of treatment that could give patients with schizophrenia a normal life expectancy.

Article Summary

Article Focus

The question of possible increases in mortality in psychosis is a current issue of concern, with both suicide and increased cardiovascular risk noted. It is know that the initial year after a diagnosis of schizophrenia is a point of high risk.

Key Message

In North Wales, access to two epidemiologically complete case registers makes it possible to demonstrate that suicide is not inherent in schizophrenia and that cardiovascular deaths are confined to elderly patients, who typically do not have a schizophrenia diagnosis.

Tackling the problem of suicides in the first year of schizophrenia has the potential to restore life expectancy to normal in this illness.

Introduction

There is growing interest in outcomes for schizophrenia and related psychoses, fuelled by consistent reports of an apparent doubling or tripling of mortality rates, along with significant reductions in life expectancy.[1-11] A double or tripling of mortality rates, equates in the case of schizophrenia to a loss of approximately 15 years of life expectancy.[11] As reported, mortality stems variously from natural causes, especially cardiovascular disorders[2, 7, 10] and from unnatural causes in particular suicide.[1, 3, 11]

After their introduction in the 1950s, the antipsychotic drugs were seen as having a beneficial effect on mortality rates in psychosis.[12, 13] However mortality rates now appear to be increasing[10, 14] and this has led to concerns that antipsychotics with adverse cardiovascular profiles could aggravate this trend, with particular concerns for the elderly.[15. 16]

The majority of studies undertaken have been cross-sectional in design. They also lack data on patients not treated with antipsychotic medication. These factors make it difficult to pinpoint a direction of causality between illness and mortality and hinder efforts to devise interventions for risks that may arise at different stages of an illness. Owing to the geographical and economic constraints imposed by North West Wales, we have been able to design a study that addresses some of these issues. We have logged all admissions for schizophrenia and related non-affective psychoses over the 17 year period from 1994 to 2010, and followed up all admissions during this period. We also have a database of all admissions to the North Wales asylum in Denbigh in the years from 1875 to 1924 complete with subsequent clinical records and thus have data on causes of mortality in an untreated cohort of psychotic patients. Finally we have separated delusional disorder, acute and transient psychoses and schizophrenia in both historical and contemporary databases in an effort to link specific hazards to clinical syndromes. The resulting databases allow different perspectives to be brought to bear on the data arising from other studies.

Method

We have used two datasets to look at outcome data for schizophrenia and other non-affective psychoses drawn from the periods 1875-1924 and 1994-2010. Geographical and financial constraints in North West Wales have conspired to ensure there was nowhere else for 19th/20th century patients to go other than the asylum at Denbigh, and 20th/21st century patients to go to

other than the District General Hospital unit in Bangor. Even patients getting sick elsewhere in both periods were returned to North West Wales for treatment.

The Datasets

The historical cohort consists of all admissions from North West Wales to the asylum at Denbigh between 1875 and 1924. The asylum records for every patient offered five sets of information relevant to diagnosis; medical and legal certificates outlining the circumstances of detention; standard demographic data including age, sex, educational, employment and marital status, family history of mental illness, prior mental or physical illness and possible social triggers; standard assessments of dangerousness, suicidality, seizure-proneness, along with food refusal and a range of clinical features; descriptions of patients' mental and physical states on admission; case notes covering patients stays in hospital until discharge or death.[17] For the historical cohort we could retrieve all possible records of patients back to 1865 to ensure that duration of illness is not being underestimated and all subsequent admissions through to 1965 in order to establish cause of death for later admissions.

The contemporary cohort is drawn from a database of all first admissions to the sole district general hospital (DGH) unit in North West Wales between 01-01-1994 and 31-12-2010, along with any admissions to the regional medium secure facility, the only other unit to which patients might have been admitted, bypassing the DGH. The catchment area for the DGH unit is the same as that for the historical cohort. Patients were included if they were native to or resident in North West Wales prior to and following their initial episode. We have not included in either the contemporary or historical cohorts patients who became ill after coming from elsewhere as students to the local university or who otherwise came from out of area and returned to their place of origin but who had a first episode of mental illness while in North West Wales. For the contemporary cohort, using their NHS number, we could track and get outcome data for the 4% of patients who left the area.

Case Definitions

The term schizophrenia was not used in asylum records until after 1924. From 1875 to 1924, psychotic patients were primarily diagnosed with "mania".[18] Accordingly a panel of clinicians covering the catchment areas from which these patients would now come reviewed records from all admissions for each patient and made retrospective diagnoses according to ICD-10 criteria.[17] All diagnoses were made before this study began. The diagnostic process is

outlined in greater detail in a paper investigating the admission incidence of psychoses across historical and contemporary periods.[19]

Patients were allocated to five diagnostic groups: schizophrenia (F20), schizoaffective disorder (F25), delusional disorder (F22), acute and transient psychoses (F23) and other patients who were difficult to classify, coded as unspecified non-organic psychosis (F29). One co-author (SCL) reviewed all affective and non-affective diagnoses covering 8 randomly picked years from the 1875-1924 period. The agreement concerning the schizophrenic diagnoses (F20) between the initial rater and SCL was 96.5%. To take account of the number of agreements expected by chance, we used Cohen's Kappa coefficient, a statistical measure of inter-rater agreement for categorical items.[20] The k coefficient (781 cases, two raters, for schizophrenia versus all other diagnoses) was 86%.

In the contemporary sample, all admissions of both patients with and without discharge codes for psychotic disorders were reviewed at regular monthly and subsequently 6-monthly intervals with both medical and nursing staff on the treating team to establish diagnoses. The diagnoses were reviewed following all subsequent admissions. These diagnoses therefore are not codes applied administratively and for instance not-unexpectedly only 49% of schizophrenic patients were given that diagnosis on first discharge.

For those unfamiliar with these methods, they greatly reduce the likelihood of false positive diagnoses. There has been some concern for example that patients who had children out of wedlock might have been admitted to asylums. Such admissions for "social" reasons happened in mid-twentieth century when admission procedures were a lot looser; they did not happen during this period in North Wales and if they had this approach would have detected them. The historical cases of schizophrenia central to this paper are therefore unlikely to contain any case that did not actually have schizophrenia.

Deaths

In the historical cohort, all deaths in hospital (N=764) were recorded in the patients' medical records. Of these, 58% had recorded post-mortems. In addition there were 10 patients who were discharged gravely ill to die at home. We have counted these patients as deaths in the year of discharge and assigned a cause of death consistent with the clinical picture outlined in

the records. There were 300 patients (28%) who were discharged recovered and healthy within the 10 years from the date of first admission, on whom there is no further data.

In following up patients in the contemporary cohort, all were tracked down using their NHS number, even when they had moved out of area. All deaths were established through coroner's records, along with contacts with the patient's general practitioner and treating team. The contemporary database was updated at regular three-monthly intervals, and accordingly all deaths were investigated and confirmed the year they happened. No patients were lost to follow-up.

Survival Analysis

To account for the different lengths of follow-up, primarily in the contemporary cohort, we have undertaken survival analyses on both historical and contemporary cohorts.[21] In the case of the historical cohort, patients discharged healthy are recorded as lost to follow-up. Our survival analysis de facto gives the same rate of death to those discharged healthy but lost to follow up as is found in the observed cohort. Because death from tuberculosis in particular was much commoner in hospital, this seems likely to under-estimate the survival probability in the historical cohort. We have therefore also undertaken a survival analysis in the historical cohort that assumes that no patients who were discharged died within the 10-year timeframe (best case scenario). The true result is likely to lie somewhat closer to the best case than to the observed outcomes.

Mortality Rates

We have used mortality data from 1900 to 1910 for England and Wales on which to base our calculations of Standardized Mortality Ratios (SMR) for 1875-1924. These data came from the Office of National Statistics; data before 1900 and for the period surrounding the Great War are not available.[22] For the historical sample we took the mean value of the years from 1901 to 1910 for each age and sex grouping. Using this group is likely to lead to higher SMRs in the historical sample than is warranted given a decline in mortality rates from 1875 to 1900 and greater mortality in the period from 1914 to 1920 linked to the Great War and the influenza epidemic of 1918-1920.

Mortality data for the contemporary sample came from the Office of National Statistics.[23] For the contemporary data we worked from available mortality data from 1994 to 2010. In the case

of contemporary suicides we have standardized deaths by suicide in all psychoses and for schizophrenia by age, sex and year against the deaths from suicide in Wales alone rather than deaths from suicide in England and Wales. Annual suicide statistics in both Wales and England include a proportion of open verdict deaths. We have taken this into account in calculating suicide specific SMRs.

When computing standardized mortality rates for successive years after year 1, in the contemporary sample, we removed all patients who died the previous year and have not included patients for whom we do not have full follow up data. This gives cohorts of 337 at year 2, 322 at year 3, 313 at year 4 and 288 at year 5. In the history sample we have similarly removed all patients who died from the calculations of mortality for subsequent years. We have then used person years at risk when calculating SMRs .

For the purposes of accounting for possible deaths in our recovered discharges from the historical cohort, when calculating standardised mortality rates, we have calculated two sets of figures. The first set assumes that patients discharged in apparent good health survived the remainder of the period of observation. A second set (worst case scenario) assumes that these apparently recovered and healthy patients died at the same rate in their year of discharge as the rate of death found in those remaining in hospital during the corresponding year of their illness. We have also assumed that those discharged continued to die at the rate observed in those remaining in hospital. The inferred deaths are added to the observed deaths to give a worst case scenario. This procedure seems likely to over-estimate the rate of death in the historical cohort.

Years of Life Lost

In both historical and contemporary cohorts we have calculated years of life lost. In the historical cohort we have taken life expectancy in the period 1901-1910 as the basis of our calculations. For patients admitted up to the age of 44 this has meant a projected life expectancy for males of 62 years and for females of 65 years; for males and females between 45 and over the figures were 68 and 71 years respectively. In the historical cohort the analysis is based on known age of death.

In the contemporary cohort we have observed years of life lost in the cohort of patients who have completed 10 years. Our sample size and the nature of the cohort does not permit a trend analysis across ages to establish projected life expectancies.

Results

This study is linked to a study looking at the incidence of admissions for schizophrenia and related psychoses and their outcomes in historical and contemporary periods. The study has identified 1074 cases of schizophreniform psychoses in the historical period and 355 cases in the contemporary period. In terms of admission incidence rates, we found an increase in the admission incidence for schizophrenia between 1875 and 1900 when standardised against population norms, and a drop in admission incidence for schizophrenia between 2005 and 2010, and finally a switch in gender ratios from an equal rate of male and female admissions in the 19th century to a rate of two males for each female admission in the contemporary sample.[19] The switch in gender ratios is of interest given the greater preponderance of female to male suicides in the contemporary mortality data.

Cause of Death

In Tables 1 and 2, we have laid out the deaths by diagnosis after 1, 5, and 10 years from first admission in the contemporary and historical samples. In Tables 3a & 3b we present the mean age of death by specific causes in both contemporary and historical samples. There is a clear difference in age of death in those dying from suicide compared with deaths from cardiovascular causes in the contemporary cohort, a clear difference in age of death for those diagnosed with schizophrenia compared with the ages of death for those other psychotic diagnoses in the contemporary cohort, and differences between age of death from tuberculosis and for instance cancer in the historical cohort.

In the case of deaths by suicide in the contemporary sample, the 16 cases comprised of 12 suicide, 3 open verdicts and one death by misadventure. The open verdicts were regarded by the treating teams as suicides. The death by misadventure involved an overdose on psychotropic drugs. We have accordingly classified these deaths with suicide rather than under the heading of “other”. Only one open verdict happened within the first year of admission, in a patient with schizophrenia.

In the historical cohort, many patients with schizophrenia spent their life in the hospital, so that we know the nature of their final illnesses. In total, 32 psychotic patients (25 with schizophrenia) died in hospital from cancer. Of these 32 deaths, 28 involved cancer of the gastro-intestinal tract. There was one breast cancer and no lung cancers. Based on the number of patient exposure years, the SMR for death from cancer in schizophrenia in this cohort was 3.49 (95% C.I., 2.25, 5.15) fold higher than the population norm at the time. As a control to these figures it can be noted that cancers were less frequently found in patients with severe melancholia during the same historical period.[24]

Tuberculosis was a hazard for patients admitted to the asylum. It was a particular hazard for younger patients, and especially those with schizophrenia, who show a spike in deaths from this cause 3-5 years after admission. The drop in mean age of death at year 5 in Table 2 reflects this. Table 3 shows a full break down of deaths by diagnosis and age. Calculating SMRs based on years exposure and deaths within the first 10 years of admission, gives an SMR of 9.37 (95% C.I., 7.64, 11.4) compared with the population in general, with the figures being twice as bad for women as for men. There were comparable death rates for tuberculosis in asylum patients with affective disorders (SMR 9.11) with women twice as badly affected as men, so this outcome does not appear to be diagnosis specific.

Survival Analysis

A survival analysis of the contemporary cohort (see Figure 1) for all psychoses shows a cumulative 10 year survival probability of 90% (90% C.I., 0.86, 0.92). For schizophrenia, the 10 year cumulative survival probability is 94% (90% C.I., 0.91, 0.96). For other psychoses the 10 year cumulative survival probability is 81% (90% C.I., 0.74, 0.87).

In the historical cohort, as outlined in methods, we have two analyses. Analyzing all discharges as dying at the same rate as those left in hospital produces 10 year cumulative survival probabilities for all psychoses of 69% (90% C.I., 0.66, 0.71); for schizophrenia of 69% (90% C.I., 0.66, 0.72) and for other psychoses of 63% (90% C.I., 0.57, 0.69). Analyzing observed deaths as though they were all deaths produces 10 year cumulative survival probabilities for all psychoses of 75% (90% C.I., 0.73, 0.77); for schizophrenia of 72% (90% C.I., 0.70, 0.75), and for other psychoses of 80% (90% C.I., 0.77, 0.83).

Standardized Mortality Rates

We have calculated standardized mortality ratios (SMR) for both the contemporary (see Table 4) and historical cohorts (Tables 5 & 6) for 1, 2, 3, 4 and 5 years from first admission. The contemporary SMRs in particular show an increase over population norms in the first year of admission. The rates thereafter remain elevated compared with population norms but fall toward rates reported by other studies. In terms of absolute numbers of deaths (Tables 1 & 2), there are more deaths in the historical cohort, but calculating SMRs shows contemporary mortality rates are as high as those found in the historical cohort.

The suicide specific SMRs in the contemporary cohort for year 1 for all psychoses is 133 (95% C.I., 58, 263) and for schizophrenia is 168 (95% C.I., 67, 346). The suicide specific SMR for years 1, 2, 3, 4, and 5 combined for all psychosis is 47 (95% C.I., 25, 81), and for schizophrenia is 51.5 (95% C.I., 25, 95). The suicide specific SMR for all psychoses for years 1-10 combined is 34 (95% C.I., 19, 55), and for schizophrenia is 35 (95% C.I., 18, 61).

There was one open verdict included in the year 1 figures, which is more likely than not to have been included in national figures as a suicide. In the case of the 10 year figures, there were in total 4 open verdicts. Excluding all of these would give a 10 year suicide specific SMR for all psychoses of 25 (95% C.I., 13, 44) and for schizophrenia of 23 (95% C.I., 10, 46).

Finally, in a parallel study of severe affective disorders we have found a similar increase in suicide rates in a contemporary compared to a historical cohort, along with deaths from tuberculosis in the historical cohort in those remaining in hospital for up to 5 years, but no increase in rates of death from cancer in the historical cohort.[24]

Years of Life Lost

In the historical cohort we have a large number of patients with confirmed deaths that allow estimates of years of life lost. For all psychoses years of life lost range from 9.8 years per patient in the confirmed death group to a possible 5.9 years per patient if those discharged died at the same rate as the rest of the population. If deaths from tuberculosis are removed the years lost drop markedly to 5.6 to 2.6 years for worst case and best case scenarios.

For schizophrenia in the historical cohort, the years of life lost range from 10.8 in the confirmed death group to 8.0 when discharged patients are included in the analysis. For other psychoses,

the years of life lost range from 6.8 years in the confirmed dead group to 2.5 years when extrapolated to include discharged patients.

In the contemporary cohort with complete 10 year follow up (N = 210), we have data on 143 patients with schizophrenia, and 67 with other psychoses. Patients with all psychoses lost 999 years between them. Patients with schizophrenia lost 613 years or 4.3 years each. Patients with other psychoses lost 5.8 years on average.

Discussion

In undertaking survival analyses and calculating standardized mortality ratios (SMRs) from contemporary and historical samples drawn from the same catchment area and diagnosed using the same criteria, we are able first to calculate historical rates of mortality, second to explore contemporary causes of mortality in a way not possible for other studies, and third to assess whether mortality rates in schizophrenia are getting worse over time.

This is the first attempt to calculate survival curves and standardized mortality rates for schizophrenia and related psychoses in an epidemiologically complete cohort of admissions from the late 19th and early 20th centuries. The survival analysis shows the absolute mortality in the historical period was higher than the absolute mortality today, but the SMRs in the historical cohort in fact overlap the SMRs for patients reported in more recent studies. If we can accept the projected 15-20 years of life lost from contemporary cohorts, then the actual years of life lost in our historical cohort are less than those lost now.[5, 11] If we remove tuberculosis as a cause of death, mortality rates for the historical cohort look very respectable compared to today's figures. It seems clear that one hazard of asylum care for younger people, particularly women, a century ago lay in the risk of contracting tuberculosis. Another hazard was lethal catatonia which seems likely to have accounted for most deaths from exhaustion.[25]

When comparing historical and contemporary SMRs for psychosis and for schizophrenia, the surprise is how comparable the figures are despite the modern elimination of tuberculosis. Calculating mortality rates at the end of their first year of admission in particular gives a higher mortality rate today than in the historical period.

Our contemporary SMRs at the end of the first year of admission and thereafter are more salient than but consistent with other findings in the contemporary literature. First, in all other reports there is a marked increase in mortality rates for patients with schizophrenia and related

psychotic disorders compared with population norms in the first year of admission.[26] Second, our SMR at 5 years across all diagnostic groups approach rates reported in cross-sectional studies.[10] Third, the greatest contribution to the elevation in mortality rates in our sample comes from suicide in the first year of admission in patients with schizophrenia and this finding is in line with other studies.[1, 6, 11]

When the data are examined by diagnostic group and according to the time from first admission in this fashion, the findings reveal patterns not apparent in both the schizophrenia and non-schizophrenia groups in cross-sectional studies. In cross-sectional studies, the impact of outcomes among first admissions for schizophrenia is likely to be missed as in these studies first admissions account for 15% or less of admissions for schizophrenic and related psychoses in any one year. As our data show, if the contribution from deaths in the first year are missed calculations of SMRs for schizophrenia will result in much lower estimates than those reported here.

The data on suicide in the historical and contemporary samples are strikingly different. In the historical records, it was mandatory for the admitting clinician to record suicide risk at admission and 25% of the historical patients at admission were considered suicidal or had threatened or attempted suicide. There is no requirement for clinicians today to record suicide risk on admission and thus comparable data do not exist for a modern sample but the rates of overt suicidality on admission for psychotic patients seem unlikely to be higher than 25%.

The lack of suicides in the historical sample raises a number of questions. Was there a bias against a diagnosis of suicide? In the case of historical patients admitted for severe depressive disorders, a number are clearly recorded as dying from suicide and as attempting suicide both in the asylum and soon after discharge so that there was no reticence about recording such verdicts for other patients at this time.[24] Furthermore the case notes of patients dying from tuberculosis and other causes contain clinical details consistent with these diagnoses. A bias against recording suicide verdicts in the schizophrenia group can probably be ruled out.

To have suicide as a cause of death you need to have opportunity to commit suicide. The registration of suicidal tendencies in the historic cohort did mean that patients were monitored. But schizophrenic and affective disorder patients were monitored in a comparable fashion and the affective disorder patients went on to commit suicide at close to expected rates whereas the schizophrenic patients did not. In addition, the monitoring of patients in the asylum was by the same methods used today. There was not an undue or unacceptable restriction of liberty by

today's standards. The patients with schizophrenia in the historical cohort spent 99% of their time at liberty working on the hospital farm, in the knitting rooms or kitchens, with ample opportunity to commit suicide if they wished.

A second issue is whether patients today are more severely ill than a century ago. This is possible but seems unlikely for a number of reasons. First some of the more malignant forms of the illness (hebephrenia/disintegrative psychosis and catatonic schizophrenia) were clearly present in the historical cohort but have close to disappeared now. Second all patients a century ago were detained compulsorily whereas a large number of patients today were admitted voluntarily – it is much easier for less severely ill patients to get admitted now. Third, patients today have immediate access to medication that for many can be expected to mitigate the most distressing aspects of their disorder. In the case of catatonic syndromes, benzodiazepines mean the disorder simply does not evolve as before; a higher proportion of these patients died in hospital historically than for any other form of psychosis (60% - see Table 2).

The importance of the historical cohort in this study is that it demonstrates that suicide is not an inherent risk of schizophrenia. The historical data suggest there is something about the modern delivery of care that contributes to suicide as an outcome, whether it stems from de-institutionalization, or from treatment. In contrast to schizophrenia suicide rates, the suicide rate for affective disorder patients in our historical sample is in line with expectations regarding the incidence of suicide in severe mood disorders and so institutionalization as such did not prevent suicides.[24, 27] We have also found increased suicide rates in contemporary affective disorder patients making it unlikely that the modern finding of increased suicide rates for schizophrenia stem from diagnostic leakage – that is the suicide rates in schizophrenia do not stem from misdiagnosed affective disorder patients.

Males are in general more likely to commit suicide than women, and in the contemporary schizophrenia sample there was a two-fold greater rate of male admissions, but the increased suicide rate in the contemporary sample does not stem from this source in that in the contemporary schizophrenia sample there was a greater proportion of female than male suicides.

If suicide risk is not inherent in the illness, another possibility lies in deinstitutionalization. As in our data, Mortensen and Juel[1] flagged up the incident year of a schizophrenic illness as problematic. They suggested that the high rates of suicide at this time might stem from de-

institutionalization. However more recent data from the Nordic countries argue against de-institutionalization as the cause of the problem, as life expectancies have slightly increased (or at least not fallen further) as de-institutionalization has progressed.[11] Our data also argue against de-institutionalization in that suicide rates are increased in both patients who were once institutionalized but are not now (schizophrenia) and patients who were never subject to long-term institutionalization (affective disorder patients). Moreover, contemporary patients with schizophrenia had a mean duration of admission lasting weeks rather than months and hence institutionalization cannot have set in.

Allied to de-institutionalization are issues of stigma, lack of family support, or untreated comorbid depression. It would clearly be difficult to discount these possibilities if the suicides were happening 5 or 10 years into the illness. But the fact that suicide is happening primarily in the first year, before stigma has set in, or supports have been lost, make such factors less likely to be sole determinants of suicides.

Wahlbeck et al report SMRs for suicide from national cohorts of patients recruited in Denmark, Finland and Sweden of 20.6 for men and 36.6 for women.[11] These figures map very closely on to the suicide specific SMR for schizophrenia reported here for years 1-10 of follow up (35) but are 5 times lower than the rates for all schizophrenia in the incident year (168). Removing all suicides from the contemporary cohort gives an SMR for schizophrenia of 1.1 (95% C.I. 0.01, 6.4), and of 1.9 (95% C.I., 1.0, 3.4) for all psychoses.

If the trigger to suicide does not lie in the effects of de-institutionalization and related losses, and is not inherent in the disease, the remaining option lies with treatment. High rates of suicide in the first year or early years of treatment, across diagnostic groups, are consistent with an initial exposure of vulnerable individuals to the dysphoric effects of antipsychotic drugs. The elimination of individuals at risk to such effects would produce the drop in SMR over time seen in our study. The antipsychotics are in fact the only element of the picture to have been shown in placebo controlled clinical trials to be linked to an excess of suicides and suicidal acts in psychosis, although the data are of poor quality.[28] A recent observational study[29] has also linked benzodiazepine usage to suicidal deaths in psychotic patients.[29]

Removing suicides leaves an SMR of 1.9 (95% C.I., 1.0, 3.4) for all psychoses. This maps very well onto figures generally cited for mortality in schizophrenia drawn from samples that contain subjects later in the trajectory of their illness. These deaths have been linked to an increase in risk from cardiovascular causes and there are indications that this is a particular hazard for older

subjects. Our data from non-schizophrenic psychoses support this. The survival analysis in the contemporary cohort makes it clear that these other areas of hazard lie primarily in the non-schizophrenic cohort.

We have found high mortality rates in the contemporary sample for patients with Acute and Transient Psychoses (F23) (Table 1). This group of patients has been rarely looked at. The data we report is consistent with other studies.[2, 25] In this group over half the mortality stems from cardiovascular causes (Table 3b).

Two observations stem from this. First, patients with acute and transient psychoses often get diagnoses of schizophrenia. Studies that do not distinguish between these two groups will on the basis of our figures have increased estimates of cardiovascular risk in schizophrenia. Second in our cohort, patients with a diagnosis of acute and transient psychosis fall into two groups, one younger and the other older. It is the older patients in this group who died from the cardiovascular causes. The average age of death in these patients was 63 years. Consistent with this, cardiovascular deaths also featured prominently in the contemporary cohort in patients with delusional disorders (F22), where the average age at death was 74 years.

Age is therefore a significant contributor to these outcomes. The antipsychotic group of drugs now come with clear warnings of the risk of cardiovascular problems in patients over the age of 65 but the interplay between treatment and age is uncertain in that a proportion of the F23 group will have lost contact with the mental health services and might not have been on treatment. Having made this point, it is clear that placebo-controlled trials in the elderly show an excess of mortality primarily from cardiovascular causes in those on active treatment.[15, 16] The debate about using antipsychotics in the elderly hitherto has focussed primarily on their use in patients with dementia but these figures suggest that attempts should be made to establish contributory risk factors in all older subjects.

These data also have implications for projected years of life lost in patients with schizophrenia. Our data open up the possibility that estimates based on diagnoses that fail to distinguish between schizophrenia and acute and transient psychoses or delusional disorders may substantially over-estimate the years of life lost in schizophrenia proper.

For instance all cancers in the contemporary cohort came from the delusional disorder or acute and transient psychosis group. This raises the possibility that these cancers antedated and contributed to the development of rather than stemmed from these mental disorders or their

treatment. This interpretation is consistent with findings we have reported for severe depressive disorders also.[23]

While data from the contemporary cohort offers no support for psychosis or its treatment as a cause of cancer, the incidence of gastro-intestinal cancers is a striking feature of the historical data. There was only one breast cancer and no lung cancers, while 28 of the 32 cancers were related to the gastro-intestinal tract. The official mortality figures for 1910 do not categorize mortality in terms of specific cancers to the extent that would permit a conclusive analysis of these data but it is worth noting that in 1910 the commonest cancers in England and Wales were of the mouth, gut and abdominal organs. Ovarian and breast cancers were commoner than found in our sample. Cancers of other bodily systems were filed under other, and were comparatively rare.

A majority of hospitalized patients with suspected cancers had post-mortems and it seems possible therefore that a proportion of the increased frequency of cancer diagnosis is an artefact of post-mortems. There was however considerable concern about food adulteration in the 19th and early 20th centuries raising questions about possible links between this and gastro-intestinal cancer as an outcome.

In summary, this study reports consistent elevations in SMRs in schizophrenia and non-affective psychoses over a century with the modern data in some respects worse than the historical data. Our data do, however, caution the need to distinguish between first episode and other admissions in studies of projected life expectancy. More generally, while it is fashionable to look now at mortality as an outcome, it must be emphasized that patients today live life outside the asylum in a way they did not do a century ago. When the antipsychotics were introduced, the benefits of recovery and possible discharge were widely viewed as warranting a potential reduction in life expectancy.[30]

Other studies have suggested that patients with schizophrenia are dying prematurely because of lack of access to healthcare resources and because of lifestyle factors, which support a case that interventions in these domains may improve life expectancy. The utility of the current data is that they point to particular hazards arising at clear periods of risk and this knowledge might enable us to get the benefits of treatment without such a high price in serious adverse events. In particular they suggest a concentration on the first years after admission in younger patients and a simple expedient of checking more closely with patients whether their medication does in

fact suit them and in the case of patients with dysphoric responses a willingness to change drug to find one that suits best.

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Competing Interests

The authors of this study declare they have no competing interests as regards the subject matter of this study.

Ethics Statement:

This study was approved by the North West Wales ethics committee.

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Legend: Figure 1

In the History Cohort we have calculated observed deaths with patients discharged and lost to follow up dying at the same rate as those remaining in hospital (History Survival) and also estimated survival curves if those lost to follow up die at the population rate rather than the hospitalized rate (History Best Survival)

Author Contribution:

Prof David Healy: principal investigator and primary author;
Dr Joanna Le Noury: data collection, analysis, study write up and review;
Ms Margaret Harris: data collection, analysis, study write up and review;
Dr Mohammed Butt: data analysis, study write up and review;
Dr Stefanie Linden: data analysis, study write up and review;
Mr Chris Whitaker: principal statistician;
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Dr Anthony P Roberts: study write up and review.

Data sharing statement:

Dataset available from the corresponding author, David Healy, at david.healy54@googlemail.com

Table 1:
Contemporary Sample:
Cause of Death by Diagnosis

Cause of death	Schizophrenia (F20/ F25) N = 227			Delusional Disorder (F22) N = 48			Acute & Transient Psychosis (F23) N = 66			Other Psychoses F29 N = 14			All Psychoses N = 355		
	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y
Suicide/Open	7	10	12	0	0	1	1	2	2	0	1	1	8	13	16
Cardiovascular	0	0	0	0	2	3	0	3	4	1	1	1	1	6	8
Respiratory	0	0	0	0	1	1	0	0	0	0	0	0	0	1	1
Cancer	0	0	0	0	1	2	1	2	2	0	1	1	1	4	5
Other	0	1	1	0	0	2	0	0	0	0	0	0	0	1	3
All causes	7	11	13	0	4	9	2	7	8	1	3	3	10	25	33
Average age of death	29.5	31.3	31.6	-	78.6	72.7	54.7	60.3	60.9	39.5	45.9	45.9	35.6	48.7	51.2

Table 2:
Historical Sample:
Cause of Death by Diagnosis

Cause of death	Schizophrenia F20/F25 N=605			Delusional Disorder F22 N=143			Acute & Transient Psychosis F23 N=143			Other Psychoses F29 N=135			Catatonia F06.1/F20.2 N=48			All Psychoses N=1074		
	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y
Suicide	1	1	2	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2
Cardiovascular	0	1	17	1	7	12	0	0	1	2	6	9	1	3	5	4	17	44
Respiratory	5	14	20	1	5	9	2	4	4	1	2	6	3	5	6	12	30	45
Cancer	0	0	0	1	1	2	0	0	0	0	2	2	0	0	0	1	3	4
TB	6	51	82	0	4	8	2	2	2	1	5	6	1	5	5	10	67	103
Dysentery	1	4	8	0	1	1	0	0	1	2	2	2	3	3	3	6	10	15
Other	2	10	24	1	5	8	3	3	3	3	6	8	7	9	10	16	33	53
All causes	15	81	153	4	23	40	7	9	11	9	23	33	15	25	29	50	161	266
Average age of death	40.4	37.0	45.6	49.5	55.6	58.4	40.5	43.3	46.2	48.2	51.2	56.6	45.7	43.3	44.7	44.9	46.1	50.3

('Other' causes of death in the historical sample include 'exhaustion', septicaemia, kidney disease and erysipelas.

TABLE 3 A
SCHIZOPHRENIA:
CAUSES OF AND AGE AT DEATH – CONTEMPORARY AND HISTORICAL SAMPLES

Age group	Cause of death	Contemporary sample			Historical sample		
		Yr1 (n=227)	Yrs2-5 (n=203)*	TOTAL 5yrs (n=203)*	Yr1 (n=653)	Yr2-5 (n=653)	TOTAL 5yrs (n=653)
15-44	TB	-	-	-	6	42	48
	Respiratory	-	-	-	5	7	12
	Cardiovascular	-	-	-	-	-	-
	Cancer	-	-	-	-	-	-
	Other	-	1	1	4	10	14
	Suicide	6	2	8	1	-	1
45-74	TB	-	-	-	1	7	8
	Respiratory	-	-	-	3	4	7
	Cardiovascular	-	-	-	1	3	4
	Cancer	-	-	-	-	-	-
	Other	-	-	-	9	3	12
	Suicide	1	1	2	-	-	-
75+	TB	-	-	-	-	-	-
	Respiratory	-	-	-	-	-	-
	Cardiovascular	-	-	-	-	-	-
	Cancer	-	-	-	-	-	-
	Other	-	-	-	-	-	-
	Suicide	-	-	-	-	-	-
All ages	**All deaths**	**7**	**4**	**11**	**30**	**76**	**106**
	All deaths (excl TB)	**7 (3.08%)**	**4 (1.97%)**	**11 (5.41%)**	**24 (3.68%)**	**34 (5.21%)**	**58 (8.88%)**

TABLE 3 B
OTHER PSYCHOSES :
CAUSES OF AND AGE AT DEATH – CONTEMPORARY AND HISTORICAL SAMPLES

Age group	Cause of death	Contemporary sample			Historical sample		
		Yr1 (n=128)	Yrs2-5 (n=104)*	TOTAL 5yrs (n=104)*	Yr1 (n=421)	Yr2-5 (n=421)	TOTAL 5yrs (n=421)
15-44	TB	-	-	-	3	4	7
	Respiratory	-	-	-	3	1	4
	Cardiovascular	1	1	2	-	1	1
	Cancer	-	-	-	-	-	-
	Other	-	-	-	2	1	3
	Suicide	1	1	2	-	-	-
45-74	TB	-	-	-	-	4	4
	Respiratory	-	-	-	1	6	7
	Cardiovascular	-	2	2	3	9	12
	Cancer	1	3	4	1	2	3
	Other	-	-	-	7	7	14
	Suicide	-	1	1	-	-	-
75+	TB	-	-	-	-	-	
	Respiratory	-	1	1	-	-	-
	Cardiovascular	-	2	2	-	-	-
	Cancer	-	-	-	-	-	-
	Other	-	-	-	-	-	-
	Suicide	-	-	-	-	-	-
All ages	**All deaths**	**3**	**11**	**14**	**20**	**35**	**55**
	All deaths (excl TB)	**3 (2.34%)**	**11 (10.57%)**	**14 (13.46%)**	**17 (4.03%)**	**27 (6.41%)**	**44 (10.45%)**

- **Figures exclude patients with incomplete 5 year histories**

Table 4: Standardized Mortality Ratios
Contemporary Sample

		SMR Y 1	SMR Y2	SMR Y3	SMR Y4	SMR Y5	Average 5yr SMR
Male	**All psychosis**	11.1 (CI 4.4, 23.0) **N = 218**	1.0 (CI 1.6, 6.6) **N = 208**	3.5 (CI 0.3, 13.0) **N = 203**	3.8 (CI 0.4, 13.9) **N = 197**	5.9 (CI 1.1, 17.2) **N = 180**	4.9 **(C.I., 0.85, 15.2)**
	Schizophrenia	28.6 (CI 7.4, 73.9) **N = 150**	1.0 (CI 7.4, 30.2) **N = 144**	7.9 (CI 0.003, 45.1) **N = 143**	16.7 (CI 1.6, 61.3) **N = 139**	1.0 (CI 8.7, 35.6) **N = 127**	11.2 **(C.I., 0.3, 51.0)**
Female	**All psychosis**	4.3 (CI 0.8, 12.7) **N = 136**	7.4 (CI 2.3, 17.3) **N = 129**	1.0 (CI 1.6, 6.5) **N = 119**	1.7 (CI 0.001, 9.8) **N = 116**	3.5 (CI 0.3, 12.9) **N = 108**	3.5 **(C.I., 0.4, 12.2)**
	Schizophrenia	44.8 (CI 8.1, 126.9) **N = 76**	16.7 (CI 0.01, 95.5) **N = 73**	1.0 (CI 16.0, 65.3) **N = 70**	1.0 (CI 16.0, 65.3) **N = 69**	1.0 (CI 18.5, 75.4) **N = 65**	13.2 **(C.I., 0.1, 89.2)**
Total	**All psychosis**	**7.5** (CI 3.6, 13.9) **N = 355**	**3.9** (CI 1.2, 9.3) **N = 337**	**1.7** (CI 0.2, 6.3) **N = 322**	**2.7** (CI 0.5, 8.0) **N = 313**	**4.6** (CI 1.5, 10.9) **N = 288**	**4.2 (C.I., 1.3, 9.9)**
	Schizophrenia	**33.3** (CI 13.2, 69.1) **N = 227**	**5.3** (CI 0.002, 30.2) **N = 217**	**5.4** (CI 0.002, 30.7) **N = 213**	**11.1** (CI 1.0, 40.9) **N = 208**	**1.0** (CI 5.9, 24.2) **N = 192**	**11.8 (C.I., 1.4, 41.3)**

Table 5: Standardized Mortality Ratios
History Sample – Observed Deaths

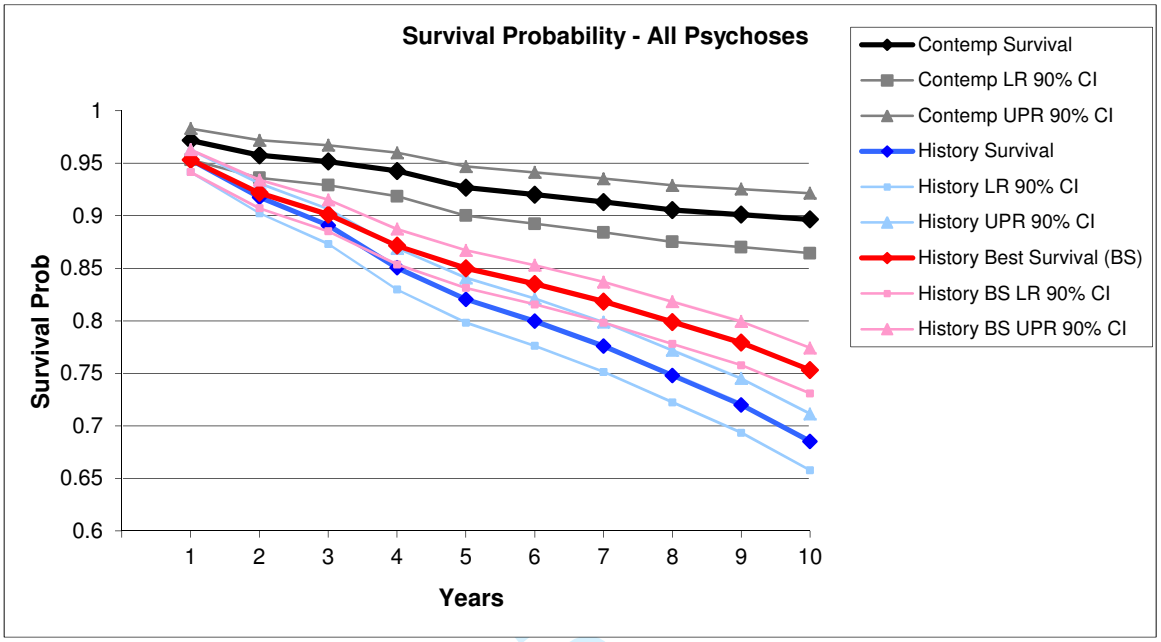
		SMR Y 1	SMR Y2	SMR Y3	SMR Y4	SMR Y5	Average 5yr SMR
Male	**All psychosis**	2.9 (CI 1.7, 4.6) **N = 516**	2.8 (CI 1.5, 5.0) **N = 385**	1.9 (CI 0.7, 3.8) **N = 354**	3.5 (CI 1.9, 6.0) **N = 337**	3.6 (CI 1.8, 6.2) **N = 313**	2.9 **(C.I., 2.2, 3.7)**
	Schizophrenia	2.1 (CI 0.7, 4.9) **N = 301**	2.8 (CI 1.0, 6.2) **N = 273**	3.0 (CI 1.1, 6.5) **N = 258**	4.1 (CI 1.8, 8.1) **N = 246**	3.7 (CI 1.5, 7.7) **N = 234**	3.1 **(C.I., 2.1, 4.4)**
Female	**All psychosis**	5.5 (CI 3.8, 7.8) **N = 558**	5.3 (CI 3.3, 8.0) **N = 410**	4.1 (CI 2.3, 6.8) **N = 366**	5.6 (CI 3.4, 8.7) **N = 340**	3.7 (CI 1.8, 6.6) **N = 306**	5.0 **(C.I., 4.0, 6.0)**
	Schizophrenia	4.3 (CI 2.0, 7.9) **N = 304**	5.7 (CI 2.9, 10.0) **N = 274**	3.7 (CI 1.5, 7.6) **N = 253**	7.0 (CI 3.7, 12.1) **N = 242**	4.1 (CI 1.6, 8.5) **N = 222**	4.9 **(C.I., 3.7, 6.5)**
Total	**All psychosis**	**4.2** (CI 3.1, 5.5) **N = 1074**	**4.1** (CI 2.8, 5.7) **N = 795**	**3.0** (CI 1.9, 4.5) **N = 720**	**4.5** (CI 3.1, 6.4) **N = 677**	**3.6** (CI 2.3, 5.4) **N = 619**	**3.9 (C.I., 3.3, 4.6)**
	Schizophrenia	**3.2** (CI 1.8, 5.2) **N = 605**	**4.3** (CI 2.5, 6.8) **N = 547**	**3.3** (CI 1.8, 5.7) **N = 511**	**5.5** (CI 3.4, 8.5) **N = 488**	**3.9** (CI 2.1, 6.6) **N = 456**	**4.0 (C.I., 3.5, 5.0)**

Table 6: Standardized Mortality Ratios
History Sample – Observed & Inferred Deaths

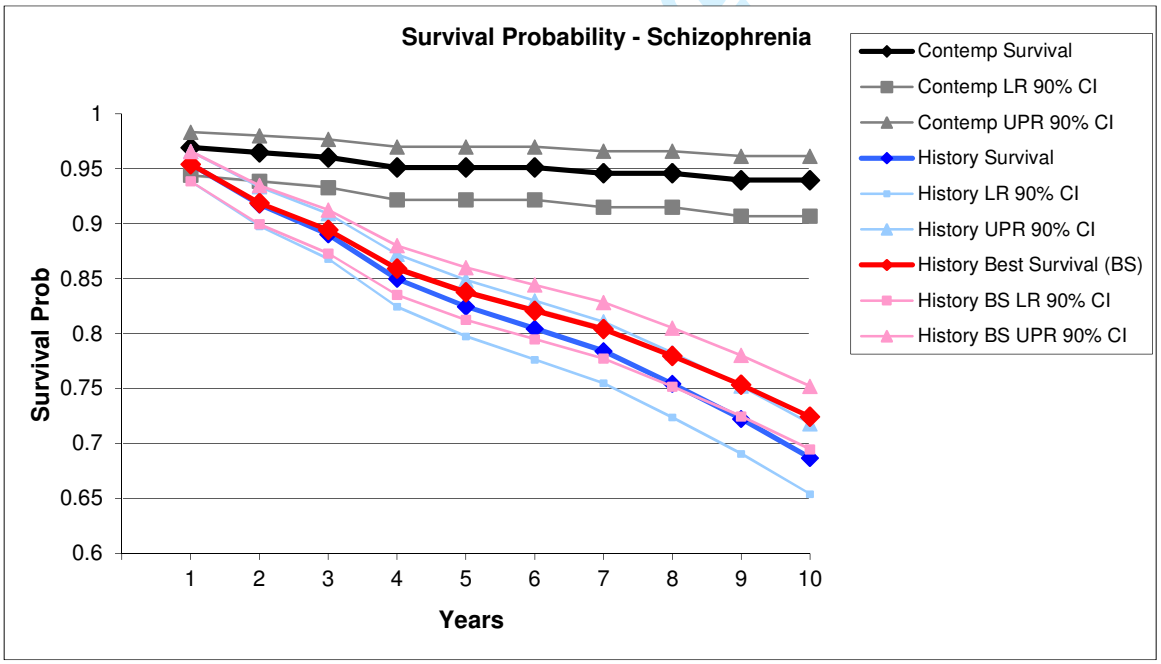
		SMR Y 1	SMR Y2	SMR Y3	SMR Y4	SMR Y5	Average 5yr SMR
Male	**All psychosis**	3.6 (CI 2.2, 5.4) **N = 516**	3.8 (CI 2.1, 6.1) **N = 385**	2.6 (CI 1.3, 4.9) **N = 354**	5.2 (CI 3.1, 8.1) **N = 337**	5.3 (CI 3.2, 8.5) **N = 313**	4.0 **(C.I., 3.2, 5.0)**
	Schizophrenia	2.5 (CI 0.9, 5.5) **N = 301**	3.3 (CI 1.3, 6.8) **N = 273**	3.5 (CI 1.4, 7.2) **N = 258**	4.6 (CI 2.1, 8.8) **N = 246**	4.2 (CI 1.8, 8.4) **N = 234**	3.6 **(C.I., 2.5, 4.9)**
Female	**All psychosis**	6.7 (CI 4.8, 9.2) **N = 558**	7.0 (CI 4.7, 10.1) **N = 410**	5.7 (CI 3.6, 8.8) **N = 366**	8.2 (CI 5.5, 11.9) **N = 340**	5.7 (CI 3.3, 9.2) **N = 306**	6.7 **(C.I., 5.6, 8.0)**
	Schizophrenia	4.7 (CI 2.3, 8.4) **N = 304**	6.2 (CI 3.3, 10.6) **N = 274**	4.2 (CI 1.8, 8.3) **N = 253**	8.1 (CI 4.5, 13.4) **N = 242**	4.7 (CI 2.0, 9.3) **N = 222**	5.6 **(C.I., 4.2, 7.2)**
Total	**All psychosis**	**5.1** (CI 3.9, 6.6) **N = 1074**	**5.4** (CI 3.9, 7.2) **N = 795**	**4.2** (CI 2.8, 5.9) **N = 720**	**6.6** (CI 4.9, 8.8) **N = 677**	**5.5** (CI 3.8, 7.7) **N = 619**	**5.3 (C.I., 4.6, 6.1)**
	Schizophrenia	**3.6** (CI 2.1, 5.7) **N = 605**	**4.7** (CI 2.9, 7.3) **N = 547**	**3.8** (CI 2.1, 6.3) **N = 511**	**6.3** (CI 4.0, 9.4) **N = 488**	**4.5** (CI 2.5, 7.2) **N = 456**	**4.5 (C.I., 3.7, 5.6)**

Figure 1:

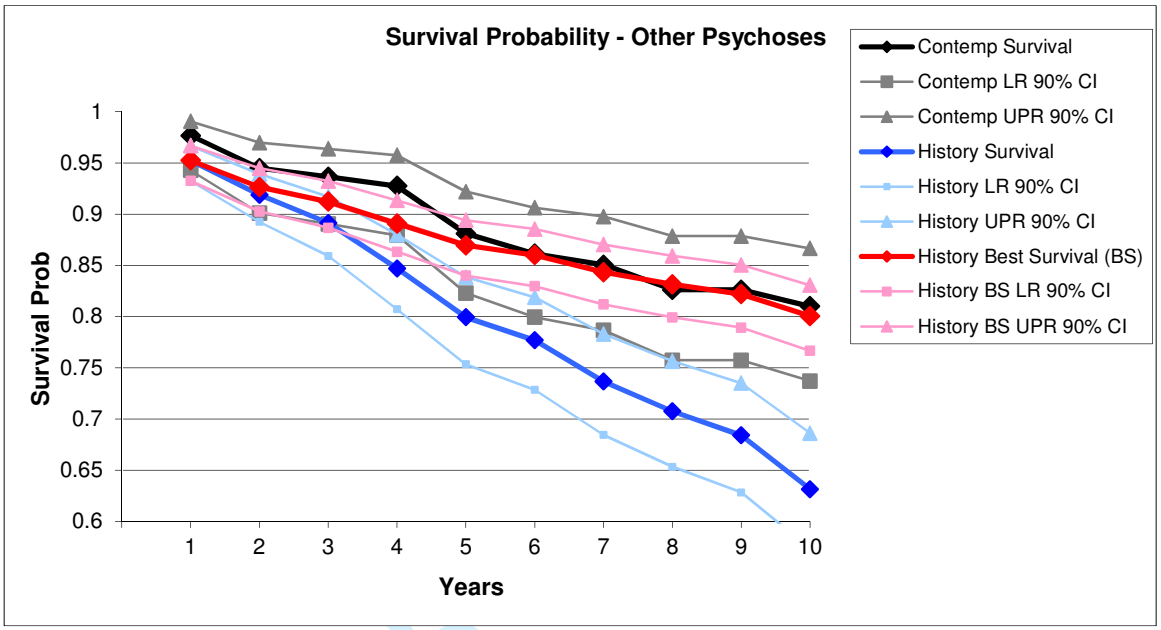
a) Survival Probabilities in All Psychoses in Contemporary & Historical Cohorts



b) Survival Probabilities in Schizophrenia (F20, 25 & 061) in Contemporary & Historical Cohorts



c) Survival Probabilities in Other Psychoses (F22, 23 & 29) in Contemporary & Historical Cohorts



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Mortality in Schizophrenia and Related Psychoses: Data from Two Cohorts, 1875-1924 & 1994-2010.

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Mortality in Schizophrenia and Related Psychoses: Data from Two Cohorts, 1875-1924 & 1994-2010

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Abstract

Objective: To investigate mortality rates in schizophrenia and related psychoses.

Design: Data from two epidemiologically complete cohorts of patients presenting for the first time to mental health services in North Wales for whom there are at least 1, and up to 10 year follow up data have been used to calculate survival rates and standardized mortality rates for schizophrenia and related psychoses.

Setting: The North Wales Asylum Denbigh (archived patient case notes) and the North West Wales District General Hospital psychiatric unit.

Population: Cohort 1: The North Wales Asylum Denbigh (archived patient case notes). Of 3168 patients admitted to the North Wales Asylum Denbigh 1875-1924, 1074 had a schizophrenic or related psychosis. Cohort 2: Patients admitted between 1994 and 2010 to the North West Wales District General Hospital psychiatric unit, of whom 355 had first admissions for schizophrenia or related psychoses.

Results: We found a 10 year survival probability of 75% in the historical cohort and a 90% survival probability in the contemporary cohort with a 4-fold increase in standardised mortality rates in schizophrenia and related psychoses in both historical and contemporary periods. Suicide is the commonest cause of death in schizophrenia in the contemporary period (SMR 35), while tuberculosis was the commonest cause historically (SMR 9). In the contemporary data, deaths from cardiovascular causes arise in the elderly and deaths from suicide in the young.

Conclusions: Contemporary mortality rates in schizophrenia and related psychoses are high but there are particular hazards and windows of risk that enable interventions. The data point to possible interventions in the incident year of treatment that could give patients with schizophrenia a normal life expectancy.

Article Summary

Article Focus

The question of possible increases in mortality in psychosis is a current issue of concern, with both suicide and increased cardiovascular risk noted. It is know that the initial year after a diagnosis of schizophrenia is a point of high risk.

Key Message

In North Wales, access to two epidemiologically complete case registers makes it possible to demonstrate that suicide is not inherent in schizophrenia and that cardiovascular deaths are confined to elderly patients, who typically do not have a schizophrenia diagnosis.

Tackling the problem of suicides in the first year of schizophrenia has the potential to restore life expectancy to normal in this illness.

Strengths of the Study

This study has unique access to a large and complete cohort of unmedicated psychotic patients, which makes it possible to separate the contributions of the illness and its treatments to mortality. The study also offers a first rigorous estimate of historical mortality in serious mental illness. The cohort design of the study highlights factors that cross-sectional studies miss.

Limitations of the Study

The size of the contemporary cohort, duration of follow-up and number of deaths preclude definitive statements about mortality.

Introduction

There is growing interest in outcomes for schizophrenia and related psychoses, fuelled by consistent reports of an apparent doubling or tripling of mortality rates, along with significant reductions in life expectancy.[1-11] A double or tripling of mortality rates, equates in the case of schizophrenia to a loss of approximately 15 years of life expectancy.[11] As reported, mortality stems variously from natural causes, especially cardiovascular disorders[2, 7, 10] and from unnatural causes in particular suicide.[1, 3, 11]

After their introduction in the 1950s, the antipsychotic drugs were seen as having a beneficial effect on mortality rates in psychosis.[12, 13] However mortality rates now appear to be increasing[10, 14] and this has led to concerns that antipsychotics with adverse cardiovascular profiles could aggravate this trend, with particular concerns for the elderly.[15. 16]

The majority of studies have been cross-sectional in design. They also lack data on patients not treated with antipsychotic medication. These factors make it difficult to pinpoint the effects of treatment and hinder efforts to devise interventions for risks that may arise at different stages of an illness. Owing to the geographical and economic constraints imposed by North West Wales, we have been able to design a study that addresses some of these issues, and overcomes selection biases. We have logged all admissions for schizophrenia and related non-affective psychoses 1994 to 2010, and followed up all admissions during this period. We also have a database of all admissions to the North Wales asylum in Denbigh between 1875 and 1924 complete with subsequent clinical records and thus have data on causes of mortality in an untreated cohort of psychotic patients. Finally we have separated delusional disorder, acute and transient psychoses and schizophrenia in both historical and contemporary databases in an effort to link specific hazards to clinical syndromes. The resulting databases allow different perspectives to be brought to bear on the data arising from other studies.

Method

We have used two datasets to look at outcome data for schizophrenia and other non-affective psychoses drawn from the periods 1875-1924 and 1994-2010. The methods used for case definition are described in detail in an accompanying article on the incidence of psychoses during these two periods.[17]

Patients in both historical and contemporary cohorts were allocated to five diagnostic groups: schizophrenia (F20), schizoaffective disorder (F25), delusional disorder (F22), acute and transient psychoses (F23) and other patients who were difficult to classify, coded as unspecified non-organic psychosis (F29). One co-author (SCL) reviewed all affective and non-affective diagnoses covering 8 randomly picked years from the 1875-1924 period. The agreement concerning the schizophrenic diagnoses (F20) between the initial rater and SCL was 96.5%. To take account of the number of agreements expected by chance, we used Cohen's Kappa coefficient, a statistical measure of inter-rater agreement for categorical items.[18] The k coefficient (781 cases, two raters, for schizophrenia versus all other diagnoses) was 86%.

Deaths

In the historical cohort, all deaths in hospital (N=764) were recorded in the patients' medical records. Of these, 58% had recorded post-mortems. In addition there were 10 patients who were discharged gravely ill to die at home. We have counted these patients as deaths in the year of discharge and assigned a cause of death consistent with the clinical picture outlined in the records. There were 300 patients (28%) who were discharged recovered and healthy within the 10 years from the date of first admission, on whom there is no further data.

We followed up contemporary patients, using their NHS number, even when they had moved out of area. All deaths were established through coroner's records, along with contacts with the patient's general practitioner and treating team. The contemporary database was updated at regular three-monthly intervals, and accordingly all deaths were investigated and confirmed the year they happened. No patients were lost to follow-up.

Survival Analysis

To account for the different lengths of follow-up, primarily in the contemporary cohort, we have undertaken survival analyses on both historical and contemporary cohorts.[19]In the case of the historical cohort, a survival analysis gives patients discharged healthy and lost to follow-up the same rate of death as is found in the observed cohort. Because death from tuberculosis in particular was much commoner in hospital, this under-estimates the survival probability in discharged patients. We have therefore undertaken a further analysis in the historical cohort that assumes no recovered patients died within the 10-year timeframe (best case scenario). The true result is likely to lie somewhat closer to the best case than to the observed outcomes.

Mortality Rates

We have used mortality data from 1900 to 1910 for England and Wales on which to base our calculations of Standardized Mortality Ratios (SMR) for 1875-1924, as data before 1900 and for the period surrounding the Great War are not available.[20] For the historical sample we took the mean value of the years from 1901 to 1910 for each age and sex grouping. Given a decline in mortality rates from 1875 to 1900 and greater mortality between 1914 and 1920 linked to the Great War and the influenza epidemic of 1918-1920, the 1901-1910 group is likely to lead to higher SMRs in the historical sample than is warranted

For the contemporary data we worked from available mortality data from 1994 to 2010. [21] In the case of contemporary suicides we have standardized deaths by suicide in all psychoses and for schizophrenia by age, sex and year against the deaths from suicide in Wales alone rather than deaths from suicide in England and Wales. Annual suicide statistics in both Wales and England include a proportion of open verdict deaths. We have taken this into account in calculating suicide specific SMRs.

When computing standardized mortality rates for successive years, we removed all patients who died the previous year and have not included patients for whom we do not have full follow up data. This gives contemporary cohorts of 337 at year 2, 322 at year 3, 313 at year 4 and 288 at year 5. We have then used person years at risk when calculating SMRs.

For the purposes of accounting for possible deaths in our recovered discharges from the historical cohort, we have calculated two sets of SMRs. A best case scenario assumes that patients discharged in apparent good health survived the remainder of the period of observation. A worst case scenario assumes that these recovered and healthy patients died at the same rate in subsequent years as those remaining in hospital. This procedure seems likely to over-estimate the rate of death in the historical cohort.

Years of Life Lost

In both historical and contemporary cohorts we have calculated years of life lost. In the historical cohort we have taken life expectancy in the period 1901-1910 as the basis of our calculations. For patients admitted up to the age of 44 this has meant a projected life expectancy for males of 62 years and for females of 65 years; for males and females between 45 and over the figures

were 68 and 71 years respectively. In the historical cohort the analysis is based on known age of death.

In the contemporary cohort we have observed years of life lost in the cohort of patients who have completed 10 years. Our sample size and the nature of the cohort does not permit a trend analysis across ages to establish projected life expectancies.

Results

This study is linked to a study looking at the incidence of admissions for schizophrenia and related psychoses that identified 1074 cases in the historical period and 355 cases in the contemporary period. We found an increase in the admission incidence for schizophrenia between 1875 and 1900 when standardised against population norms, a drop in admission incidence for schizophrenia between 2005 and 2010, and a switch in gender ratios from an equal rate of male and female admissions in the 19th century to a rate of two males for each female admission in the contemporary sample.[17]

Cause of Death

Causes of death by diagnosis after 1, 5, and 10 years from first admission in the contemporary and historical samples are laid out in Tables 1 and 2.

There is a clear difference in age of death in those dying from suicide compared with deaths from cardiovascular causes and a clear difference in age of death for those diagnosed with schizophrenia compared with the ages of death for those other psychotic diagnoses in the contemporary cohort. There are differences between age of death from tuberculosis and cancer in the historical cohort. To explore the interaction between age, diagnosis and cause of death we have laid out the mean age of death by specific causes in both contemporary and historical samples in Tables 3a and 3b.

In the case of contemporary suicides, the 16 deaths comprised of 12 suicide, 3 open verdicts and one death by misadventure. The open verdicts were regarded by the treating teams as suicides. The death by misadventure involved an overdose on psychotropic drugs. We have accordingly classified these deaths with suicide rather than under the heading of “other”. Only one open verdict happened within the first year of admission, in a patient with schizophrenia.

In the historical cohort, many patients with schizophrenia spent their life in the hospital, so that we know the nature of their final illnesses. In total, 32 psychotic patients (25 with schizophrenia) died in hospital from cancer. Of these 32 deaths, 28 involved cancer of the gastro-intestinal tract. There was one breast cancer and no lung cancers.

Tuberculosis was the greatest hazard for patients admitted to the asylum, especially for younger patients, who show a spike in deaths from this cause 3-5 years after admission. The drop in mean age of death at year 5 in Table 2 reflects this. Table 3 shows a full break down of deaths by diagnosis and age.

Survival Analysis

A survival analysis of the contemporary cohort for all psychoses shows a cumulative 10 year survival probability of 90% (90% C.I., 0.86, 0.92) (Figure 1a). For schizophrenia, the 10 year cumulative survival probability is 94% (90% C.I., 0.91, 0.96) (Figure 1b). For other psychoses the 10 year cumulative survival probability is 81% (90% C.I., 0.74, 0.87) (Figure 1c).

In the historical cohort, analyzing all discharges as dying at the same rate as those left in hospital produces 10 year cumulative survival probabilities for all psychoses of 69% (90% C.I., 0.66, 0.71); for schizophrenia of 69% (90% C.I., 0.66, 0.72) and for other psychoses of 63% (90% C.I., 0.57, 0.69). Analyzing observed deaths as though they were all deaths (best case scenario) produces 10 year cumulative survival probabilities for all psychoses of 75% (90% C.I., 0.73, 0.77); for schizophrenia of 72% (90% C.I., 0.70, 0.75), and for other psychoses of 80% (90% C.I., 0.77, 0.83).

Standardized Mortality Rates

We have calculated standardized mortality ratios (SMR) for contemporary (see Table 4) and historical cohorts (Tables 5 & 6) for 1, 2, 3, 4 and 5 years from first admission. The contemporary SMRs show a marked increase over population norms in the first year of admission. The rates thereafter remain elevated compared with population norms but fall toward rates reported by other studies. Contemporary mortality rates are as high as those found in the historical cohort.

The suicide specific SMR in the contemporary cohort for year 1 for all psychoses is 133 (95% C.I., 58, 263) and for schizophrenia is 168 (95% C.I., 67, 346). The suicide specific SMR for years 1 to 5 combined for all psychosis is 47 (95% C.I., 25, 81), and for schizophrenia is 51.5(95% C.I., 25, 95).The suicide specific SMR for all psychoses for years 1-10 combined is 34 (95% C.I., 19, 55), and for schizophrenia is 35 (95% C.I., 18, 61).

There was one open verdict in the year 1 figures, which is more likely than not to have been included in national figures as a suicide. In the case of the 10 year figures, there were in total 4 open verdicts. Excluding all of these would give a 10 year suicide specific SMR for all psychoses of 25 (95% C.I., 13, 44) and for schizophrenia of 23 (95% C.I., 10, 46).

Based on the number of patient exposure years, the SMR for death from cancer in the historical cohort was 3.49 (95% C.I., 2.25, 5.15) fold higher than the population norm at the time. Calculating a SMR for deaths from tuberculosis based on years exposure and deaths within the first 10 years of admission, gives an SMR of 9.37 (95% C.I., 7.64, 11.4) compared with the population in general, with the figures being twice as bad for women as for men.

Years of Life Lost

In the historical cohort the confirmed deaths allow estimates of years of life lost. For all psychoses years of life lost range from 9.8 years per patient in the confirmed death group to a possible 5.9 years per patient if those discharged died at the same rate as the rest of the population. For schizophrenia in the historical cohort, the years of life lost range from 10.8 in the confirmed death group to 8.0 when discharged patients are included in the analysis. For other psychoses, the years of life lost range from 6.8 years in the confirmed dead group to 2.5 years when extrapolated to include discharged patients.

In the contemporary cohort with complete 10 year follow up (N = 210), we have data on 143 patients with schizophrenia, and 67 with other psychoses. Patients with all psychoses lost 999 years between them. Patients with schizophrenia lost 613 years or 4.3 years each. Patients with other psychoses lost 5.8 years on average.

Discussion

This is the first attempt to calculate survival curves and standardized mortality rates for schizophrenia and related psychoses in an epidemiologically complete cohort of admissions

from the late 19th and early 20th centuries. It enables us to explore contemporary causes of mortality in a way not possible for other studies, and to assess whether mortality rates in schizophrenia are getting worse over time.

The survival analysis shows the absolute mortality in the historical period was higher than today, but historical SMRs overlap the SMRs for patients reported in recent studies. The actual years of life lost in our historical cohort are less than those lost now.[5, 11] The main hazard of asylum care for younger people, particularly women, a century ago lay in the risk of contracting tuberculosis. Another hazard was lethal catatonia which seems likely to have accounted for most deaths from exhaustion.[22]

The SMR we report for schizophrenia at the end of the first year of admission is higher than the SMR from the historical cohort but is consistent with reports showing increased mortality rates for patients with psychotic disorders in the first year of admission today[23], and reports indicating this stems primarily from suicide. [1, 6,11] Our contemporary SMR at 5 years for all psychoses moreover overlaps rates reported in other studies.[10]

This combination of findings brings out the value of a cohort study and the importance of diagnosis. When the data are examined by diagnosis and time from first admission, the findings reveal patterns not apparent in cross-sectional studies. Cross-sectional studies miss the impact of first admissions which account for less than 15% of admissions for psychosis.

The data on suicide in the historical and contemporary samples are strikingly different. In the historical records, it was mandatory for the admitting clinician to record suicide risk and 25% of the historical patients at admission had threatened or attempted suicide. The lack of subsequent suicides raises a number of questions. Was there a bias against a diagnosis of suicide? In the case of historical patients admitted for severe depressive disorders, a number are clearly recorded as dying from suicide and as attempting suicide both in the asylum and soon after discharge so that there was no reticence about recording such verdicts for other patients at this time.[24] Furthermore the case notes of patients dying from tuberculosis and other causes contain clinical details consistent with these diagnoses. A bias against recording suicide verdicts in the schizophrenia group can probably be ruled out.

To suicide you need to have opportunity to commit suicide. The registration of suicidal tendencies in the historic cohort meant that patients were monitored. Both schizophrenic and affective disorder patients were monitored, but affective disorder patients went on to commit

suicide at expected rates whereas the schizophrenic patients did not. In addition, the monitoring of patients in the asylum was by the same methods used today. There was not an undue restriction of liberty by today's standards. Historical patients with schizophrenia spent 99% of their time at liberty working on the hospital farm, in the knitting rooms or kitchens, with ample opportunity to commit suicide.

A second issue is whether patients today are more severely ill than a century ago. This seems unlikely for a number of reasons. First the more malignant psychoses (hebephrenic and catatonic schizophrenia) were present in the historical cohort but have close to disappeared now. Second historical patients were detained compulsorily whereas many patients today are voluntary admissions; it is therefore easier for less severely ill patients to get admitted now. Third, patients today have immediate access to medication that for many can be expected to mitigate the most distressing aspects of their disorder. In the case of catatonic syndromes, benzodiazepines eliminate the disorder now, while a higher proportion of these patients died in hospital historically than for any other form of psychosis (60% - see Table 2).

The importance of the historical cohort in this study is that it demonstrates that suicide is not an inherent risk of schizophrenia. The historical data suggest there is something about the modern delivery of care that contributes to suicide as an outcome. If suicide risk is not inherent in the illness, another possibility lies in deinstitutionalization. As in our data, Mortensen and Juel[1] flagged up the incident year of a schizophrenic illness as problematic. They suggest the high rates of suicide at this time might stem from de-institutionalization. However more recent Nordic data argue against de-institutionalization as the cause of the problem, as life expectancies have slightly increased (or at least not fallen further) as de-institutionalization has progressed[11], and suicide rates have fallen rather than got worse.[25] Moreover, contemporary patients with schizophrenia had a mean duration of admission lasting weeks rather than months and hence institutionalization cannot have set in.

Patients who have schizophrenia are also subject to stigma, and lack of family support. It has also been argued that antipsychotics can restore insight and this might lead to suicide. It would clearly be difficult to discount these possibilities if the suicides were happening 5 or 10 years into the illness. But the fact that suicides happen in the first year, before stigma has set in, or supports have been lost, make such factors less likely to be sole determinants of suicides.

Males are in general more likely to commit suicide than women, and in the contemporary schizophrenia sample there was a two-fold greater rate of male admissions than in the historical cohort, but the increased suicide rate in the contemporary sample does not stem from this source in that in the contemporary schizophrenia sample there was a greater proportion of female than male suicides.

Suicide in schizophrenia is likely to be multifactorial in origin. One contributory factor may be treatment. A high rate of suicide in the first year of treatment, across diagnostic groups, is consistent with an initial exposure of vulnerable individuals to the dysphoric effects of antipsychotics. The elimination of individuals at risk to such effects would produce precisely the drop in SMR over time found in our study. The antipsychotics are in fact the only element of the picture to have been shown in placebo controlled trials to be linked to an excess of suicides in psychosis, although the data are of poor quality.[26] A recent observational study has also linked benzodiazepine usage to suicidal deaths in psychotic patients.[27]

Wahlbeck et al report SMRs for suicide from national cohorts of patients recruited in Denmark, Finland and Sweden of 20.6 for men and 36.6 for women.[11] These figures map on to the suicide specific SMR for schizophrenia reported here for years 1-10 of follow up (35). Removing all suicides from the contemporary cohort gives an SMR for schizophrenia of 1.1 (95% C.I. 0.01, 6.4), and of 1.9 (95% C.I., 1.0, 3.4) for all psychoses.

An SMR of 1.9 maps onto figures cited for mortality in schizophrenia drawn from samples that contain subjects later in the trajectory of their illness. The deaths in these other studies have been linked to an increase in risk from cardiovascular causes. Our data support this. We have found high mortality rates in the contemporary patients with Acute and Transient Psychoses (F23) (Table 1). Our data is consistent with other studies.[2, 23] In this group over half the mortality stems from cardiovascular causes (Table 3b).

Two observations stem from this. First, patients with acute and transient psychoses often get diagnoses of schizophrenia. Studies that do not distinguish between these two groups will lead to increased estimates of cardiovascular risk in schizophrenia. Second it is older patients in our acute and transient cohort who died from cardiovascular causes. Their average age of death was 63 years. Consistent with this, cardiovascular deaths also featured prominently in the contemporary cohort in patients with delusional disorders (F22), where the average age at death was 74 years. Age is therefore a significant contributor to cardiovascular deaths.

Placebo-controlled trials of antipsychotics in the elderly show an excess of mortality primarily from cardiovascular causes in those on active treatment.[15, 16] The debate about using antipsychotics in the elderly has focussed primarily on their use in dementia patients but our figures suggest the risk may apply in all older subjects.

These data have implications for projected years of life lost in patients with schizophrenia. Our data open up the possibility that estimates based on diagnoses that fail to distinguish between schizophrenia and acute and transient psychoses or delusional disorders may substantially over-estimate the years of life lost in schizophrenia proper. For instance all cancers in the contemporary cohort came from the delusional disorder or acute and transient psychosis group. This raises the possibility that these cancers antedated and contributed to the development of rather than stemmed from these mental disorders or their treatment.

While data from the contemporary cohort offers no support for psychosis or its treatment as a cause of cancer, the incidence of gastro-intestinal cancers is a striking feature of the historical data. There was only one breast cancer and no lung cancers, while 28 of the 32 cancers were related to the gastro-intestinal tract. The official mortality figures for 1910 do not categorize mortality in terms of specific cancers to the extent that would permit a conclusive analysis of these data but it is worth noting that in 1910 the commonest cancers in England and Wales were of the mouth, gut and abdominal organs. Ovarian and breast cancers were commoner than found in our sample. Cancers of other bodily systems were filed under other, and were comparatively rare.

A majority of hospitalized patients with suspected cancers had post-mortems and it is possible that a proportion of the increased frequency of cancer diagnosis is an artefact of post-mortems. There was however concern about food adulteration in the 19th and early 20th centuries raising questions about possible links between this and gastro-intestinal cancer as an outcome.

In summary, this study reports elevations in SMRs in schizophrenia and related psychoses over a century with the modern data in some respects worse than the historical data. While it is fashionable to look at mortality as an outcome, it must be emphasized that patients today live outside the asylum. When the antipsychotics were introduced, the benefits of recovery and discharge were widely viewed as warranting a potential reduction in life expectancy.[28]

Other studies have suggested that patients with schizophrenia are dying prematurely because of lifestyle factors and lack of access to healthcare resources, leading to calls for interventions

in these domains. In contrast, the current data point to different hazards arising at different periods of risk, allowing differential interventions. The most striking figure in this study is that eliminating suicide in schizophrenia would restore life expectancy to normal. Checking for dysphoric responses to medication, and being willing to change medication if indicated, is worth pursuing as it might offer one of the greatest possible public health gains in any area of medicine at minimal cost.

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Competing Interests

The authors of this study declare they have no competing interests as regards the subject matter of this study.

Ethics Statement:

This study was approved by the North West Wales ethics committee.

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Legend: Figure 1

In the History Cohort we have calculated observed deaths with patients discharged and lost to follow up dying at the same rate as those remaining in hospital (History Survival) and also estimated survival curves if those lost to follow up die at the population rate rather than the hospitalized rate (History Best Survival)

Author Contribution:

All authors have been involved in this piece of research in terms of contributing to the design, data acquisition, analysis/interpretation along with drafting/revising the manuscript in preparation for the final publication:

Prof David Healy: principal investigator and primary author;

Dr Joanna Le Noury: data collection, analysis, study write up and review;

Ms Margaret Harris: data collection, analysis, study write up and review;

Dr Mohammed Butt: data analysis, study write up and review;

Dr Stefanie Linden: data analysis, study write up and review;

Mr Chris Whitaker: principal statistician;

Ms Lu Zou: statistician

Dr Anthony P Roberts: study write up and review.

Data sharing statement:

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.b6t13

Table 1:
Contemporary Sample:
Cause of Death by Diagnosis

Cause of death	Schizophrenia (F20/ F25) N = 227			Delusional Disorder (F22) N = 48			Acute & Transient Psychosis (F23) N = 66			Other Psychoses F29 N = 14			All Psychoses N = 355		
	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y
Suicide/Open	7	10	12	0	0	1	1	2	2	0	1	1	8	13	16
Cardiovascular	0	0	0	0	2	3	0	3	4	1	1	1	1	6	8
Respiratory	0	0	0	0	1	1	0	0	0	0	0	0	0	1	1
Cancer	0	0	0	0	1	2	1	2	2	0	1	1	1	4	5
Other	0	1	1	0	0	2	0	0	0	0	0	0	0	1	3
All causes	7	11	13	0	4	9	2	7	8	1	3	3	10	25	33
Average age of death	29.5	31.3	31.6	-	78.6	72.7	54.7	60.3	60.9	39.5	45.9	45.9	35.6	48.7	51.2

Table 2:
Historical Sample:
Cause of Death by Diagnosis

Cause of death	Schizophrenia F20/F25 N=605			Delusional Disorder F22 N=143			Acute & Transient Psychosis F23 N=143			Other Psychoses F29 N=135			Catatonia F06.1/F20.2 N=48			All Psychoses N=1074		
	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y
Suicide	1	1	2	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2
Cardiovascular	0	1	17	1	7	12	0	0	1	2	6	9	1	3	5	4	17	44
Respiratory	5	14	20	1	5	9	2	4	4	1	2	6	3	5	6	12	30	45
Cancer	0	0	0	1	1	2	0	0	0	0	2	2	0	0	0	1	3	4
TB	6	51	82	0	4	8	2	2	2	1	5	6	1	5	5	10	67	103
Dysentery	1	4	8	0	1	1	0	0	1	2	2	2	3	3	3	6	10	15
Other	2	10	24	1	5	8	3	3	3	3	6	8	7	9	10	16	33	53
All causes	15	81	153	4	23	40	7	9	11	9	23	33	15	25	29	50	161	266
Average age of death	40.4	37.0	45.6	49.5	55.6	58.4	40.5	43.3	46.2	48.2	51.2	56.6	45.7	43.3	44.7	44.9	46.1	50.3

('Other' causes of death in the historical sample include 'exhaustion', septicaemia, kidney disease and erysipelas.

TABLE 3 A
SCHIZOPHRENIA:
CAUSES OF AND AGE AT DEATH – CONTEMPORARY AND HISTORICAL SAMPLES

Age group	Cause of death	Contemporary sample			Historical sample		
		Yr1 (n=227)	Yrs2-5 (n=203)*	TOTAL 5yrs (n=203)*	Yr1 (n=653)	Yr2-5 (n=653)	TOTAL 5yrs (n=653)
15-44	TB	-	-	-	6	42	48
	Respiratory	-	-	-	5	7	12
	Cardiovascular	-	-	-	-	-	-
	Cancer	-	-	-	-	-	-
	Other	-	1	1	4	10	14
	Suicide	6	2	8	1	-	1
45-74	TB	-	-	-	1	7	8
	Respiratory	-	-	-	3	4	7
	Cardiovascular	-	-	-	1	3	4
	Cancer	-	-	-	-	-	-
	Other	-	-	-	9	3	12
	Suicide	1	1	2	-	-	-
75+	TB	-	-	-	-	-	-
	Respiratory	-	-	-	-	-	-
	Cardiovascular	-	-	-	-	-	-
	Cancer	-	-	-	-	-	-
	Other	-	-	-	-	-	-
	Suicide	-	-	-	-	-	-
All ages	**All deaths**	**7**	**4**	**11**	**30**	**76**	**106**
	All deaths (excl TB)	**7 (3.08%)**	**4 (1.97%)**	**11 (5.41%)**	**24 (3.68%)**	**34 (5.21%)**	**58 (8.88%)**

TABLE 3 B
OTHER PSYCHOSES :
CAUSES OF AND AGE AT DEATH – CONTEMPORARY AND HISTORICAL SAMPLES

Age group	Cause of death	Contemporary sample			Historical sample		
		Yr1 (n=128)	Yrs2-5 (n=104)*	TOTAL 5yrs (n=104)*	Yr1 (n=421)	Yr2-5 (n=421)	TOTAL 5yrs (n=421)
15-44	TB	-	-	-	3	4	7
	Respiratory	-	-	-	3	1	4
	Cardiovascular	1	1	2	-	1	1
	Cancer	-	-	-	-	-	-
	Other	-	-	-	2	1	3
	Suicide	1	1	2	-	-	-
45-74	TB	-	-	-	-	4	4
	Respiratory	-	-	-	1	6	7
	Cardiovascular	-	2	2	3	9	12
	Cancer	1	3	4	1	2	3
	Other	-	-	-	7	7	14
	Suicide	-	1	1	-	-	-
75+	TB	-	-	-	-	-	
	Respiratory	-	1	1	-	-	-
	Cardiovascular	-	2	2	-	-	-
	Cancer	-	-	-	-	-	-
	Other	-	-	-	-	-	-
	Suicide	-	-	-	-	-	-
All ages	**All deaths**	**3**	**11**	**14**	**20**	**35**	**55**
	All deaths (excl TB)	**3 (2.34%)**	**11 (10.57%)**	**14 (13.46%)**	**17 (4.03%)**	**27 (6.41%)**	**44 (10.45%)**

- **Figures exclude patients with incomplete 5 year histories**

Table 4: Standardized Mortality Ratios
Contemporary Sample

		SMR Y 1	SMR Y2	SMR Y3	SMR Y4	SMR Y5	Average 5yr SMR
Male	**All psychosis**	11.1 (CI 4.4, 23.0) **N = 218**	1.0 (CI 1.6, 6.6) **N = 208**	3.5 (CI 0.3, 13.0) **N = 203**	3.8 (CI 0.4, 13.9) **N = 197**	5.9 (CI 1.1, 17.2) **N = 180**	4.9 **(C.I., 0.85, 15.2)**
	Schizophrenia	28.6 (CI 7.4, 73.9) **N = 150**	1.0 (CI 7.4, 30.2) **N = 144**	7.9 (CI 0.003, 45.1) **N = 143**	16.7 (CI 1.6, 61.3) **N = 139**	1.0 (CI 8.7, 35.6) **N = 127**	11.2 **(C.I., 0.3, 51.0)**
Female	**All psychosis**	4.3 (CI 0.8, 12.7) **N = 136**	7.4 (CI 2.3, 17.3) **N = 129**	1.0 (CI 1.6, 6.5) **N = 119**	1.7 (CI 0.001, 9.8) **N = 116**	3.5 (CI 0.3, 12.9) **N = 108**	3.5 **(C.I., 0.4, 12.2)**
	Schizophrenia	44.8 (CI 8.1, 126.9) **N = 76**	16.7 (CI 0.01, 95.5) **N = 73**	1.0 (CI 16.0, 65.3) **N = 70**	1.0 (CI 16.0, 65.3) **N = 69**	1.0 (CI 18.5, 75.4) **N = 65**	13.2 **(C.I., 0.1, 89.2)**
Total	**All psychosis**	**7.5** (CI 3.6, 13.9) **N = 355**	**3.9** (CI 1.2, 9.3) **N = 337**	**1.7** (CI 0.2, 6.3) **N = 322**	**2.7** (CI 0.5, 8.0) **N = 313**	**4.6** (CI 1.5, 10.9) **N = 288**	**4.2 (C.I., 1.3, 9.9)**
	Schizophrenia	**33.3** (CI 13.2, 69.1) **N = 227**	**5.3** (CI 0.002, 30.2) **N = 217**	**5.4** (CI 0.002, 30.7) **N = 213**	**11.1** (CI 1.0, 40.9) **N = 208**	**1.0** (CI 5.9, 24.2) **N = 192**	**11.8 (C.I., 1.4, 41.3)**

Table 5: Standardized Mortality Ratios
History Sample – Observed Deaths

		SMR Y 1	SMR Y2	SMR Y3	SMR Y4	SMR Y5	Average 5yr SMR
Male	**All psychosis**	2.9 (CI 1.7, 4.6) **N = 516**	2.8 (CI 1.5, 5.0) **N = 385**	1.9 (CI 0.7, 3.8) **N = 354**	3.5 (CI 1.9, 6.0) **N = 337**	3.6 (CI 1.8, 6.2) **N = 313**	2.9 **(C.I., 2.2, 3.7)**
	Schizophrenia	2.1 (CI 0.7, 4.9) **N = 301**	2.8 (CI 1.0, 6.2) **N = 273**	3.0 (CI 1.1, 6.5) **N = 258**	4.1 (CI 1.8, 8.1) **N = 246**	3.7 (CI 1.5, 7.7) **N = 234**	3.1 **(C.I., 2.1, 4.4)**
Female	**All psychosis**	5.5 (CI 3.8, 7.8) **N = 558**	5.3 (CI 3.3, 8.0) **N = 410**	4.1 (CI 2.3, 6.8) **N = 366**	5.6 (CI 3.4, 8.7) **N = 340**	3.7 (CI 1.8, 6.6) **N = 306**	5.0 **(C.I., 4.0, 6.0)**
	Schizophrenia	4.3 (CI 2.0, 7.9) **N = 304**	5.7 (CI 2.9, 10.0) **N = 274**	3.7 (CI 1.5, 7.6) **N = 253**	7.0 (CI 3.7, 12.1) **N = 242**	4.1 (CI 1.6, 8.5) **N = 222**	4.9 **(C.I., 3.7, 6.5)**
Total	**All psychosis**	**4.2** (CI 3.1, 5.5) **N = 1074**	**4.1** (CI 2.8, 5.7) **N = 795**	**3.0** (CI 1.9, 4.5) **N = 720**	**4.5** (CI 3.1, 6.4) **N = 677**	**3.6** (CI 2.3, 5.4) **N = 619**	**3.9 (C.I., 3.3, 4.6)**
	Schizophrenia	**3.2** (CI 1.8, 5.2) **N = 605**	**4.3** (CI 2.5, 6.8) **N = 547**	**3.3** (CI 1.8, 5.7) **N = 511**	**5.5** (CI 3.4, 8.5) **N = 488**	**3.9** (CI 2.1, 6.6) **N = 456**	**4.0 (C.I., 3.5, 5.0)**

Table 6: Standardized Mortality Ratios
History Sample – Observed & Inferred Deaths

		SMR Y 1	SMR Y2	SMR Y3	SMR Y4	SMR Y5	Average 5yr SMR
Male	**All psychosis**	3.6 (CI 2.2, 5.4) **N = 516**	3.8 (CI 2.1, 6.1) **N = 385**	2.6 (CI 1.3, 4.9) **N = 354**	5.2 (CI 3.1, 8.1) **N = 337**	5.3 (CI 3.2, 8.5) **N = 313**	4.0 **(C.I., 3.2, 5.0)**
	Schizophrenia	2.5 (CI 0.9, 5.5) **N = 301**	3.3 (CI 1.3, 6.8) **N = 273**	3.5 (CI 1.4, 7.2) **N = 258**	4.6 (CI 2.1, 8.8) **N = 246**	4.2 (CI 1.8, 8.4) **N = 234**	3.6 **(C.I., 2.5, 4.9)**
Female	**All psychosis**	6.7 (CI 4.8, 9.2) **N = 558**	7.0 (CI 4.7, 10.1) **N = 410**	5.7 (CI 3.6, 8.8) **N = 366**	8.2 (CI 5.5, 11.9) **N = 340**	5.7 (CI 3.3, 9.2) **N = 306**	6.7 **(C.I., 5.6, 8.0)**
	Schizophrenia	4.7 (CI 2.3, 8.4) **N = 304**	6.2 (CI 3.3, 10.6) **N = 274**	4.2 (CI 1.8, 8.3) **N = 253**	8.1 (CI 4.5, 13.4) **N = 242**	4.7 (CI 2.0, 9.3) **N = 222**	5.6 **(C.I., 4.2, 7.2)**
Total	**All psychosis**	**5.1** (CI 3.9, 6.6) **N = 1074**	**5.4** (CI 3.9, 7.2) **N = 795**	**4.2** (CI 2.8, 5.9) **N = 720**	**6.6** (CI 4.9, 8.8) **N = 677**	**5.5** (CI 3.8, 7.7) **N = 619**	**5.3 (C.I., 4.6, 6.1)**
	Schizophrenia	**3.6** (CI 2.1, 5.7) **N = 605**	**4.7** (CI 2.9, 7.3) **N = 547**	**3.8** (CI 2.1, 6.3) **N = 511**	**6.3** (CI 4.0, 9.4) **N = 488**	**4.5** (CI 2.5, 7.2) **N = 456**	**4.5 (C.I., 3.7, 5.6)**

Figure 1a:Survival Probabilities in All Psychose in Contemporary & Historical Cohorts

Figure 1b: Survival Probabilities in Schizophrenia (F20, 25 & 061) in Contemporary & Historical Cohorts

Figure 1c:Survival Probabilities in Other Psychoses (F22, 23 & 29) in Contemporary & Historical Cohorts

			Schizophrenia diagnosis (N = 355)
			Suicide
N deaths within 5 years of admission			10
N deaths within 10 years of admission			12
Year 1 after admission	Male		
		observed	4
		expected	0.053
	Female		
		observed	3
		expected	0.007
	O/E (95% CI)		117(47,240)
Years 2-5 after admission	Male		
		observed	2
		expected	0.189
	Female		
		observed	1
		expected	0.026
	O/E (95% CI)		14(3,41)
Within 5 years of admission	O/E (95% CI)		36 (17,67)
Within 10 years of admission	O/E (95% CI)		25 (13,44)

Suicide + open verdict + misadventure
13
16
5
0.053
3
0.007
133(58,263)
4
0.189
1
0.026
23(8,54)
47(25,81)
34(19,55)

			Schizophrenia diagnosis (N = 227)
			Suicide
N deaths within 5 years of admission			7
N deaths within 10 years of admission			8
Year 1 after admission	Male		
		observed	3
		expected	0.038
	Female		
		observed	3
		expected	0.004
	O/E (95% CI)		144 (53, 313)
Years 2-5 after admission	Male		
		observed	0
		expected	0.138
	Female		
		observed	1
		expected	0.014
	O/E (95% CI)		6.6 (0.2, 36.5)
Within 5 years of admission	O/E (95% CI)		36 (14, 74)
Within 10 years of admission	O/E (95% CI)		23 (10, 46)

Suicide + open verdict + misadventure	10	12	4
			3
168 (67, 346)			2
			1
20 (4, 57)			
51 (25, 95)			
35 (18, 61)			

Mortality in Schizophrenia and Related Psychoses:
Data from Two Cohorts, 1875-1924 & 1994-2010

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Abstract

Objective: To investigate mortality rates in schizophrenia and related psychoses.

Design: Data from two epidemiologically complete cohorts of patients presenting for the first time to mental health services in North Wales for whom there are at least 1, and up to 10 year follow up data have been used to calculate survival rates and standardized mortality rates for schizophrenia and related psychoses.

Setting: The North Wales Asylum Denbigh (archived patient case notes) and the North West Wales District General Hospital psychiatric unit.

Population: Cohort 1: The North Wales Asylum Denbigh (archived patient case notes). Of 3168 patients admitted to the North Wales Asylum Denbigh 1875-1924, 1074 had a schizophrenic or related psychosis. Cohort 2: Patients admitted between 1994 and 2010 to the North West Wales District General Hospital psychiatric unit, of whom 355 had first admissions for schizophrenia or related psychoses.

~~**Results**: This study reports a 4 fold increased mortality rate in schizophrenia and related psychoses in the historical period compared to population norms then and in the contemporary period compared to population norms now.~~ **Results**: We found a 10 year survival probability of 75% in the historical cohort and a 90% survival probability in the contemporary cohort with a 4-fold increase in standardised mortality rates in schizophrenia and related psychoses in both historical and contemporary periods. Suicide is the commonest cause of death in schizophrenia in the contemporary period (SMR 35), while tuberculosis was the commonest cause historically (SMR 9). In the contemporary data, deaths from cardiovascular causes arise in the elderly and deaths from suicide ~~arise at different illness stages and at different ages~~.in the young.

Conclusions: Contemporary mortality rates in schizophrenia and related psychoses are high but there are particular hazards and windows of risk that enable interventions. The data point to ~~a clear intervention~~ possible interventions in the incident year of treatment that could give patients with schizophrenia a normal life expectancy.

Article Summary

Article Focus

The question of possible increases in mortality in psychosis is a current issue of concern, with both suicide and increased cardiovascular risk noted. It is know that the initial year after a diagnosis of schizophrenia is a point of high risk.

Key Message

In North Wales, access to two epidemiologically complete case registers makes it possible to demonstrate that suicide is not inherent in schizophrenia and that cardiovascular deaths are confined to elderly patients, who typically do not have a schizophrenia diagnosis.

Tackling the problem of suicides in the first year of schizophrenia has the potential to restore life expectancy to normal in this illness.

Strengths of the Study

This study has unique access to a large and complete cohort of unmedicated psychotic patients, which makes it possible to separate the contributions of the illness and its treatments to mortality. The study also offers a first rigorous estimate of historical mortality in serious mental illness. The cohort design of the study highlights factors that cross-sectional studies miss.

Limitations of the Study

The size of the contemporary cohort, duration of follow-up and number of deaths preclude definitive statements about mortality.

Introduction

There is growing interest in outcomes for schizophrenia and related psychoses, fuelled by consistent reports of an apparent doubling or tripling of mortality rates, along with significant reductions in life expectancy.[1-11] A double or tripling of mortality rates, equates in the case of schizophrenia to a loss of approximately 15 years of life expectancy.[11] As reported, mortality stems variously from natural causes, especially cardiovascular disorders[2, 7, 10] and from unnatural causes in particular suicide.[1, 3, 11]

After their introduction in the 1950s, the antipsychotic drugs were seen as having a beneficial effect on mortality rates in psychosis.[12, 13]However mortality rates now appear to be increasing[10, 14] and this has led to concerns that antipsychotics with adverse cardiovascular profiles could aggravate this trend, with particular concerns for the elderly.[15. 16]

The majority of studies have been cross-sectional in design. They also lack data on patients not treated with antipsychotic medication. These factors make it difficult to pinpoint ~~a direction~~ the effects of ~~causality between illness and mortality~~ treatment and hinder efforts to devise interventions for risks that may arise at different stages of an illness. Owing to the geographical and economic constraints imposed by North West Wales, we have been able to design a study that addresses some of these issues, and overcomes selection biases. We have logged all admissions for schizophrenia and related non-affective psychoses ~~over the 17 year period~~ from 1994 to 2010, and followed up all admissions during this period. We also have a database of all admissions to the North Wales asylum in Denbigh ~~in the years from~~ between 1875 and 1924 complete with subsequent clinical records and thus have data on causes of mortality in an untreated cohort of psychotic patients. Finally we have separated delusional disorder, acute and transient psychoses and schizophrenia in both historical and contemporary databases in an effort to link specific hazards to clinical syndromes. The resulting databases allow different perspectives to be brought to bear on the data arising from other studies.

Method

We have used two datasets to look at outcome data for schizophrenia and other non-affective psychoses drawn from the periods 1875-1924 and 1994-2010. ~~Geographical and financial constraints in North West Wales have conspired to ensure there was nowhere else for 19th/20th century patients to go other than the asylum at Denbigh, and 20th/21st century patients to go to~~

other than the District General Hospital unit in Bangor. Even patients getting sick elsewhere in both periods were returned to North West Wales for treatment.

The **Datasets**

The historical cohort consists of all admissions from North West Wales to the asylum at Denbigh between 1875 and 1924. The asylum records for every patient offered five sets of information relevant to diagnosis; medical and legal certificates outlining the circumstances of detention; standard demographic data including age, sex, educational, employment and marital status, family history of mental illness, prior mental or physical illness and possible social triggers; standard assessments of dangerousness, suicidality, seizure-proneness, along with food refusal and a range of clinical features; descriptions of patients' mental and physical states on admission; case notes covering patients stays in hospital until discharge or death.[17]For the historical cohort we could retrieve all possible records of patients back to 1865 to ensure that duration of illness is not being underestimated and all subsequent admissions through to 1965 in order to establish cause of death for later admissions.

The contemporary cohort is drawn from a database of all first admissions to the sole district general hospital (DGH) unit in North West Wales between 01-01-1994 and 31-12-2010, along with any admissions to the regional medium secure facility, the only other unit to which patients might have been admitted, bypassing the DGH. The catchment area for the DGH unit is the same as that for the historical cohort. Patients were included if they were native to or resident in North West Wales prior to and following their initial episode. We have not included in either the contemporary or historical cohorts patients who became ill after coming from elsewhere as students to the local university or who otherwise came from out of area and returned to their place of origin but who had a first episode of mental illness while in North West Wales. For the contemporary cohort, using their NHS number, we could track and get outcome data for the 4% of patients who left the area.

Case Definitions

The term schizophrenia was not used in asylum records until after 1924. From 1875 to 1924, psychotic patients were primarily diagnosed with "mania".[18]Accordingly a panel of clinicians covering the catchment areas from which these patients would now come reviewed records from all admissions for each patient and made retrospective diagnoses according to ICD-10 criteria.[17] All diagnoses were made before this study began. The diagnostic process is

~~outlined in greater~~ The methods used for case definition are described in detail in an accompanying article on the incidence of psychoses ~~across historical and contemporary periods.[19~~ during these two periods. [17]

Patients in both historical and contemporary cohorts were allocated to five diagnostic groups: schizophrenia (F20), schizoaffective disorder (F25), delusional disorder (F22), acute and transient psychoses (F23) and other patients who were difficult to classify, coded as unspecified non-organic psychosis (F29). One co-author (SCL) reviewed all affective and non-affective diagnoses covering 8 randomly picked years from the 1875-1924 period. The agreement concerning the schizophrenic diagnoses (F20) between the initial rater and SCL was 96.5%. To take account of the number of agreements expected by chance, we used Cohen's Kappa coefficient, a statistical measure of inter-rater agreement for categorical items.[18] The k coefficient (781 cases, two raters, for schizophrenia versus all other diagnoses) was 86%.

~~In the contemporary sample, all admissions of both patients with and without discharge codes for psychotic disorders were reviewed at regular monthly and subsequently 6-monthly intervals with both medical and nursing staff on the treating team to establish diagnoses. The diagnoses were reviewed following all subsequent admissions. These diagnoses therefore are not codes applied administratively and for instance not unexpectedly only 49% of schizophrenic patients were given that diagnosis on first discharge.~~

~~For those unfamiliar with these methods, they greatly reduce the likelihood of false positive diagnoses. There has been some concern for example that patients who had children out of wedlock might have been admitted to asylums. Such admissions for "social" reasons happened in mid-twentieth century when admission procedures were a lot looser; they did not happen during this period in North Wales and if they had this approach would have detected them. The historical cases of schizophrenia central to this paper are therefore unlikely to contain any case that did not actually have schizophrenia.~~

Deaths

In the historical cohort, all deaths in hospital (N=764) were recorded in the patients' medical records. Of these, 58% had recorded post-mortems. In addition there were 10 patients who were discharged gravely ill to die at home. We have counted these patients as deaths in the year of discharge and assigned a cause of death consistent with the clinical picture outlined in

the records. There were 300 patients (28%) who were discharged recovered and healthy within the 10 years from the date of first admission, on whom there is no further data.

We followed up ~~patients in the~~ contemporary ~~cohort, all were tracked down~~ patients, using their NHS number, even when they had moved out of area. All deaths were established through coroner's records, along with contacts with the patient's general practitioner and treating team. The contemporary database was updated at regular three-monthly intervals, and accordingly all deaths were investigated and confirmed the year they happened. No patients were lost to follow-up.

Survival Analysis

To account for the different lengths of follow-up, primarily in the contemporary cohort, we have undertaken survival analyses on both historical and contemporary cohorts.[19] In the case of the historical cohort, a survival analysis gives patients discharged healthy and lost to follow-up ~~Our survival analysis de facto gives~~ the same rate of death ~~to those discharged healthy but lost to follow up~~ as is found in the observed cohort. Because death from tuberculosis in particular was much commoner in hospital, this under-estimates the survival probability in ~~the historical cohort~~.discharged patients. We have therefore undertaken a further analysis in the historical cohort that assumes no recovered patients ~~who were discharged~~ died within the 10-year timeframe (best case scenario). The true result is likely to lie somewhat closer to the best case than to the observed outcomes.

Mortality Rates

We have used mortality data from 1900 to 1910 for England and Wales on which to base our calculations of Standardized Mortality Ratios (SMR) for 1875-1924~~. These data came from the Office of National Statistics; ,~~ as data before 1900 and for the period surrounding the Great War are not available.[20] For the historical sample we took the mean value of the years from 1901 to 1910 for each age and sex grouping. ~~Using this group is likely to lead to higher SMRs in the historical sample than is warranted given~~ Given a decline in mortality rates from 1875 to 1900 and greater mortality ~~in the period from~~ between 1914 and 1920 linked to the Great War and the influenza epidemic of 1918-1920, the 1901-1910 group is likely to lead to higher SMRs in the historical sample than is warranted.

Mortality data for the contemporary sample came from the Office of National Statistics.[23] For the contemporary data we worked from available mortality data from 1994 to 2010.[21] In the case of contemporary suicides we have standardized deaths by suicide in all psychoses and for schizophrenia by age, sex and year against the deaths from suicide in Wales alone rather than deaths from suicide in England and Wales. Annual suicide statistics in both Wales and England include a proportion of open verdict deaths. We have taken this into account in calculating suicide specific SMRs.

When computing standardized mortality rates for successive years after year 1, in the contemporary sample, we removed all patients who died the previous year and have not included patients for whom we do not have full follow up data. This gives contemporary cohorts of 337 at year 2, 322 at year 3, 313 at year 4 and 288 at year 5. In the history sample we have similarly removed all patients who died from the calculations of mortality for subsequent years. We have then used person years at risk when calculating SMRs.

For the purposes of accounting for possible deaths in our recovered discharges from the historical cohort, when calculating standardised mortality rates, we have calculated two sets of figures. The first set SMRs. A best case scenario assumes that patients discharged in apparent good health survived the remainder of the period of observation. A worst case scenario assumes that these recovered and healthy patients died at the same rate in their year of discharge as the rate of death found in subsequent years as those remaining in hospital. during the corresponding year of their illness. We have also assumed that those discharged continued to die at the rate observed in those remaining in hospital. The inferred deaths are added to the observed deaths to give a worst case scenario.. This procedure seems likely to over-estimate the rate of death in the historical cohort.

Years of Life Lost

In both historical and contemporary cohorts we have calculated years of life lost. In the historical cohort we have taken life expectancy in the period 1901-1910 as the basis of our calculations. For patients admitted up to the age of 44 this has meant a projected life expectancy for males of 62 years and for females of 65 years; for males and females between 45 and over the figures were 68 and 71 years respectively. In the historical cohort the analysis is based on known age of death.

In the contemporary cohort we have observed years of life lost in the cohort of patients who have completed 10 years. Our sample size and the nature of the cohort does not permit a trend analysis across ages to establish projected life expectancies.

Results

This study is linked to a study looking at the incidence of admissions for schizophrenia and related psychoses ~~and their outcomes in historical and contemporary periods. The study has~~ that identified 1074 cases ~~of schizophreniform psychoses~~ in the historical period and 355 cases in the contemporary period. We found an increase in the admission incidence for schizophrenia between 1875 and 1900 when standardised against population norms, a drop in admission incidence for schizophrenia between 2005 and 2010, and a switch in gender ratios from an equal rate of male and female admissions in the 19th century to a rate of two males for each female admission in the contemporary sample ~~[19] The switch in gender ratios is of interest given the greater preponderance of female to male suicides in the contemporary mortality data.~~ [17]

Cause of Death

~~In Tables 1 and 2, we have laid out the deaths by~~ Causes of death by diagnosis after 1, 5, and 10 years from first admission in the contemporary and historical samples are laid out in Tables ~~3a & 3b we present the mean age of death by specific causes in both contemporary~~ 1 and ~~historical samples.~~ 2.

There is a clear difference in age of death in those dying from suicide compared with deaths from cardiovascular causes ~~in the contemporary cohort,~~ and a clear difference in age of death for those diagnosed with schizophrenia compared with the ages of death for those other psychotic diagnoses in the contemporary cohort. There are differences between age of death from tuberculosis and cancer in the historical cohort. To explore the interaction between age, diagnosis and cause of death we have laid out the mean age of death by specific causes in both contemporary and historical samples in Tables 3a and 3b.

In the case of ~~deaths by suicide in the~~ contemporary ~~sample~~ suicides, the 16 ~~cases~~ deaths comprised of 12 suicide, 3 open verdicts and one death by misadventure. The open verdicts were regarded by the treating teams as suicides. The death by misadventure involved an

overdose on psychotropic drugs. We have accordingly classified these deaths with suicide rather than under the heading of "other". Only one open verdict happened within the first year of admission, in a patient with schizophrenia.

In the historical cohort, many patients with schizophrenia spent their life in the hospital, so that we know the nature of their final illnesses. In total, 32 psychotic patients (25 with schizophrenia) died in hospital from cancer. Of these 32 deaths, 28 involved cancer of the gastro-intestinal tract. There was one breast cancer and no lung cancers. ~~Based on the number of patient exposure years, the SMR for death from cancer in schizophrenia in this cohort was 3.49 (95% C.I., 2.25, 5.15) fold higher than the population norm at the time. As a control to these figures it can be noted that cancers were less frequently found in patients with severe melancholiaduring the same historical period.[24]~~

Tuberculosis was the greatest hazard for patients admitted to the asylum~~. It was a particular hazard ,~~ especially for younger patients, ~~and especially those with schizophrenia,~~ who show a spike in deaths from this cause 3-5 years after admission. The drop in mean age of death at year 5 in Table 2 reflects this. Table 3 shows a full break down of deaths by diagnosis and age. ~~Calculating SMRs based on years exposure and deaths within the first 10 years of admission, gives an SMR of 9.37 (95% C.I., 7.64, 11.4) compared with the population in general, with the figures being twice as bad for women as for men. There were comparable death rates for tuberculosis in asylum patients with affective disorders (SMR 9.11) with women twice as badly affected as men, so this outcome does not appear to be diagnosis specific.~~

Survival Analysis

A survival analysis of the contemporary cohort ~~(see Figure 1)~~ for all psychoses shows a cumulative 10 year survival probability of 90% (90% C.I., 0.86, 0.92) (Figure 1a). For schizophrenia, the 10 year cumulative survival probability is 94% (90% C.I., 0.91, 0.96) (Figure 1b). For other psychoses the 10 year cumulative survival probability is 81% (90% C.I., 0.74, 0.87) (Figure 1c).

In the historical cohort, ~~as outlined in methods, we have two analyses. Analyzing~~ analyzing all discharges as dying at the same rate as those left in hospital produces 10 year cumulative survival probabilities for all psychoses of 69% (90% C.I., 0.66, 0.71); for schizophrenia of 69% (90% C.I., 0.66, 0.72) and for other psychoses of 63% (90% C.I., 0.57, 0.69). Analyzing

observed deaths as though they were all deaths (best case scenario) produces 10 year cumulative survival probabilities for all psychoses of 75% (90% C.I., 0.73, 0.77); for schizophrenia of 72% (90% C.I., 0.70, 0.75), and for other psychoses of 80% (90% C.I., 0.77, 0.83).

Standardized Mortality Rates

We have calculated standardized mortality ratios (SMR) for contemporary (see Table 4) and historical cohorts (Tables 5 & 6) for 1, 2, 3, 4 and 5 years from first admission. The contemporary SMRs show a marked increase over population norms in the first year of admission. The rates thereafter remain elevated compared with population norms but fall toward rates reported by other studies. ~~In terms of absolute numbers of deaths (Tables 1 & 2), there are more deaths in the historical cohort, but calculating SMRs shows contemporary~~ Contemporary mortality rates are as high as those found in the historical cohort.

The suicide specific SMR in the contemporary cohort for year 1 for all psychoses is 133 (95% C.I., 58, 263) and for schizophrenia is 168 (95% C.I., 67, 346). The suicide specific SMR for years 1 to 5 combined for all psychosis is 47 (95% C.I., 25, 81), and for schizophrenia is 51.5(95% C.I., 25, 95).The suicide specific SMR for all psychoses for years 1-10 combined is 34 (95% C.I., 19, 55), and for schizophrenia is 35 (95% C.I., 18, 61).

There was one open verdict in the year 1 figures, which is more likely than not to have been included in national figures as a suicide. In the case of the 10 year figures, there were in total 4 open verdicts. Excluding all of these would give a 10 year suicide specific SMR for all psychoses of 25 (95% C.I., 13, 44) and for schizophrenia of 23 (95% C.I., 10, 46).

~~Finally, in a parallel study of severe affective disorders we have found a similar increase in suicide rates in a contemporary compared to a historical cohort, along with deaths from tuberculosis in the historical cohort in those remaining in hospital for up to 5 years, but no increase in rates of death from cancer in the historical cohort.[24]~~

Based on the number of patient exposure years, the SMR for death from cancer in the historical cohort was 3.49 (95% C.I., 2.25, 5.15) fold higher than the population norm at the time. Calculating a SMR for deaths from tuberculosis based on years exposure and deaths within the

first 10 years of admission, gives an SMR of 9.37 (95% C.I., 7.64, 11.4) compared with the population in general, with the figures being twice as bad for women as for men.

Years of Life Lost

In the historical cohort ~~we have a large number of patients with~~ the confirmed deaths allow estimates of years of life lost. For all psychoses years of life lost range from 9.8 years per patient in the confirmed death group to a possible 5.9 years per patient if those discharged died at the same rate as the rest of the population. ~~If deaths from tuberculosis are removed the years lost drop markedly to 5.6 to 2.6 years for worst case and best case scenarios.~~ For schizophrenia in the historical cohort, the years of life lost range from 10.8 in the confirmed death group to 8.0 when discharged patients are included in the analysis. For other psychoses, the years of life lost range from 6.8 years in the confirmed dead group to 2.5 years when extrapolated to include discharged patients.

In the contemporary cohort with complete 10 year follow up (N = 210), we have data on 143 patients with schizophrenia, and 67 with other psychoses. Patients with all psychoses lost 999 years between them. Patients with schizophrenia lost 613 years or 4.3 years each. Patients with other psychoses lost 5.8 years on average.

Discussion

~~In undertaking survival analyses and calculating standardized mortality ratios (SMRs) from contemporary and historical samples drawn from the same catchment area and diagnosed using the same criteria, we are able first to calculate historical rates of mortality, second to explore contemporary causes of mortality in a way not possible for other studies, and third to assess whether mortality rates in schizophrenia are getting worse over time.~~

This is the first attempt to calculate survival curves and standardized mortality rates for schizophrenia and related psychoses in an epidemiologically complete cohort of admissions from the late 19th and early 20th centuries. It enables us to explore contemporary causes of mortality in a way not possible for other studies, and to assess whether mortality rates in schizophrenia are getting worse over time.

The survival analysis shows the absolute mortality in the historical period was higher than ~~the absolute mortality~~ today, but historical SMRs overlap the SMRs for patients reported in recent studies. ~~If we can accept the projected 15-20 years of life lost from contemporary cohorts, then~~

~~the~~ The actual years of life lost in our historical cohort are less than those lost now.[5, 11] ~~If we remove tuberculosis as a cause of death, mortality rates for the historical cohort look very respectable compared to today's figures. It seems clear that one~~ The main hazard of asylum care for younger people, particularly women, a century ago lay in the risk of contracting tuberculosis. Another hazard was lethal catatonia which seems likely to have accounted for most deaths from exhaustion.[22]

~~When comparing historical and contemporary SMRs for psychosis and~~ The SMR we report for schizophrenia~~, the surprise is how comparable the figures are despite the modern elimination of tuberculosis. Calculating mortality rates~~ at the end of the first year of admission ~~in particular gives a~~ is higher ~~mortality rate today~~ than the SMR from the historical ~~period.~~

~~Our contemporary SMRs at the end of the first year of admission and thereafter are more salient than~~ cohort but is consistent with ~~other findings in the contemporary literature. First, in all other~~ reports ~~there is a marked increase in~~ showing increased mortality rates for patients with ~~schizophrenia and related~~ psychotic disorders ~~compared with population norms~~ in the first year of admission ~~[26]Second, our SMR at 5 years across all diagnostic groups approach rates reported in cross-sectional studies.[10]Third, the greatest contribution to the elevation in mortality rates in our sample comes from suicide in the first year of admission in patients with schizophrenia~~ today[23], and reports indicating this ~~finding is in line with other studies.[1, 6, 11~~ stems primarily from suicide.[1, 6,11] Our contemporary SMR at 5 years for all psychoses moreover overlaps rates reported in other studies.[10]

This combination of findings brings out the value of a cohort study and the importance of diagnosis. When the data are examined by ~~diagnostic group~~ diagnosis and ~~according to the~~ time from first admission, the findings reveal patterns not apparent in ~~both the schizophrenia and non-schizophrenia groups in cross~~ cross-sectional studies. Cross-sectional studies ~~In cross-sectional studies,~~ miss the impact of ~~outcomes among~~ first admissions ~~for schizophrenia is likely to be missed as in these studies first admissions~~ which account for ~~15% or~~ less than 15% of admissions for ~~schizophrenic and related psychoses in any one year. As our data show, if the contribution from deaths in the first year are missed calculations of SMRs for schizophrenia will result in much lower estimates than those reported here~~ psychosis.

The data on suicide in the historical and contemporary samples are strikingly different. In the historical records, it was mandatory for the admitting clinician to record suicide risk ~~at admission~~ and 25% of the historical patients at admission ~~were considered suicidal or~~ had threatened or

attempted suicide. ~~There is no requirement for clinicians today to record suicide risk on admission and thus comparable data do not exist for a modern sample but the rates of overt suicidality on admission for psychotic patients seem unlikely to be higher than 25%.~~ The lack of subsequent suicides ~~in the historical sample~~ raises a number of questions. Was there a bias against a diagnosis of suicide? In the case of historical patients admitted for severe depressive disorders, a number are clearly recorded as dying from suicide and as attempting suicide both in the asylum and soon after discharge so that there was no reticence about recording such verdicts for other patients at this time.[24] Furthermore the case notes of patients dying from tuberculosis and other causes contain clinical details consistent with these diagnoses. A bias against recording suicide verdicts in the schizophrenia group can probably be ruled out.

To commit suicide you need to have opportunity to commit suicide. The registration of suicidal tendencies in the historic cohort meant that patients were monitored. Both schizophrenic and affective disorder patients were monitored, but affective disorder patients went on to commit suicide at expected rates whereas the schizophrenic patients did not. In addition, the monitoring of patients in the asylum was by the same methods used today. There was not an undue restriction of liberty by today's standards. Historical patients with schizophrenia spent 99% of their time at liberty working on the hospital farm, in the knitting rooms or kitchens, with ample opportunity to commit suicide.

A second issue is whether patients today are more severely ill than a century ago. This seems unlikely for a number of reasons. First the more malignant ~~forms of the illness (hebephrenia/disintegrative psychosis~~ psychoses (hebephrenic and catatonic schizophrenia) were present in the historical cohort but have close to disappeared now. Second historical patients ~~a century ago~~ were detained compulsorily whereas ~~a large number of patients today were admitted voluntarily~~ many patients today are voluntary admissions; it is therefore easier for less severely ill patients to get admitted now. Third, patients today have immediate access to medication that for many can be expected to mitigate the most distressing aspects of their disorder. In the case of catatonic syndromes, benzodiazepines ~~mean~~ eliminate the disorder ~~simply does not evolve as before;~~now, while a higher proportion of these patients died in hospital historically than for any other form of psychosis (60% - see Table 2).

The importance of the historical cohort in this study is that it demonstrates that suicide is not an inherent risk of schizophrenia. The historical data suggest there is something about the modern delivery of care that contributes to suicide as an outcome~~, whether it stems from de-~~

institutionalization, or from treatment. In contrast to schizophrenia suicide rates, the suicide rate for affective disorder patients in our historical sample is in line with expectations regarding the incidence of suicide in severe mood disorders and so institutionalization as such did not prevent suicides.[24, 27]We have also found increased suicide rates in contemporary affective disorder patients making it unlikely that the modern finding of increased suicide rates for schizophrenia stem from diagnostic leakage – that is the suicide rates in schizophrenia do not stem from misdiagnosed affective disorder patients.

Males are in general more likely to commit suicide than women, and in the contemporary schizophrenia sample there was a two-fold greater rate of male admissions, but the increased suicide rate in the contemporary sample does not stem from this source in that in the contemporary schizophrenia sample there was a greater proportion of female than male suicides.. If suicide risk is not inherent in the illness, another possibility lies in deinstitutionalization. As in our data, Mortensen and Juel[1] flagged up the incident year of a schizophrenic illness as problematic. They suggest the high rates of suicide at this time might stem from de-institutionalization. However more recent Nordic data argue against de-institutionalization as the cause of the problem, as life expectancies have slightly increased (or at least not fallen further) as de-institutionalization has progressed.[11] Our data also argue against de-institutionalization in that suicide rates are increased in both patients who were once institutionalized but are not now (schizophrenia) and patients who were never subject to long-term institutionalization (affective disorder patients).], and suicide rates have fallen rather than got worse.[25] Moreover, contemporary patients with schizophrenia had a mean duration of admission lasting weeks rather than months and hence institutionalization cannot have set in.

Allied to de-institutionalization Patients who have schizophrenia are issues of also subject to stigma, and lack of family support. or untreated comorbid depression. It has also been argued that antipsychotics can restore insight and this might lead to suicide. It would clearly be difficult to discount these possibilities if the suicides were happening 5 or 10 years into the illness. But the fact that suicide is happening primarily suicides happen in the first year, before stigma has set in, or supports have been lost, make such factors less likely to be sole determinants of suicides.

Wahlbeck et al report SMRs for suicide from national cohorts of patients recruited in Denmark, Finland and Sweden of 20.6 for men and 36.6 for women.[11]These figures map very closely on to the suicide specific SMR for schizophrenia reported here for years 1-10 of follow up (35) but

~~are 5 times lower than the rates for all schizophrenia in the incident year (168).Removing all suicides from the contemporary cohort gives an SMRfor schizophrenia of 1.1 (95% C.I. 0.01, 6.4), and of 1.9 (95% C.I., 1.0, 3.4) for all psychoses.~~

~~If the trigger to suicide does not lie in the effects of de-institutionalization and related losses, and is not inherent in the disease, the remaining option lies with treatment. High rates~~

Males are in general more likely to commit suicide than women, and in the contemporary schizophrenia sample there was a two-fold greater rate of male admissions than in the historical cohort, but the increased suicide rate in the contemporary sample does not stem from this source in that in the contemporary schizophrenia sample there was a greater proportion of female than male suicides.

Suicide in schizophrenia is likely to be multifactorial in origin. One contributory factor may be treatment. A high rate of suicide in the first year ~~or early years~~ of treatment, across diagnostic groups, is consistent with an initial exposure of vulnerable individuals to the dysphoric effects of antipsychotics. The elimination of individuals at risk to such effects would produce precisely the drop in SMR over time found in our study. The antipsychotics are in fact the only element of the picture to have been shown in placebo controlled trials to be linked to an excess of suicides ~~and suicidal acts~~ in psychosis, although the data are of poor quality.[26] A recent observational study[29] has also linked benzodiazepine usage to suicidal deaths in psychotic patients.[27]

Wahlbeck et al report SMRs for suicide from national cohorts of patients recruited in Denmark, Finland and Sweden of 20.6 for men and 36.6 for women.[11] These figures map on to the suicide specific SMR for schizophrenia reported here for years 1-10 of follow up[35]. Removing all suicides from the contemporary cohort gives anan SMR for schizophrenia of 1.1 (95% C.I. 0.01, 6.4), and of 1.9 (95% C.I., 1.0, 3.4) for all psychoses.

An SMR of 1.9 ~~(95% C.I., 1.0, 3.4) for all psychoses. This~~ maps onto figures cited for mortality in schizophrenia drawn from samples that contain subjects later in the trajectory of their illness. The deaths in these other studies have been linked to an increase in risk from cardiovascular causes ~~and there are indications that this is a particular hazard for older subjects.~~ Our data ~~from non-schizophrenic psychoses~~ support this. ~~The survival analysis in the contemporary cohort makes it clear that these other areas of hazard lie primarily in the non-schizophrenic cohort.~~

We have found high mortality rates in the contemporary patients with Acute and Transient Psychoses (F23) (Table 1). ~~This group of patients has been rarely looked at. The~~ Our data is consistent with other studies.[2, 23] In this group over half the mortality stems from cardiovascular causes (Table 3b).

Two observations stem from this. First, patients with acute and transient psychoses often get diagnoses of schizophrenia. Studies that do not distinguish between these two groups will ~~on the basis of our figures have~~ lead to increased estimates of cardiovascular risk in schizophrenia. Second it is older patients ~~with a diagnosis of~~ in our acute and transient ~~psychosis fall into two groups, one younger and the other older. It is the older patients in this group~~ cohort who died from cardiovascular causes. Their average age of death was 63 years. Consistent with this, cardiovascular deaths also featured prominently in the contemporary cohort in patients with delusional disorders (F22), where the average age at death was 74 years. Age is therefore a significant contributor to ~~these outcomes. The antipsychotic group of drugs now come with clear warnings of the risk of~~ cardiovascular ~~problems in patients over the age of 65 but the interplay between treatment and age is uncertain in that a proportion of the F23 group will have lost contact with the mental health services and might not have been on treatment. Having made this point, it is clear that placebo~~ deaths.

Placebo-controlled trials of antipsychotics in the elderly show an excess of mortality primarily from cardiovascular causes in those on active treatment.[15, 16] The debate about using antipsychotics in the elderly has focussed primarily on their use in dementia patients but our figures suggest ~~that attempts should be made to establish contributory~~ the risk ~~factors~~ may apply in all older subjects.

These data have implications for projected years of life lost in patients with schizophrenia. Our data open up the possibility that estimates based on diagnoses that fail to distinguish between schizophrenia and acute and transient psychoses or delusional disorders may substantially over-estimate the years of life lost in schizophrenia proper. For instance all cancers in the contemporary cohort came from the delusional disorder or acute and transient psychosis group. This raises the possibility that these cancers antedated and contributed to the development of rather than stemmed from these mental disorders or their treatment. ~~This interpretation is consistent with findings we have reported for severe depressive disorders also.[23]~~

While data from the contemporary cohort offers no support for psychosis or its treatment as a cause of cancer, the incidence of gastro-intestinal cancers is a striking feature of the historical

data. There was only one breast cancer and no lung cancers, while 28 of the 32 cancers were related to the gastro-intestinal tract. The official mortality figures for 1910 do not categorize mortality in terms of specific cancers to the extent that would permit a conclusive analysis of these data but it is worth noting that in 1910 the commonest cancers in England and Wales were of the mouth, gut and abdominal organs. Ovarian and breast cancers were commoner than found in our sample. Cancers of other bodily systems were filed under other, and were comparatively rare.

A majority of hospitalized patients with suspected cancers had post-mortems and it is possible that a proportion of the increased frequency of cancer diagnosis is an artefact of post-mortems. There was however concern about food adulteration in the 19th and early 20th centuries raising questions about possible links between this and gastro-intestinal cancer as an outcome.

In summary, this study reports ~~consistent~~ elevations in SMRs in schizophrenia and ~~non-affective~~ related psychoses over a century with the modern data in some respects worse than the historical data. ~~Our data do, however, caution the need to distinguish between first episode and other admissions in studies of projected life expectancy. More generally, while~~ While it is fashionable to look at mortality as an outcome, it must be emphasized that patients today live ~~life~~ outside the asylum ~~in a way they did not do a century ago~~. When the antipsychotics were introduced, the benefits of recovery and discharge were widely viewed as warranting a potential reduction in life expectancy.[28]

Other studies have suggested that patients with schizophrenia are dying prematurely because of lifestyle factors and lack of access to healthcare resources ~~and because of lifestyle factors, which support a case that ,~~ leading to calls for interventions in these domains ~~may improve life expectancy. The utility of the .~~ In contrast, the current data point to different hazards arising at different periods of risk ~~and this knowledge might enable us to get the benefits of treatment without such a high price in serious adverse events. In particular they suggest a concentration on the first years after admission in younger patients and a simple expedient of checking more closely with patients whether their medication does in fact suit them and in the case of patients with dysphoric responses a willingness to change drug to find one that suits best,~~ allowing differential interventions. The most striking figure in this study is that eliminating suicide in schizophrenia would restore life expectancy to normal. Checking for dysphoric responses to medication, and being willing to change medication if indicated, is worth pursuing as it might offer one of the greatest possible public health gains in any area of medicine at minimal cost.

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Competing Interests

The authors of this study declare they have no competing interests as regards the subject matter of this study.

Ethics Statement:

This study was approved by the North West Wales ethics committee.

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Legend: Figure 1

In the History Cohort we have calculated observed deaths with patients discharged and lost to follow up dying at the same rate as those remaining in hospital (History Survival) and also estimated survival curves if those lost to follow up die at the population rate rather than the hospitalized rate (History Best Survival)

Author Contribution:

All authors have been involved in this piece of research in terms of contributing to the design, data acquisition, analysis/interpretation along with drafting/revising the manuscript in preparation for the final publication:

Prof David Healy: principal investigator and primary author;

Dr Joanna Le Noury: data collection, analysis, study write up and review;

Ms Margaret Harris: data collection, analysis, study write up and review;

Dr Mohammed Butt: data analysis, study write up and review;

Dr Stefanie Linden: data analysis, study write up and review;

Mr Chris Whitaker: principal statistician;

Ms Lu Zou: statistician

Dr Anthony P Roberts: study write up and review.

Data sharing statement:

Dataset available from the corresponding author, David Healy, at david.healy54@googlemail.com

Table 1:
Contemporary Sample:
Cause of Death by Diagnosis

Cause of death	Schizophrenia (F20/ F25) N = 227			Delusional Disorder (F22) N = 48			Acute & Transient Psychosis (F23) N = 66			Other Psychoses F29 N = 14			All Psychoses N = 355		
	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y
Suicide/Open	7	10	12	0	0	1	1	2	2	0	1	1	8	13	16
Cardiovascular	0	0	0	0	2	3	0	3	4	1	1	1	1	6	8
Respiratory	0	0	0	0	1	1	0	0	0	0	0	0	0	1	1
Cancer	0	0	0	0	1	2	1	2	2	0	1	1	1	4	5
Other	0	1	1	0	0	2	0	0	0	0	0	0	0	1	3
All causes	7	11	13	0	4	9	2	7	8	1	3	3	10	25	33
Average age of death	29.5	31.3	31.6	-	78.6	72.7	54.7	60.3	60.9	39.5	45.9	45.9	35.6	48.7	51.2

Table 2:
Historical Sample:
Cause of Death by Diagnosis

Cause of death	Schizophrenia F20/F25 N=605			Delusional Disorder F22 N=143			Acute & Transient Psychosis F23 N=143			Other Psychoses F29 N=135			Catatonia F06.1/F20.2 N=48			All Psychoses N=1074		
	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y	1Y	5Y	10Y
Suicide	1	1	2	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2
Cardiovascular	0	1	17	1	7	12	0	0	1	2	6	9	1	3	5	4	17	44
Respiratory	5	14	20	1	5	9	2	4	4	1	2	6	3	5	6	12	30	45
Cancer	0	0	0	1	1	2	0	0	0	0	2	2	0	0	0	1	3	4
TB	6	51	82	0	4	8	2	2	2	1	5	6	1	5	5	10	67	103
Dysentery	1	4	8	0	1	1	0	0	1	2	2	2	3	3	3	6	10	15
Other	2	10	24	1	5	8	3	3	3	3	6	8	7	9	10	16	33	53
All causes	15	81	153	4	23	40	7	9	11	9	23	33	15	25	29	50	161	266
Average age of death	40.4	37.0	45.6	49.5	55.6	58.4	40.5	43.3	46.2	48.2	51.2	56.6	45.7	43.3	44.7	44.9	46.1	50.3

('Other' causes of death in the historical sample include 'exhaustion', septicaemia, kidney disease and erysipelas.

TABLE 3 A
SCHIZOPHRENIA:
CAUSES OF AND AGE AT DEATH – CONTEMPORARY AND HISTORICAL SAMPLES

Age group	Cause of death	Contemporary sample			Historical sample		
		Yr1 (n=227)	Yrs2-5 (n=203)*	TOTAL 5yrs (n=203)*	Yr1 (n=653)	Yr2-5 (n=653)	TOTAL 5yrs (n=653)
15-44	TB	-	-	-	6	42	48
	Respiratory	-	-	-	5	7	12
	Cardiovascular	-	-	-	-	-	-
	Cancer	-	-	-	-	-	-
	Other	-	1	1	4	10	14
	Suicide	6	2	8	1	-	1
45-74	TB	-	-	-	1	7	8
	Respiratory	-	-	-	3	4	7
	Cardiovascular	-	-	-	1	3	4
	Cancer	-	-	-	-	-	-
	Other	-	-	-	9	3	12
	Suicide	1	1	2	-	-	-
75+	TB	-	-	-	-	-	-
	Respiratory	-	-	-	-	-	-
	Cardiovascular	-	-	-	-	-	-
	Cancer	-	-	-	-	-	-
	Other	-	-	-	-	-	-
	Suicide	-	-	-	-	-	-
All ages	**All deaths**	**7**	**4**	**11**	**30**	**76**	**106**
	All deaths (excl TB)	**7 (3.08%)**	**4 (1.97%)**	**11 (5.41%)**	**24 (3.68%)**	**34 (5.21%)**	**58 (8.88%)**

TABLE 3 B
OTHER PSYCHOSES :
CAUSES OF AND AGE AT DEATH – CONTEMPORARY AND HISTORICAL SAMPLES

Age group	Cause of death	Contemporary sample			Historical sample		
		Yr1 (n=128)	Yrs2-5 (n=104)*	TOTAL 5yrs (n=104)*	Yr1 (n=421)	Yr2-5 (n=421)	TOTAL 5yrs (n=421)
15-44	TB	-	-	-	3	4	7
	Respiratory	-	-	-	3	1	4
	Cardiovascular	1	1	2	-	1	1
	Cancer	-	-	-	-	-	-
	Other	-	-	-	2	1	3
	Suicide	1	1	2	-	-	-
45-74	TB	-	-	-	-	4	4
	Respiratory	-	-	-	1	6	7
	Cardiovascular	-	2	2	3	9	12
	Cancer	1	3	4	1	2	3
	Other	-	-	-	7	7	14
	Suicide	-	1	1	-	-	-
75+	TB	-	-	-	-	-	
	Respiratory	-	1	1	-	-	-
	Cardiovascular	-	2	2	-	-	-
	Cancer	-	-	-	-	-	-
	Other	-	-	-	-	-	-
	Suicide	-	-	-	-	-	-
All ages	**All deaths**	**3**	**11**	**14**	**20**	**35**	**55**
	All deaths (excl TB)	**3 (2.34%)**	**11 (10.57%)**	**14 (13.46%)**	**17 (4.03%)**	**27 (6.41%)**	**44 (10.45%)**

- **Figures exclude patients with incomplete 5 year histories**

Table 4: Standardized Mortality Ratios
Contemporary Sample

		SMR Y 1	SMR Y2	SMR Y3	SMR Y4	SMR Y5	Average 5yr SMR
Male	**All psychosis**	11.1 (CI 4.4, 23.0) **N = 218**	1.0 (CI 1.6, 6.6) **N = 208**	3.5 (CI 0.3, 13.0) **N = 203**	3.8 (CI 0.4, 13.9) **N = 197**	5.9 (CI 1.1, 17.2) **N = 180**	4.9 **(C.I., 0.85, 15.2)**
	Schizophrenia	28.6 (CI 7.4, 73.9) **N = 150**	1.0 (CI 7.4, 30.2) **N = 144**	7.9 (CI 0.003, 45.1) **N = 143**	16.7 (CI 1.6, 61.3) **N = 139**	1.0 (CI 8.7, 35.6) **N = 127**	11.2 **(C.I., 0.3, 51.0)**
Female	**All psychosis**	4.3 (CI 0.8, 12.7) **N = 136**	7.4 (CI 2.3, 17.3) **N = 129**	1.0 (CI 1.6, 6.5) **N = 119**	1.7 (CI 0.001, 9.8) **N = 116**	3.5 (CI 0.3, 12.9) **N = 108**	3.5 **(C.I., 0.4, 12.2)**
	Schizophrenia	44.8 (CI 8.1, 126.9) **N = 76**	16.7 (CI 0.01, 95.5) **N = 73**	1.0 (CI 16.0, 65.3) **N = 70**	1.0 (CI 16.0, 65.3) **N = 69**	1.0 (CI 18.5, 75.4) **N = 65**	13.2 **(C.I., 0.1, 89.2)**
Total	**All psychosis**	**7.5** (CI 3.6, 13.9) **N = 355**	**3.9** (CI 1.2, 9.3) **N = 337**	**1.7** (CI 0.2, 6.3) **N = 322**	**2.7** (CI 0.5, 8.0) **N = 313**	**4.6** (CI 1.5, 10.9) **N = 288**	**4.2 (C.I., 1.3, 9.9)**
	Schizophrenia	**33.3** (CI 13.2, 69.1) **N = 227**	**5.3** (CI 0.002, 30.2) **N = 217**	**5.4** (CI 0.002, 30.7) **N = 213**	**11.1** (CI 1.0, 40.9) **N = 208**	**1.0** (CI 5.9, 24.2) **N = 192**	**11.8 (C.I., 1.4, 41.3)**

Table 5: Standardized Mortality Ratios
History Sample – Observed Deaths

		SMR Y 1	SMR Y2	SMR Y3	SMR Y4	SMR Y5	Average 5yr SMR
Male	**All psychosis**	2.9 (CI 1.7, 4.6) **N = 516**	2.8 (CI 1.5, 5.0) **N = 385**	1.9 (CI 0.7, 3.8) **N = 354**	3.5 (CI 1.9, 6.0) **N = 337**	3.6 (CI 1.8, 6.2) **N = 313**	2.9 **(C.I., 2.2, 3.7)**
	Schizophrenia	2.1 (CI 0.7, 4.9) **N = 301**	2.8 (CI 1.0, 6.2) **N = 273**	3.0 (CI 1.1, 6.5) **N = 258**	4.1 (CI 1.8, 8.1) **N = 246**	3.7 (CI 1.5, 7.7) **N = 234**	3.1 **(C.I., 2.1, 4.4)**
Female	**All psychosis**	5.5 (CI 3.8, 7.8) **N = 558**	5.3 (CI 3.3, 8.0) **N = 410**	4.1 (CI 2.3, 6.8) **N = 366**	5.6 (CI 3.4, 8.7) **N = 340**	3.7 (CI 1.8, 6.6) **N = 306**	5.0 **(C.I., 4.0, 6.0)**
	Schizophrenia	4.3 (CI 2.0, 7.9) **N = 304**	5.7 (CI 2.9, 10.0) **N = 274**	3.7 (CI 1.5, 7.6) **N = 253**	7.0 (CI 3.7, 12.1) **N = 242**	4.1 (CI 1.6, 8.5) **N = 222**	4.9 **(C.I., 3.7, 6.5)**
Total	**All psychosis**	**4.2** (CI 3.1, 5.5) **N = 1074**	**4.1** (CI 2.8, 5.7) **N = 795**	**3.0** (CI 1.9, 4.5) **N = 720**	**4.5** (CI 3.1, 6.4) **N = 677**	**3.6** (CI 2.3, 5.4) **N = 619**	**3.9 (C.I., 3.3, 4.6)**
	Schizophrenia	**3.2** (CI 1.8, 5.2) **N = 605**	**4.3** (CI 2.5, 6.8) **N = 547**	**3.3** (CI 1.8, 5.7) **N = 511**	**5.5** (CI 3.4, 8.5) **N = 488**	**3.9** (CI 2.1, 6.6) **N = 456**	**4.0 (C.I., 3.5, 5.0)**

Table 6: Standardized Mortality Ratios
History Sample – Observed & Inferred Deaths

		SMR Y 1	SMR Y2	SMR Y3	SMR Y4	SMR Y5	Average 5yr SMR
Male	**All psychosis**	3.6 (CI 2.2, 5.4) **N = 516**	3.8 (CI 2.1, 6.1) **N = 385**	2.6 (CI 1.3, 4.9) **N = 354**	5.2 (CI 3.1, 8.1) **N = 337**	5.3 (CI 3.2, 8.5) **N = 313**	4.0 **(C.I., 3.2, 5.0)**
	Schizophrenia	2.5 (CI 0.9, 5.5) **N = 301**	3.3 (CI 1.3, 6.8) **N = 273**	3.5 (CI 1.4, 7.2) **N = 258**	4.6 (CI 2.1, 8.8) **N = 246**	4.2 (CI 1.8, 8.4) **N = 234**	3.6 **(C.I., 2.5, 4.9)**
Female	**All psychosis**	6.7 (CI 4.8, 9.2) **N = 558**	7.0 (CI 4.7, 10.1) **N = 410**	5.7 (CI 3.6, 8.8) **N = 366**	8.2 (CI 5.5, 11.9) **N = 340**	5.7 (CI 3.3, 9.2) **N = 306**	6.7 **(C.I., 5.6, 8.0)**
	Schizophrenia	4.7 (CI 2.3, 8.4) **N = 304**	6.2 (CI 3.3, 10.6) **N = 274**	4.2 (CI 1.8, 8.3) **N = 253**	8.1 (CI 4.5, 13.4) **N = 242**	4.7 (CI 2.0, 9.3) **N = 222**	5.6 **(C.I., 4.2, 7.2)**
Total	**All psychosis**	**5.1** (CI 3.9, 6.6) **N = 1074**	**5.4** (CI 3.9, 7.2) **N = 795**	**4.2** (CI 2.8, 5.9) **N = 720**	**6.6** (CI 4.9, 8.8) **N = 677**	**5.5** (CI 3.8, 7.7) **N = 619**	**5.3 (C.I., 4.6, 6.1)**
	Schizophrenia	**3.6** (CI 2.1, 5.7) **N = 605**	**4.7** (CI 2.9, 7.3) **N = 547**	**3.8** (CI 2.1, 6.3) **N = 511**	**6.3** (CI 4.0, 9.4) **N = 488**	**4.5** (CI 2.5, 7.2) **N = 456**	**4.5 (C.I., 3.7, 5.6)**

Figure 1a:

Survival Probabilities in All Psychoses in Contemporary & Historical Cohorts

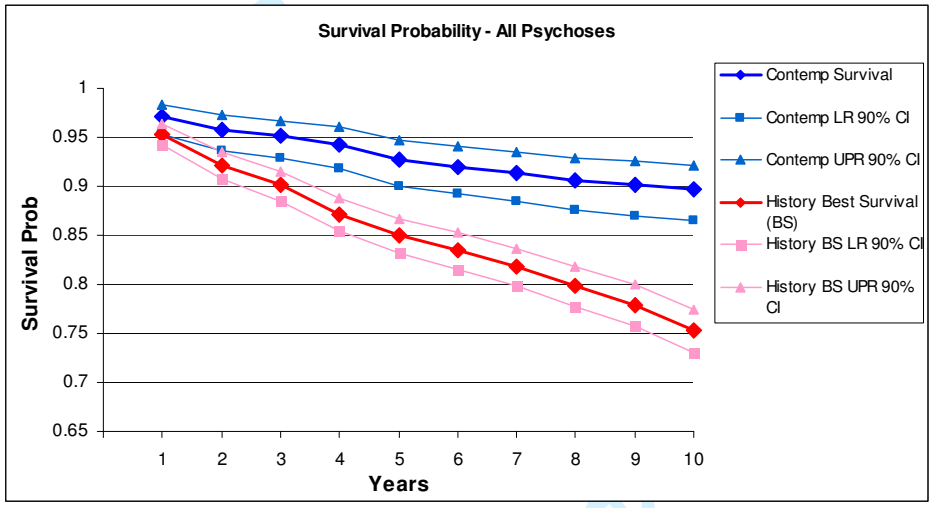

Figure 1b:

Survival Probabilities in Schizophrenia (F20, 25 & 061) in Contemporary & Historical Cohorts

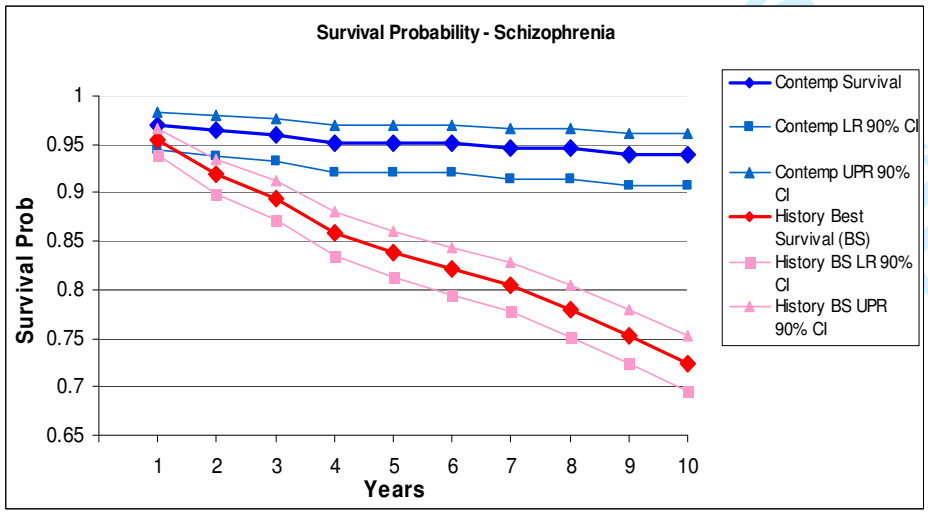

Figure 1c:

Survival Probabilities in Other Psychoses (F22, 23 & 29) in Contemporary & Historical Cohorts

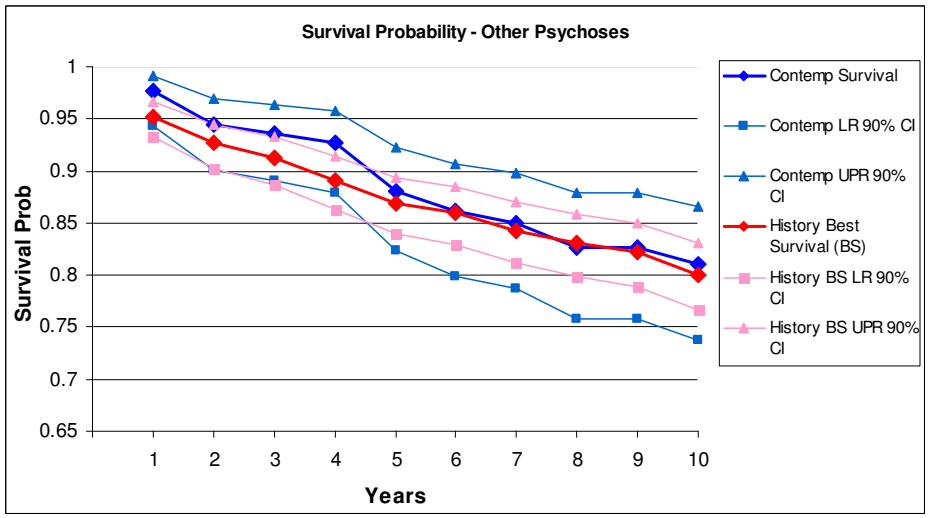

Figure 1a:

Survival Probabilities in All Psychoses
in Contemporary & Historical Cohorts

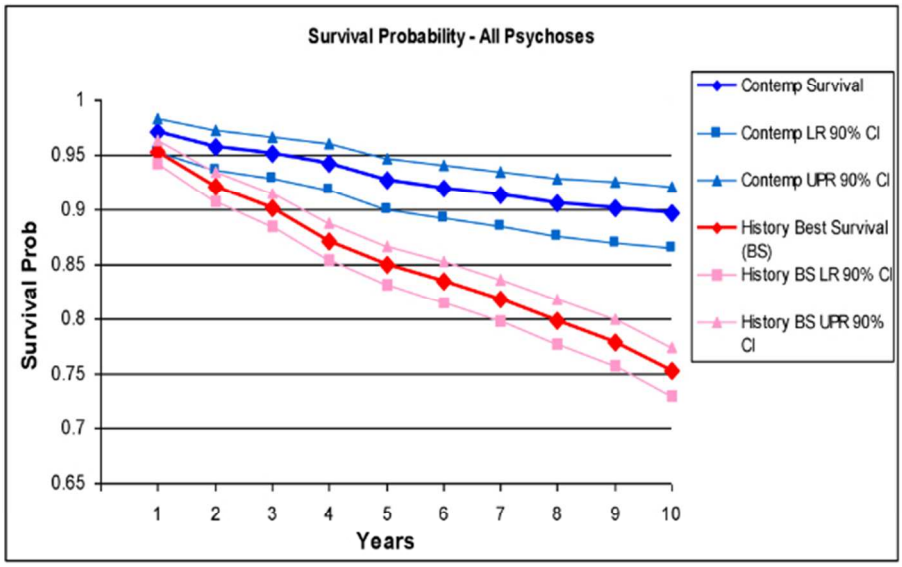

Figure 1b:

Survival Probabilities in Schizophrenia (F20, 25 & 061)
in Contemporary & Historical Cohorts

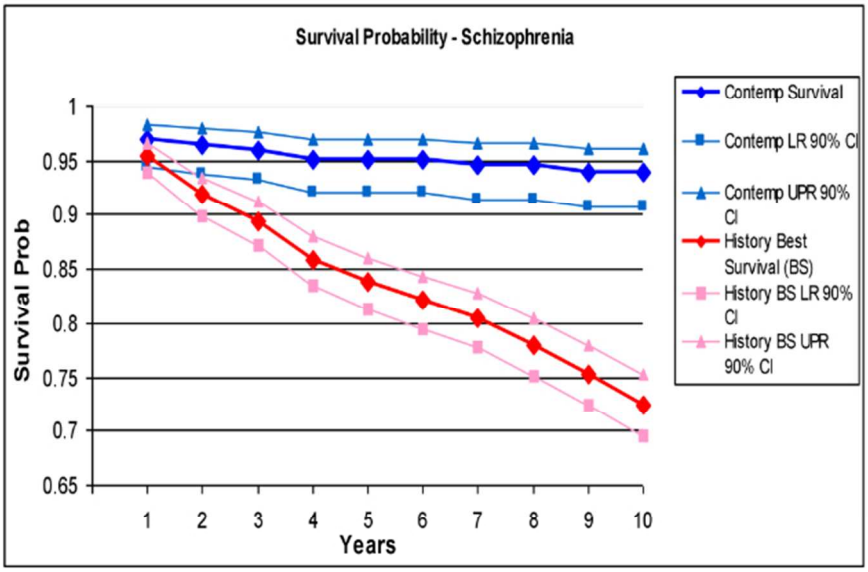

Figure 1c:

Survival Probabilities in Other Psychoses (F22, 23 & 29) in Contemporary & Historical Cohorts