UNIVERSITY OF SOUTHAMPTON

THE EXCESS MORTALITY OF SCHIZOPHRENIA

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ABSTRACT

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by Archibald Stephen Brown

Aims: Mortality is the most fundamental outcome of disease and by inference of medical treatment. Mortality studies in schizophrenia, the most disabling mental disease of young adults, consistently show excess mortality but lack the clinical details necessary to explain individual deaths and suggest means of prevention. This study uses a systematic review of the literature and individual follow-up of a cohort with schizophrenia to describe the excess mortality of the disease.

Methods: I searched the medical literature for reports of schizophrenia mortality, checking each citation until I found no new references. I then aggregated the data from all studies which met predetermined inclusion criteria and measured mortality by the Standardised Mortality Ratio (SMR) with 95% confidence intervals.

I then traced at 13 years, a cohort of 370 patients with schizophrenia, identified from service contacts in 1981-2. I took cause of death from death certificates and clinical details from medical records, calculated SMRs from UK national mortality tables by the added years method and examined the circumstances of each death.

Results: Meta-analysis of the literature showed an overall SMR of 151 (CI 148-154) which was higher among males and the young and fell with length of illness. Nearly half the excess deaths were unnatural, most from suicide. The excess natural mortality was spread across most disease categories. This pattern suggests that suicide is intrinsic to schizophrenia but the excess natural mortality is largely due to altered exposure to environmental risk factors.

The local cohort had 58 natural (SMR 232, CI 176-296) and 19 unnatural deaths (SMR 1273, CI 767-1988), an overall SMR of 299 (CI 236-372). The pattern of deaths was similar to previous studies. The excess mortality was not explained by social disadvantage. Some of the mechanisms of excess mortality include unhealthy lifestyle, poor treatment of chronic disease and treatment compliance and failed recognition of acute medical disease.

Conclusions: Many of the excess deaths are potentially preventable by better medical treatment, risk management and modification of known risk factors, especially cigarette smoking. Mortality will probably remain raised through failure to seek help or rejection of optimal treatment and because some factors which contribute to the excess mortality are not susceptible to medical intervention.

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Preface

The Southampton psychiatric services moved from the county asylum, Knowle Hospital, to a new unit at the Royal South Hants Hospital, a District General Hospital in central Southampton, in 1979. Two years later Jane Gibbons, a Senior Lecturer at Southampton University, identified 370 patients with a clinical diagnosis of schizophrenia as subjects in a study of how well the new service was meeting the needs of local patients with schizophrenia and their families. Her results were published in national and local reports (Gibbons *et al,* 1984).

I was appointed as senior registrar at the Department of Psychiatry in Southampton in 1992. My clinical supervisor Brian Barraclough suggested that a follow-up study might produce important material about the prognosis of schizophrenia and the performance of local services.

I started to trace these patients in 1993 and quickly realised that the mortality was much higher than I would have expected in such a relatively young cohort. I looked at the literature on the mortality of schizophrenia and found a lot of evidence that schizophrenia had a high mortality but little about the mechanisms which lay behind this. This thesis therefore presents a statistical and descriptive examination of the mortality of 370 local patients with schizophrenia.

Acknowledgements

I must first acknowledge the immense support and encouragement which I have received from Dr Brian Barraclough, emeritus senior lecturer in the Department of Psychiatry at Southampton University. Brian proposed the initial project, offered critical support throughout, put me in contact with other crucial figures and has been particularly helpful with advice about writing this thesis.

I must also acknowledge the support of Professor Chris Thompson and of the other members of the Southampton University Mental Health Group, who encouraged me to apply for an NHS Executive, Research and Development grant which funded much of the work. The study would also have been impossible without the mortality statistics which were calculated at the MRC Environmental Epidemiology Unit by Paul Winter and Shelley Hutton under the supervision of Dr Hazel Inskip. Additional statistical advice came from Dr Peter Smith and Dr Nigel Baker and computer advice from Nik Martin.

I thank Jane Gibbons for the use of data collected during their original study, Dr Elizabeth King for access to the Wessex suicide database and Dr Clare Harris for her comments on the manuscript and meta-analysis. I thank all other colleagues in the Wessex mental health services for their time and patience in supplying information and particularly thank Lyn Benham and her colleagues in the medical records department at the Department of Psychiatry.

Chapter 1: Introduction

The importance of mental illness mortality studies

Mortality is the most fundamental and objective measure of disease outcome, and by inference, of medical treatment. Measures such as infant mortality are used to judge the effectiveness of government policy and of national health services, and to assess the performance of individual clinicians, units and treatments. Psychiatric outcome has traditionally been measured by changes in symptomatology, social performance or patient satisfaction. Thus important changes, such as the move from hospital to community based treatment, have occurred without assessment of their impact on patient mortality.

The excess mortality associated with mental illness was first quantified by William Farr in 1841. He concluded that part of this excess was intrinsic to insanity and part caused by environmental factors. The diagnostic patterns of mental illness and the conditions experienced by the mentally ill may have changed but the excess mortality remains (Harris & Barraclough, 1998).

Schizophrenia: A brief clinical description

Cohort studies of schizophrenia, the most disabling mental illness of young adults, show an increased risk of premature death. Schizophrenia is characterised by a range of unusual internal experiences, socially inappropriate behaviour and withdrawal from ordinary activities which are distressing to patients and families (Fadden *et al*, 1987). The exact aetiology is unknown, indeed it is uncertain whether schizophrenia is a single disease or a collection of similar syndromes (Gelder *et al*, 1996).

Most authorities consider that schizophrenia is caused by an interaction of genetic predisposition and environmental factors (Gelder *et al*, 1996). There is evidence of brain abnormalities, (Hyde & Weinberger, 1990) of genetic (Kendler & Diehl, 1993), and neurodevelopmental (Pilowsky *et al,* 1993) origin. None of these are consistently present hence diagnosis is based on the

presence of particular symptom patterns for a prescribed length of time as defined in either the International Classification of Disease (ICD) or the American Diagnostic Statistical Manual (DSM).

The features of schizophrenia vary from one individual to another and may vary over time in the same individual (Gelder *et al,* 1996). Only a quarter of patients make a good recovery from a first episode (Ram *et al,* 1992), fewer remain well without medication (Mason *et al,* 1995). The chronic form of the disease is often characterised by disordered thought, under-activity, lack of drive, social withdrawal and emotional apathy (Malmberg & David, 1993).

The seriousness and chronicity of schizophrenia thus make it an appropriate marker of the effectiveness of mental health policy and services, while high mortality in an identifiable group demands examination of possible causes and interventions.

Current knowledge about the mortality of schizophrenia

Improving the health of the mentally ill, an explicit government target (Department of Health, 1992), requires a thorough understanding of the reasons for any excess mortality. That mortality is harder to measure in chronic psychiatric diseases than in acute or highly lethal physical conditions, should not prevent its use as an outcome measure.

Authors from Farr (1841) onwards identified an excess mortality in the asylum population and subsequently among asylum patients with schizophrenia. A number of more recent studies have examined schizophrenia mortality outside the psychiatric hospitals. Most report that schizophrenia has a significantly increased mortality compared to the general population and a significant excess unnatural mortality, especially from suicide. There is less agreement about the pattern of natural mortality.

There are still large gaps in our knowledge. The few published reviews (Simpson & Tsuang, 1988; Allebeck, 1989; Caldwell & Gottesman,1990) do

not meet modern systematic standards. No published studies have been able to explain the reasons why mortality is increased, hence there is no satisfactory evidence base for interventions designed to reduce mortality. Many frequently cited studies; are of small (Black *et al,* 1985) or old and probably unrepresentative (Tsuang & Woolson, 1977) cohorts. There are wide variations in published mortality rates (eg: a three fold variation in SMRs and fifteen fold variation in suicide SMRs between Mortensen & Juel's 1990 and 1993 cohorts).

The most important reason for studying schizophrenia mortality is the expectation that better understanding will reveal ways of reducing the number of premature deaths. This already happens, for example where reports of high mortality have prompted the withdrawal or strict control of certain drugs. Mortality is also an important measurement of the effects of changes in treatment and policy. Mortality studies may also be important for any light they may cast on the aetiology of schizophrenia or on the treatment of other diseases, for example excess endocrine deaths might implicate particular neurotransmitter systems while Mortensen (1987; 1989; 1992) contends that neuroleptic drugs may reduce cancer.

There is therefore a definite need for a systematic review of recent mortality studies, which will enable the non-specialist psychiatrist integrate the results of different studies and identify the most important service issues. There is also a need for individual follow-up studies which can look at the circumstances of particular deaths and provide an evidence base for interventions.

Aims of this study

This thesis divides into two related parts, a systematic review of the literature on schizophrenia mortality and a follow-up study of a local cohort, designed to elicit possible reasons for any excess mortality.

The literature review aims to quantify various aspects of the mortality

associated with a diagnosis of schizophrenia using the techniques of systematic review and meta-analysis. It further aims to identify gaps in our current knowledge and identify and explain differences in reported mortality rates. The systematic review will be augmented by a narrative review of evidence from studies which do not meet the criteria for inclusion in the systematic review but which nevertheless contribute to our knowledge of the subject.

The follow-up study aims to use standard statistical techniques to examine various aspects of the mortality of a local cohort with schizophrenia identified in 1981-2. It will measure overall mortality, mortality in particular subgroups and from particular diseases. It further aims to identify incident variables which predict individuals at risk of premature death and to measure the proportion of deaths which might be prevented by better medical treatment. The quantitative study will be augmented by a qualitative analysis of the circumstances of individual deaths, which aims to identify possible causes of each death and any missed opportunities for intervention.

Research questions

The questions addressed by this research all relate to the mortality experience of a local cohort with schizophrenia:

- What is the overall mortality, the mortality of particular subgroups and the mortality from particular causes?
- What is the excess mortality from preventable causes?
- Is it possible to identify particular individuals who are at high risk of premature death?
- Does a qualitative examination of the circumstances of these deaths give useful information on which to plan preventative strategies?

Applications and limitations of the proposed research method

This study follows the methodology of most modern studies of mental illness mortality in using an observational design and comparing the observed cohort mortality with the mortality that would be expected in an age and gender matched sample of the general population calculated by the person-years method (Breslow & Day, 1987). This is a generally appropriate method for measuring cohort mortality as proposed in this study.

The study however follows-up a cohort identified for different purposes. This means that cohort size is fixed and may not be large enough for some of the proposed calculations. It also makes it impossible to obtain data missing from case notes or original research pro-forma, precluding measurement of the effect of clinically important variables including illicit drugs, alcohol, prescribed medication, diet exercise, obesity and hypertension .

Observational studies such as this can demonstrate an association between a particular variable and a variation from expected mortality but cannot prove a causal relationship. Neither can they test hypotheses such as the effect of a particular intervention. Any associations identified in this study would therefore need to be tested in a prospective study to establish a causal relationship and provide a solid evidence base for changes in clinical practice. Such prospective studies often require a large cohort and long follow-up time to prove causality hence clinicians sometimes have to base decisions on the findings of observational research.

The qualitative part of the study is limited by the quality of information available in case notes and other contemporary sources. This part of the study is further limited by the absence of a mechanism for evaluating the significance and generaliseability of any findings. It is probably best viewed as a means of identifying potential causes of variation in mortality which can then be examined in quantitative studies.

Chapter 2: The history of psychiatric mortality studies

Introduction

There is much debate about the antiquity of schizophrenia. Some authorities claim to identify affected patients in ancient writings (Jeste *et al,* 1985), others such as Hare (1983), propose that the condition first appeared in the 18th Century. A third group, represented principally by Szasz (1960), claim that there is no such disease. I shall assume, for the purpose of this thesis, that the term schizophrenia describes a disease diagnosed by standard criteria, suffered by a discrete and identifiable group of individuals.

The most informative way of describing disease mortality is by comparison with the general population. This in turn requires relatively sophisticated systems for registering deaths, measuring the size of the general population and of the disease prevalence. Specific commentary on the mortality of schizophrenia necessarily dates from its delineation by Kraepelin at the end of the last century but that on mental illness dates back many centuries. In this chapter I briefly discuss those developments in the collection of public health and mental illness statistics which were necessary for calculating the mortality of mental illness. I then review early comments on mortality and mental illness and conclude with an overview of the state of knowledge immediately before the introduction of neuroleptic drugs.

The historical development of public health and mental illness statistics

Egypt had an elaborate, though not comprehensive, death registration system from about 1250 BC. Roman officials were recording deaths by 500 BC (Brockington, 1975). A later Roman census features in the nativity story. Records were also collected in 10th Century Japan (Brockington, 1975) and probably elsewhere. The registration of births and deaths was sufficiently advanced in parts of Europe by 1705 for Halley to calculate a table of life

expectancy at various ages (Greenwood, 1948).

The first English public health records were probably the London Bills of Mortality of 1532, in which the clergy of certain parishes made weekly records of births, baptisms and deaths. The next major step was the introduction of the decennial national census in 1801, which provided a denominator for calculations of mortality rates. The 'Births, Marriages and Deaths Registration Act' (1837) provided for the voluntary registration of births, deaths and marriages, under the supervision of the Registrar General. Compulsory registration of deaths which was introduced in Finland in 1628, reached Scotland in 1855 and England and Wales in 1875 (Brockington, 1975). Most countries outside western Europe and north America still lack these statistics.

Death registers in England and Wales

Registers of deaths recorded alphabetically in quarterly folio sized volumes are available for public scrutiny at St Catherine's House in the Strand. Ethically approved studies may also verify deaths through the National Health Service (NHS) Central Register, held by the Office of National Statistics (ONS), formerly the Office of Population Census and Surveys (OPCS), at Southport. Both of these databases miss some of the deaths of those British citizens who die abroad. Neither death registration nor population census is completely accurate hence mortality studies provide only an approximation of the truth.

Mental illness statistics in England and Wales

Systematic collection of mental illness statistics in England and Wales started with the 'Act for Regulating of Madhouses' (1774). This Act established five commissioners, responsible for inspecting and licensing private madhouses in London and Middlesex, who were supposed to be notified of each admission. The 1774 Act was superseded by the 'Madhouse Act' and 'County Asylums Act' (1828) which *inter alia* created the Metropolitan Commissioners in

Lunacy, and required magistrates to submit statistics of admissions and deaths to the Secretary of State. The 'Lunatics Act' (1845) created a national body, the Commissioners in Lunacy, whose annual reports to the Lord Chancellor included statistics of asylum populations and deaths (Butler, 1985). Comprehensive national psychiatric statistics, long available in Scandinavia, have never been collected for England and Wales. In-patient statistics were published in the Mental Health Enquiry until 1986 but comparable national data on treatment outside hospital has never been systematically collected.

Early comments on the mortality of mental illness

The ancient Egyptians and Mesopotamians believed madness was caused by magic, the Bible contains descriptions of madness, suicide and melancholia, other references appear in ancient Indian and Chinese writings (Alexander & Selesnick, 1967). Classical physicians followed Hippocrates' belief that madness was localised in the brain and due to humoral imbalance (Alexander & Selesnick, 1967) and recognised the link between madness and unnatural death. Caelius Aurelianus wrote in the second century that 'victims of madness have often killed themselves by jumping out of windows' (Rosen, 1968). Artaeus noted that 'madness is attended with anger and these sometimes rend their clothes, kill their keepers and lay violent hands upon themselves' (Rosen, 1968). Glimpses of madness in the Middle Ages emerge from case histories, legal documents and records of monies spent. St Bartholomew's Hospital records describe twelfth century psychiatric cases, while the Bethlem Hospital was admitting lunatic patients by 1403 (Hunter & Macalpine, 1963). Contemporary law differentiated self-killing consequent upon madness, as in the case of John Pavey who was 'mad for one month, and with his knife four inches long killed himself' (Smith & Barraclough, 1995), from self-murder, a grave offence punishable by burial in unconsecrated ground and confiscation of wealth. Burton acknowledged the connection between melancholia and suicide in 'The

anatomy of melancholy' (1621), stating that 'seldom this malady procures death, except they make themselves away'. Francis Bacon commented in 1638 that 'many mad folks in Bethlem Hospital in the suburbs of London do live very long'. Graunt (1662) noted that 158 deaths in an estimated population of 229,250 recorded in the London Bills of Mortality were attributed to "lunacie", but commented "I fear many more than are set down in our bills, few being entered for such but those who die at Bedlam; and there all seem to die of their lunacie who die lunaticks; for there is much difference in computing the number of lunaticks that die (though of fevers and all other diseases) and those that die by reason of their madness".

Details of patient mortality in seventeenth century Bethlem Hospital are preserved in records of the Spital sermons which reviewed the work of the London. Hospitals. Hicke's 1684 sermon informed that 'in the previous year brought into Bethlem Hospital distracted men and women 75. Cured of their lunacy and discharged thence the same year 41; distracted persons buried last year 13; now remaining under cure 118' (Hunter & Macalpine, 1963). If the number 'remaining under cure' represented the population of the hospital, the annual mortality would have been about 10%. Halley's 1705 life table (Greenwood, 1948) showed that 92% of people in the general population who reached the age of thirty would survive a further five years. Thus contemporary mortality in Bethlem was probably five times that of the general population. Black (1811) reported that of 2858 patients treated at Bethlem between 1772 and 1787, 924 were discharged cured, 250 died and 1694 were deemed incurable. He noted that deaths from scurvy fell after the introduction of vegetables to the patients' diet and that deaths from smallpox had also fallen. Crowther (1811) ascribed the relative immunity of asylum inmates to epidemic infection to their seclusion from the general population.

Esquirol (1838) reported wide variations between the mortality in different French asylums (Table 2.1). He found mortality to be highest in the first two

years after admission, higher during the winter months and higher among males than among females and concluded that mortality was influenced by a variety of local factors including diet, quality of treatment and the general environment of the asylum. Esquirol also calculated a ratio of deaths to admissions of 1:3 in dementia, 1:12 in melancholia, 1:16 in monomania (the condition corresponding most closely with modern schizophrenia) and 1:25 in mania. These figures date from the early years of 'moral treatment'. Mortality may well have been higher during the era of widespread physical restraint.

Table 2.1: Mortality in three French asylums 1784-1805

Hospital	Admissions	Deaths	Deaths/admissions
Bicêtre (male) 1784-94	1405	685	48.5%
Salpetrière (female) 1801-5	1002	250	25%
Charenton (mixed) 1803	499	82	16.5%

Esquirol (1838).

Esquirol did not discuss the causes of death in monomania but a series of melancholic deaths (Table 2.2) suggests most were probably secondary to poor diet and general health.

Table 2.2: Cause of death in 176 patients with melancholia 1784-1805

Cause of death	Number (%)
Pulmonary consumption	62 (35%)
Chronic slowness of the abdomen	32 (18%)
Scurvy	26 (15%)
Fever of emaciation	24 (14%)
Maladies of the heart	16 (9%)
Fever of inactivity	10 (6%)
Apoplexy	6 (3%)

Esquirol (1838).

Asylum mortality in England and Wales (1840-1914)

William Farr, Compiler of Abstracts to the Registrar General and Chief Statistician to the Registrar General's Office, produced the first systematic study of asylum mortality in 1841. Farr compared the gender specific annual mortality/1000 population in different asylums with national rates in the age group 30-35, the modal age group of asylum patients. This procedure probably overestimated asylum mortality as the asylum cohorts will have included older patients with a higher expected mortality, but is otherwise very similar to the Standardised Mortality Ratio (SMR). Farr found similar patterns of excess mortality to Esquirol. He calculated that asylum mortality varied between three and fourteen times that of the general population, concluding that some of the excess deaths '...may be fairly ascribed to insanity. The excess above this must be attributed to the diseases generated by the limited space in which the unhappy lunatics are confined - to the collection of large numbers under the same roof - the impurity of the atmosphere - the want of exercise and warmth - the poor unvaried diet - and the deficiency of medical attendance' (Farr, 1841). Part of the excess asylum mortality was due to the high prevalence of neuropsychiatric diseases. Prichard (1835) estimated that most of the one sixth of admissions suffering from general paralysis of the insane (GPI) died within three years. Conolly (1847) attributed the higher excess male mortality to a higher prevalence of GPI and epilepsy. The Commissioners in Lunacy (1902) recorded that about a third of asylum deaths were from neuropsychiatric disease. Most other deaths were from infectious or heart disease (Table 2.3). These diagnoses are probably reliable as the autopsy rate at Colney Hatch Asylum, and by inference other asylums, was over 90% (Hunter & Macalpine, 1973).

Table 2.3: Leading causes of death in English asylums in 1901

Cause of death	Proportion of asylum deaths	Death rate/1000 patients
Tuberculosis	17%	18.2
GPI	16%	17.6
Heart disease	11%	11.4
Senile decay	9%	10.1
Epilepsy	5%	5.0
Dysentery	5%	5.0

Commissioners in Lunacy (1902).

The mortality of individual asylums was also affected by the varying health and circumstances of patients prior to admission. Sykes (1840), Farr (1841) and Thurnam (1845) noted a higher mortality in the county asylums which treated paupers, than in the charitable asylums which admitted only private patients. Parry Jones (1972) observed the same pattern in private Oxfordshire madhouses (Table 2.4), where a fifth (21%) of deaths occurred within four weeks of admission, suggesting that many pauper patients were moribund on admission.

Table 2.4: Mortality in neighbouring Oxfordshire madhouses 1839-1843.

	Number (%) Hook Norton	Number (%) Witney
Total admissions	634	111
Private patients	137 (22%)	107 (96%)
Pauper patients	497 (78%)	4 (4%)
Poor health on admission	129 (20%)	4 (4%)
Deaths	139 (22%)	10 (9%)

Parry Jones (1972).

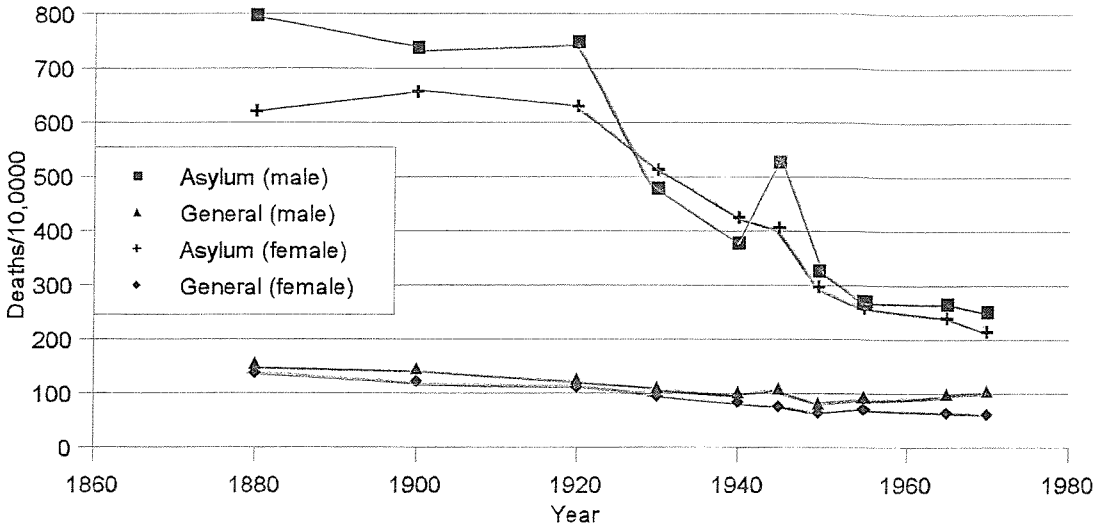
Mortality was also affected by the regime and circumstances of individual institutions. Thurnam (1845) commented on the importance of nutrition. Conolly (1847) claimed a 30% reduction in mortality at Hanwell Asylum, by

improving the diet. West Yorkshire Asylum reported 15% cholera mortality during the 1848-9 national epidemic, asylums with safe water supplies reported no cholera deaths (Wright, 1850). The Commissioners in Lunacy reported one or two suicides each year in most asylums. They also reported accidental deaths notably a 1902 tragedy when 51 patients died in a fire at Colney Hatch Asylum. Assaults by fellow patients or attendants were common and occasionally fatal. Schizophrenia was not recognised in England and Wales at this time but contemporary case notes (Renvoize & Beveridge, 1989; Turner, 1990; Parker *et al,* 1993) suggest that a quarter of asylum patients would now receive such a diagnosis. Renvoize & Beveridge (1989) assigned research diagnostic criteria (Spitzer *et al,* 1978) diagnoses to 76 Victorian patients in the York Retreat and reported that 38% of those with schizophrenia but only 15% of those with affective disease died in hospital. Taken with Farr's contemporary evidence (1841), these figures strongly suggest an excess contemporary mortality in schizophrenia, mostly from infectious disease (Commissioners in Lunacy, 1902).

Asylum mortality in the pre-neuroleptic era

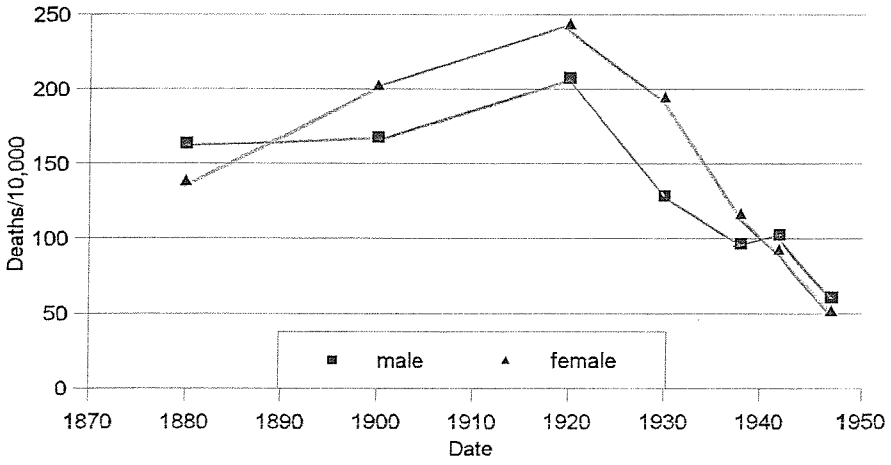
The asylum population of England and Wales grew from 74,000 in 1900 to 140,000 in 1930 peaking at 151,400, 0.3% of the population, in 1954 (Jones, 1972). The pattern was similar elsewher in Western Europe, Australasia and North America. The best continuous data on asylum mortality during this period come from Norwegian national statistics (Ødegård, 1952; Saugstad & Ødegård, 1979). These show that asylum mortality was fairly stable between 1880 and 1920, but fell sharply over the next thirty years, apart from a small peak during the second world war, due to malnutrition (Ødegård, 1952). Male asylum mortality then stabilised at about three times the population rate, female mortality continued to fall. These changes occurred against a steady fall in general population mortality (Figure 2.1), producing a peak excess asylum mortality in the 1920s (Figure 2.2).

Figure 2.1: Annual mortality in the Norwegian asylums and general population by gender 1870-1974



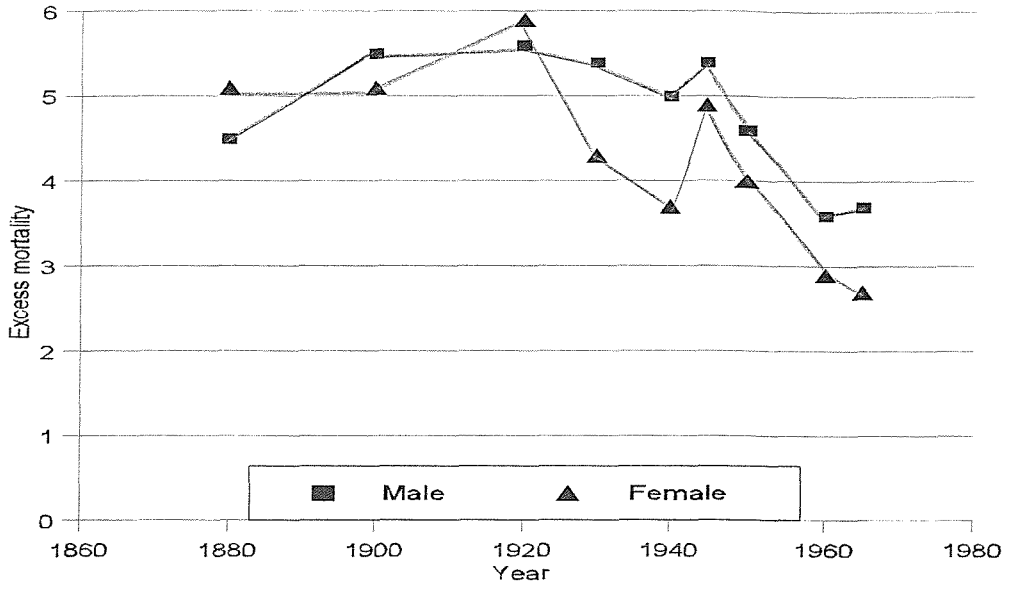
Ødegård (1952), Saugstad & Ødegård (1979).

Figure 2.2: Excess mortality in Norwegian psychiatric hospitals 1880-1970



Odegård (1952), Saugstad & Ødegård (1979).

Figure 2.3: Annual tuberculosis mortality /10,000 population in Norwegian psychiatric hospitals



Ødegård (1952), Saugstad & Ødegård (1979).

Some of the change in asylum mortality was due to the fall in incidence of GPI (Grob, 1983). Most reflected changes in mortality from tuberculosis (TB) (Figure 2.3). TB mortality in the general population started to fall in the 1880s as a result of increased resistance secondary to better living standards, possibly exacerbated by a decline in pathogenicity. This decline, hastened by X-Ray screening and the isolation of patients with active TB, predated the introduction of streptomycin. The high asylum TB mortality, recognised as early as 1909 (Mott), continued to increase until the 1920s. This was partly because asylums were slow to introduce X-Ray screening and isolation of affected patients but more importantly because wards were overcrowded and patients malnourished (Alström, 1942), ideal circumstances for the mycobacterium to flourish.
Many extra asylum deaths occured during both world wars from malnutrition and increased susceptibility to disease (Alström, 1942; Ødegård, 1952). Most of an estimated 17,000 extra asylum deaths in England and Wales, officially

ascribed to the influenza epidemic of 1918-19, were probably from TB consequent on malnutrition (Crammer, 1992). Contemporary mortality varied enormously between asylums and many deaths resulted from unnecessary cutting of rations by over zealous Hospital Management Committees (Crammer, 1992). During the second world war the asylum TB mortality increased in Norway (Ødegård, 1952) Sweden (Alström, 1942), Finland (Ekblom & Frisk, 1961) and probably in other countries both combatant and neutral. People with schizophrenia were among the 200,000 mentally and physically disabled murdered in Germany often with the complicity of psychiatrists and other mental health workers (Burleigh, 1994). In England and Wales the improved diet consequent on effective food distribution prevented a repeat of the raised asylum mortality of the first world war.

Schizophrenia mortality in the pre-neuroleptic era

Schizophrenia was delineated by Kraepelin (1893) under the name dementia praecox and named by Bleuler in 1911. By the 1930s patients with schizophrenia constituted about two thirds of the asylum population (Alström, 1942). Some would not meet modern diagnostic criteria, but it is likely that many asylum deaths were of patients with schizophrenia.

Kraepelin commented of dementia praecox, that 'life is threatened only very slightly'. He noted that suicide occurred in the acute and chronic stages, and speculated that negativism, inadequate diet and poor cooperation with treatment of concurrent medical disorders also contributed to the increased mortality (Kraepelin, 1919). Bleuler calculated that schizophrenia was associated with an excess mortality of 1.4:1, and remarked that death usually resulted from 'the indirect consequences of psychosis: refusal of food, intentional or unintentional injuries, suicide, tuberculosis and other diseases resulting from unhygienic ways of life' (Bleuler, 1911).

The first specific analyses of schizophrenia mortality were in three large asylum

based studies, from the USA (Malzburg, 1934), Norway (Ødegård, 1936) and Sweden (Alström, 1942). All reported significantly raised SMRs. Schizophrenia SMRs were higher in females than males and highest during the first years of hospital treatment. These SMRs were however lower than those of the whole asylum population (Table 2.5) which still included many patients with neuropsychiatric diseases. The higher SMR of Ødegård's (1936) study was probably because he included the first world war years. Most extra deaths were from TB or pneumonia. Suicide was increased but uncommon.

Table 2.5: The excess mortality of schizophrenia and in all asylum patients 1916-40

	SMR all asylum patients		SMR schizophrenia	
Author	Male	Female	Male	Female
Ødegård (Norway, 1916-40)	470	550	320	480
Malzberg (USA, 1928-31)	470	520	230	250
Alström (Sweden, 1924-36)	400	440	190	230

Iatrogenic mortality

Bleuler (1978) estimated that 17% of deaths in a schizophrenic cohort followed at the Bürgholzi Hospital in Zürich from 1942-65, were treatment related. Henderson & Gillespie (1952) reported mortality of up to 5% for continuous narcosis treatment (introduced in 1901), mostly from respiratory infection, 0.6% for insulin coma therapy (introduced in 1933), 0.1% for cardiazol induced convulsions (introduced in 1934) and 0.5% for unmodified ECT (introduced in 1937). Most of the 100,000 leucotomies performed worldwide between 1935 and 1960, with an operative mortality between 0.8% and 2.5% (Swayze, 1995), were for schizophrenia.

Schizophrenia mortality outside the asylum

More than half the patients admitted to hospital with a diagnosis of schizophrenia during the first half of this century were subsequently discharged (Rennie, 1939; Kay & Lindelius, 1970). There must therefore have been a substantial population with recovered or partially recovered schizophrenia living outside hospital. Little is known about their mortality. Kay & Lindelius (1970), report high death rates from contemporary follow-up studies, mostly from Germany, unstandardised and with high rates of attrition.

Three long term follow up studies reported lower SMRs than those seen in asylum studies (Table 2.6). Kay & Lindelius (1970) confirmed the high asylum mortality from TB and pneumonia but did not examine deaths outside the asylum. Tsuang *et al* (1980) and Kendler (1986) reported increased unnatural and a small increase in natural deaths. None of these studies reported where subjects were living at the time of death so it is impossible to separate disease from asylum related mortality. The relatively lower SMRs may reflect reduced exposure to TB (Ødegård, 1952) or may be due to confounding variables, principally the long follow-up times. The lack of contemporary data about mortality outside the asylums makes comparison with modern, predominantly community based, mortality rates inappropriate.

Table 2.6: SMRs in follow-up studies of patients with schizophrenia 1900-81

Author	Follow up	Male SMR	Female SMR
Kay & Lindelius (Sweden)	1900/10-1958	160	210
Kendler (USA)	1917/27-1981	180	
Tsuang & Woolson (USA)	1935/44-1974	144	180

Summary of studies from the pre-neuroleptic era

The mortality of mental illness and subsequently of schizophrenia has probably always been higher than that of the general population. The available literature

suggests that some of this excess mortality was directly related to disease and treatment, but much was a by product of the living conditions experienced by the unfortunate patients. Modern patients are exposed to different risk factors than their predecessors. It is impossible to define a precise point when conditions changed but the introduction of chlorpromazine, in 1952, provides a convenient starting point for a modern analysis of mortality.

Chapter 3: Modern psychiatric mortality studies

Introduction

Most modern studies of psychiatric mortality identify a patient cohort and then measure mortality at a defined point. Outcome is established by individual follow-up or by record linkage to standard databases. In either case accuracy depends on the detail of the method. How well results represent disease mortality depends on the selection procedure. All published studies but one are of patients in contact with psychiatric services hence this thesis might better be titled 'The mortality of patients with schizophrenia in contact with psychiatric services'.

The sole population based study (Bruce *et al,* 1994) included too few patients with schizophrenia to give a useful indication of the representativeness of current findings. Published studies probably overestimate disease mortality as most patients without specialised psychiatric contact probably have less severe disease and are thus at lower risk of premature death. This is perhaps an academic issue as psychiatrists can only hope to influence the mortality of patients who are known to them.

Some errors are common to record linkage and follow up studies, some specific to each method. The methods are complementary as record linkage studies yield statistically powerful analyses while follow up studies can provide the clinical details necessary to interpret these results. I will now critically describe methods of measuring the mortality of mental illness before summarising findings in chapter four.

Record linkage studies

The term record linkage, which dates from 1947 (Acheson, 1967), describes a process whereby identifying characteristics, usually name and date of birth, are used to bring together separately recorded data about an individual. In psychiatric mortality studies the most common linkage is between case register

entries and death certificates. This process has been greatly facilitated by the introduction of computerised databases which allow large cohorts to be studied with consequent high statistical power. The best of these studies provide a comprehensive and reliable analysis of the mortality of a particular cohort.

The psychiatric case register

The sampling frame in psychiatric record linkage studies is usually provided by a psychiatric case register. These registers which date back to at least 1877 (Ten Horn, 1986), were developed in response to concerns about the adequacy of asylum records (Thurnam, 1845). Registers vary in their inclusion criteria (Ten Horn, 1986) but share the characteristic that each individual has one entry, with subsequent contacts added to the original record. Scandinavian case registers are particularly comprehensive; the Norwegian In-Patient Register, established in 1936 (Ten Horn, 1986) is probably the longest running. The Danish National Register provided subjects for the largest and most statistically powerful studies of schizophrenia mortality (Mortensen & Juel, 1990; 1993). The UK does not have a national psychiatric case register. Some of the local registers, established by the NHS in Aberdeen, Camberwell, Cardiff, Edinburgh, Nottingham, Oxford and Salford have been used in schizophrenia mortality studies (Herrman *et al,* 1983; Hassall *et al,* 1988; Baxter, 1996). Most subjects in this follow-up study were identified from the Southampton case register.

Measurement of attrition in psychiatric record linkage mortality studies

Simple linkage of case register and death certificate (Babigian & Odoroff, 1969; Eastwood *et al,* 1982; Haugland *et al,* 1983; Allebeck & Wistedt, 1986; Black, 1988; Hassall *et al,* 1988, Zilber *et al,* 1989; Newman & Bland, 1991) does not measure completeness of follow-up. Subjects without death certificates are assumed to be alive with a consequent underestimate of cohort mortality. Herrman *et al* (1983) estimated loss to follow up due to migration out of the

catchment area at 10% and Black *et al* (1985) at 6%. National cohorts may have lower attrition rates as people are probably more likely to move within a country than to emigrate.

Completeness of follow-up can be measured by linking the sampling frame both to a death register and to an ongoing population (Saku *et al*, 1995; Amaddeo *et al,* 1996) or case register (Weiner & Marvit, 1977; Mortensen & Juel, 1990; 1993; Baxter, 1996). In England and Wales this can be done through NHS Central Records which list all patient registrations with General Practitioners (GPs), or through local case registers. Neither are entirely reliable as people move without informing the database. Mortality is probably higher in subjects lost to follow-up because of third world emigration or loss of medical contact, hence studies with known attrition probably still underestimate SMRs.

Other errors of record linkage studies

Subjects may be missed because of lost or incomplete records or treatment outside a particular service. Recording errors, introduced by subject or recorder, may prevent correct matching. Such errors are common, Baldwin (1971) reported a 12% variation in multiply recorded case register dates of birth. A link may be missed if someone changes their name, or be made incorrectly when two individuals have similar personal details. The likelihood of such errors decreases with the amount of information on each individual. The NHS number, a unique identifier, is rarely recorded in case registers (Baldwin, 1971). Pilot studies have produced varying estimates of error. Wood *et al* (1985) compared deaths recorded on two separate databases and concluded that the mortality estimate could be as poor as 75% of the true value.

The validity of case register diagnoses is also questionable. Clinicians vary in their diagnostic practices, registers vary in their data collection and coding procedures (Sytema *et al,* 1989). Diagnosis is rarely verifiable as limited space means few clinical details are recorded.

Individual follow-up studies

In these studies subjects, identified from case register (Lesage *et al,* 1990), service contact (Martin *et al,* 1985; Anderson *et al,* 1991) or population survey (Bruce *et al,* 1994), are followed until a specified date. The fact of death is established by record linkage but further details are taken from case notes, death certificates and other relevant sources. Attrition is easily measured. Recording and linking errors are unlikely because of the greater volume of data. Diagnosis can be verified from case records. Mortality is probably higher among subjects lost to follow-up, hence these studies probably also underestimate mortality. Individual follow-up theoretically provides details of illness, treatment and individual deaths which explain raised SMRs and lead to changes in clinical practice. Data can be descriptive and quantitative but the process is time consuming, which perhaps explains why schizophrenic cohorts have, to date, been small. SMRs, useful for assessing generaliseability, have only been reported in four cohorts, with a combined total of 87 deaths (Martin *et al,* 1985; Lesage *et al,* 1990; Anderson *et al,* 1991; Bruce *et al,* 1994). None of these papers described the circumstances of death systematically. Lesage *et al* (1990) and Anderson *et al* (1991) listed causes of death and described the circumstances of a few unusual deaths. Allebeck *et al* (1986) discussed those unnatural deaths where cause was undetermined. These small subject numbers raise doubts about generalisation to other situations.

Analysis of in-patient records

These studies use statistics about in-patient deaths (Giel *et al,* 1978; Saugstad & Ødegård, 1979; Brook, 1985) to measure the hospital mortality of particular patient groups. Hospital deaths are well documented and series likely to be complete, but subjects are lost to follow-up after discharge. Since most people with schizophrenia now spend little time in hospital, these studies are no longer representative of the broad population with schizophrenia.

Statistical analysis

Crude measures of mortality are adequate in acute or highly lethal medical conditions. A more sophisticated analysis is needed in schizophrenia, a chronic disease where death is infrequent. The most widely used measure of psychiatric mortality is the SMR, the ratio of observed deaths to expected deaths, multiplied by 100. A cohort with a raised risk of death will have an SMR greater than 100 and one with a reduced risk an SMR of less than 100. Tests of differences between SMRs are usually based on the Poisson distribution (Gardner & Altman, 1989), though some earlier analyses used chi squared statistics. Expected deaths are calculated by computing age and gender stratified person-years of follow up (Breslow & Day, 1987) and multiplying these figures by the appropriate general population death rates.

The SMR can be used to examine overall cohort mortality, mortality from specific causes and mortality of subgroups. The proportion of false positive results produced by repeated SMR calculations on the same cohort is properly addressed by the Bonferroni calculation (Bland, 1995), however the small number of deaths in most cohorts makes this impracticable. Multiple SMRs should therefore be interpreted conservatively.

The use of the SMR in schizophrenia research has also been questioned (Daly *et al,* 1991), on the basis that it may obscure important age related differences in mortality. An alternative analysis which measures the years of potential life lost (YPLL) through premature death (Daly *et al,* 1991) may be more appropriate. Brief mention should also be made of the, now discredited, proportional mortality (PM) analysis. This analysis, which compares the proportion of deaths from a particular cause with the proportion of such deaths in the general population, is flawed because a high mortality from an unusual cause, such as suicide, may produce low PMs from causes where mortality is actually raised (Fox, 1978).

Chapter 4: Meta-analysis

Introduction

In this chapter I outline the method used in the meta-analysis of modern studies of schizophrenia mortality. I then report the results of the meta-analysis.

Background

Literature review has an important and well-established role in refining otherwise unmanageable volumes of original research for use by clinicians and other decision makers. The traditional narrative review structure has been criticised for lack of detail about search protocols, study selection and statistical techniques (Mulrow, 1987). Modern evidence based medicine demands systematic review in which these processes are made explicit allowing the reader to judge the validity of conclusions (Mulrow, 1995; Lancet, 1997). Systematic review is often complemented by the statistical technique of meta-analysis, in which numerical information from individually non-significant clinical studies is combined to produce statistically powerful answers to research hypotheses.

The 'gold standard' in medical research remains the randomised controlled trial (RCT) of sufficient size to provide a definitive answer to the question being addressed, but meta-analysis can offer useful guidance when such data are not available. Meta-analysis also identifies studies where results fall outside the expected parameters, and hence warrant further investigation. The technique, used in medicine since the mid 80s (Chalmers & Haynes, 1995), is most commonly used to study therapeutic interventions, but can also be applied to epidemiological studies.

Bailir (1997) and others question the value of producing a 'best estimate' figure of effect, claiming this oversimplifies a complex problem by assuming that differences in outcome, actually caused by differences in the populations, treatments, outcome measurements, study design and quality, are due to chance

(Naylor, 1997). Comparison of meta-analysis with later RCTs show about 80% directional agreement but much lower agreement about whether findings are statistically significant (Villar *et al,* 1995; Cappelleri *et al,* 1996; Lelorier *et al,* 1997). This may lead to the recommendation of ineffective treatment or rejection of useful treatments in up to a third of cases (Lelorier *et al,* 1997).

The use of meta-analysis in observational studies

Most aetiological studies necessarily use an observational design as the RCT, the principal research design in the evaluation of medical interventions, is ethically or practicably inappropriate (Egger et al, 1998). Meta-analysis is increasingly used to summarise the results of observational studies. Observational studies differ from RCTs in being far less able to eliminate the effects of bias and confounding variables, cohort studies being particularly susceptible to the effects of confounding variables (Egger et al, 1998) Meta-analysis proceeds from the assumption that differences in results are due to chance (Bailir, 1997). If differences are due to confounding variables then the process of meta-analysis attaches spurious precision to incompatible data sets (Egger et al, 1998).
I nevertheless believe that the use of meta-analysis to produce a quantitative measure of excess mortality remains a useful exercise. The procedure provides useful comparative data (eg: the relative proportion of excess deaths from particular ICD-9 disease categories), identifies gaps in our knowledge and identifies studies with outlying results. I also believe that the presentation of data in this way can aid the understanding of complex issues and otherwise unmanageable volumes of information.

Method

I identified papers from searches of Medline and the Bath Information and Data Services (BIDS) Gateway database, using the key words 'mortality', follow up' and 'outcome' with 'schizophrenia' and mental illness'. The resulting citations

were checked until no new references were forthcoming. The search was restricted to English language publications for reasons of expediency. Papers were included in the meta-analysis if they met the following criteria:

- they described subjects with a diagnosis of schizophrenia.
- they gave the number of observed deaths.
- they gave the number of expected deaths or included sufficient details to allow this to be calculated without reference to external sources.
- the cohort was recruited after 1952, contained at least 100 subjects at inception and was followed for at least two years.
- there was a stated loss to follow up of less than 15%.

I excluded cohorts of fewer than 100 subjects from the meta-analysis to reduce potential bias from the preferential publication of studies reporting extreme variations from expected mortality; studies of less than two years duration to reduce bias from the clustering of suicides around contact with psychiatric services; cohorts with a drop out rate above 15% as mortality is probably higher among subjects lost to follow-up (Sims, 1973). In cases of duplicate publication (Tramèr *et al,* 1997) I took data from the paper describing the largest cohort. The cut-off date for inclusion was 31.12.97.

Statistical methods

I calculated:

- Aggregate SMRs by dividing the sum of the observed deaths by the sum of the expected deaths and multiplying the resulting figure by 100. Confidence intervals (CI) and significance statistics were calculated from the Poisson distribution (Gardner & Altman, 1989) and heterogeneity of cohorts measured as described by Thompson (1993). CIs are significant at the 5% level when the lower value is greater than 100 or the upper value lower than 100.

- Total patient years at risk by multiplying the number of subjects in each cohort by the mean length of follow-up and summing the resulting figures.
- Annual mortality/10,000 population by dividing the observed deaths in each cohort by the mean length of follow-up and converting the results to rate/10,000.
- Weighted aggregate annual mortality/10,000 population by multiplying each individual figure by the number of subjects then dividing the sum of these figures by the total number of subjects in the meta-analysis.
- Excess deaths by subtracting expected from observed deaths.
- Contribution of a disease category to the overall excess mortality by dividing the number of excess deaths in that category by the total number of excess deaths.

Results

Nineteen studies satisfied the criteria for inclusion in the meta-analysis (Table 4.1). These examined the mortality of an estimated 66,833 subjects over 447,789 subject years. Mortality was increased in every study in the meta-analysis. The aggregate annual CMR was 189 deaths/10,000 population, a ten year survival of 81%, and the aggregate SMR 151 (CI 148-154).

Trends in mortality

Two Danish studies which measured the five-year SMR in successive national cohorts during the 1970s and 80s suggest that the SMR is rising in first episode schizophrenia (Munk-Jørgensen & Mortensen, 1992) but falling in chronic schizophrenia (Licht *et al,* 1993). These findings are not inconsistent. The mortality of chronic schizophrenia, largely from natural causes (Mortensen & Juel, 1990), is susceptible to improved medical treatment. The excess mortality in first episode disease is mostly from suicide, which appears to be increasing

(Mortensen & Juel, 1993).

This meta-analysis found a significantly higher ($P<0.001$) aggregate SMR from studies published in the 1980s (SMR 191, CI 183-199) than from studies published in 1970s (SMR 152, CI 144-160) or 1990s (SMR 140, CI 137-143). These differences are probably due to confounding variables as the differences were non-significant when the comparison was restricted to studies of mixed phase of illness cohorts (1970s SMR 178, CI 166-191; 1980s SMR 201, CI 192-210; 1990s SMR 192, CI 180-204).

The lack of asylum-era data about schizophrenia mortality in patients living outside the asylums means that we do not know whether the change to non-hospital based treatment has altered the overall mortality. In-patient mortality has fallen from pre-war levels (Saugstad & Ødegård, 1979) but first episode SMR (Mortensen & Juel, 1993) is similar to the SMR of the asylums (Malzburg, 1934; Ødegård, 1936; Alström, 1942). It is therefore quite possible that all the improvements in treatment of the last half century have not led to any reduction in patient mortality (Hansen *et al,* 1997).

Table 4.1: All cause mortality of schizophrenia

First author (Reference date)	Country	Source of diagnosis	Study method	Cohort size	Follow-up (years)	Deaths		SMR (95% CI)
						Observed	Expected	
Babigian (1969)	USA	case register	Record linkage	*8080	0- 6	541	310	175 (160-189)
Weiner (1977)	USA	case register	Record linkage	1689	10	219	116	188 (164-210)
Giel (1978)	Netherlands	case register	In-patient records	8142	2	537	426	126 (116-136)
Eastwood (1982)	Canada	ICD-8	Record linkage	182	9	7	5	145 (57-273)
Haugland (1983)	USA	DSM-II	Record linkage	351	3 .5	20	11	181 (110-270)
Herrman (1983)	UK	ICD-8	Record linkage	592	4	57	30	192 (146-246)
Brook (1985)	Netherlands	case register	In-patient records	5226	2	486	305	159 (145-174)
Wood (1985)	USA	DSM-III	Record linkage	*8779	5	709	379	187 (174-201)
Allebeck (1986)	Sweden	ICD-9	Record linkage	1190	10	231	96	239 (209-271)
Black (1988)	USA	ICD-9	Record linkage	891	0-10	45	18	260 (178-358)
Hassall (1988)	UK	case register	Record linkage	695	2-11	68	39	173 (134-217)
Zilber (1989)	Israel	ICD-9	Record linkage	*9178	5	816	395	207 (192-221)
Mortensen (1990)	Denmark	'Kraeplinian lines'	Record linkage	6152	0-30	4569	3882	118 (114-122)
Anderson (1991)	UK	ICD-9	Follow up	532	2-14	69	28	249 (194-312
Newman (1991)	Canada	ICD-9	Record linkage	3623	0-10	301	116	259 (231-290)
Mortensen (1993)	Denmark	ICD-8	Record linkage	9156	10-18	1100	329	334 (315-354)
Amaddeo (1995)	Italy	ICD-9	Record linkage	*305	0-10	23	13	176 (111-255)
Baxter (1996)	UK	ICD-9	Record linkage	1398	10-18	462	291	159 (144-173)
Hansen (1997)	Norway	ICD-9	Record linkage	672	1-12	91	45	200 (160-250)
Total				66833		10351	6833	151 (148-154)

* calculated from data supplied in the text.

Gender.

Twelve studies measured gender specific mortality (Table 4.2). Aggregate mortality was significantly increased in both males and females. There was no gender difference in natural SMR but a significantly higher male unnatural SMR. This produced a small but significantly higher overall male mortality (aggregate male SMR 148, CI 144-152; aggregate female SMR 139, CI 134-144). There was no significant gender difference in the SMR from accidents but the male suicide SMR (943, CI 873-1015) was significantly higher than the equivalent female figure (673, CI 591-763).

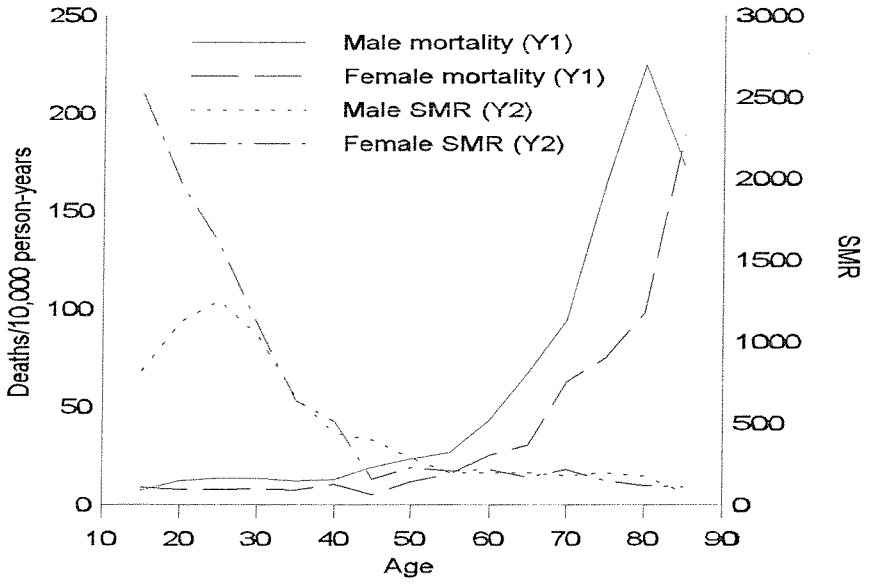
Table 4.2: Mortality by gender.

First author	Male deaths			Female deaths		
(Reference date)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
Giel (1978)	266	220	121 (107-136)	271	206	131 (116-148)
Eastwood (1982)	3	3	100 (18-245)	4	2	223 (58-493)
Herrman (1983)	32	16	197 (135-474)	25	13	187 (121-267)
Brook (1985)	249	159	157 (138-177)	237	146	162 (142-184)
Allebeck (1986)	110	47	232 (191-277)	121	49	246 (204-292)
Black (1988)	21	10	216 (134-319)	24	8	300 (192-432)
Hassall (1988)	21	6	328 (203-483)	47	33	143 (105-187)
Mortensen (1990)	2207	1886	117 (112-122)	2362	1920	123 (118-128)
Newman (1991)	190	68	279 (241-321)	111	48	231 (190-276)
Mortensen (1993)	707	151	468 (434-503)	393	168	234 (211-256)
Amaddeo (1995)	13	5	273 (146-438)	10	8	120 (57-207)
Hansen (1997)	65	19	350 (270-440)	26	10	250 (160-370)
Natural causes (001-799)	2533	2046	124 (119-129)	2566	2056	125 (120-130)
Unnatural causes (E800-E999)	715	141	508 (471-586)	351	102	345 (310-382)
Total	3884	2590	148 (144-152)	3631	2611	139 (134-144)

Age

Most deaths in schizophrenia, as in the general population, occur in the elderly (Mortensen & Juel, 1993). In first episode disease the absolute mortality was probably increased at all ages (Figure 4.1), though rates in the very old had wide confidence intervals (Mortensen & Juel, 1993). The SMR was highest in the young, principally due to high rates of suicide (Anderson *et al,* 1991; Newman & Bland, 1991; Mortensen & Juel, 1993), falling with increasing age.

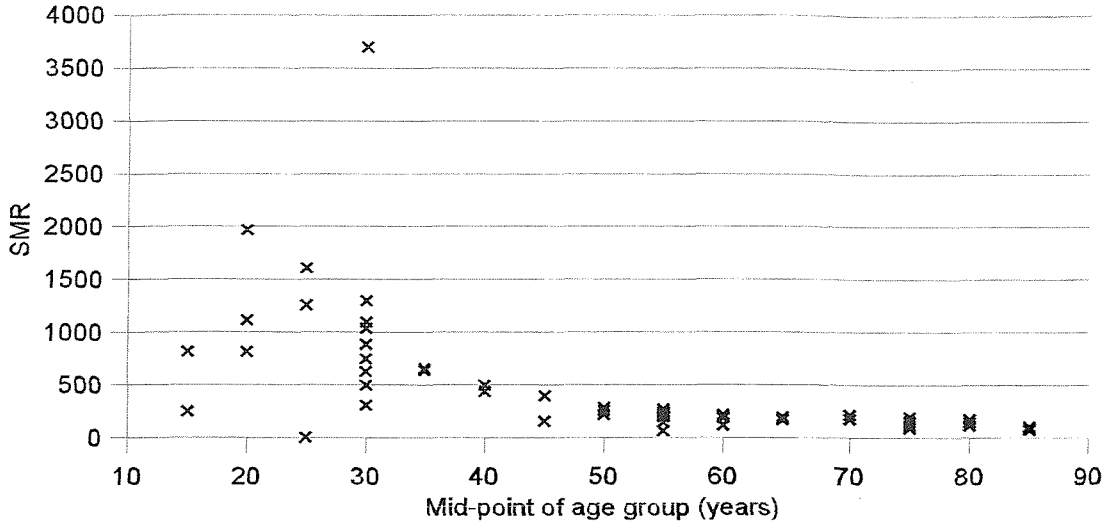
Figure 4.1: Absolute mortality and SMR in first episode schizophrenia



(Figure drawn from data in Mortensen & Juel, 1993).

The overall SMR falls with age in most cohorts (Figure 4.2) and has important confounding effects on cohort mortality. The aggregate natural SMR among first episode subjects was significantly higher than the equivalent rate among chronic patients in the two Danish national cohorts (Mortensen & Juel 1990; 1993). Suicide, cardiovascular and probably respiratory SMRs fall with increasing age (Mortensen & Juel, 1993).

Figure 4.2: Variation of SMR with age at recruitment



Reference: Giel *et al* (1978); Brook (1985); Black (1988); Hassall *et al* (1988); Zilber (1989); Anderson *et al* (1991); Newman & Bland (1991); Mortensen & Juel (1993).

Phase of illness

The results of the studies included in the meta-analysis were significantly heterogeneous (Thompson, 1993; Chi squared=65.9, df=17, P<0.001). Analysis of data by phase of illness showed that first episode schizophrenia (Eastwood *et al,* 1982; Mortensen & Juel, 1993) had an SMR of 332 (CI 312-351) and chronic schizophrenia (Giel *et al,* 1978; Brook, 1985; Mortensen & Juel, 1990) an SMR of 121 (CI 118-124). Cohorts of subjects at varying points in their illness had an SMR of 193 (CI 187-206). Division of the cohorts in this way, led to a substantial fall in heterogeneity (Chi squared=6.9, df=15, P=0.5) suggesting that phase of illness explains a large part of the original heterogeneity. The size of this effect suggests that phase of illness is an important confounding variable which should be addressed in future mortality studies.

First episode cohort studies provide the best estimate of disease mortality as other cohorts will have lost some of those subjects at highest risk (Newman & Bland, 1991; Munk-Jørgensen & Mortensen, 1992; Mortensen & Juel, 1993). Even first-episode studies underestimate 'true' disease mortality as some people with schizophrenia die, for example from suicide, before being recognised by the

mental health services. Nevertheless the aggregate first episode SMR (332, CI 312-351) is probably the best current estimate of excess mortality.

Length of follow-up

The all cause SMR fell incrementally over the five years following a first episode of schizophrenia (Munk-Jørgensen & Mortensen, 1992), and fell with length of follow-up in most (Black, 1988; Hassall *et al,* 1988; Newman & Bland, 1991), though not all (Allebeck & Wistedt, 1986) cohorts recruited later in their illness. This was largely due a clustering of suicides at the start of follow-up (Black, 1988; Hassall *et al,* 1988; Newman & Bland, 1991; Mortensen & Juel, 1993). Mortensen & Juel (1993) found an excess suicide risk in the first year of follow-up in all age bands, except middle aged and very elderly women. This was especially marked among the young. There is no direct evidence that the natural cause SMR falls with length of follow-up, however this was significantly lower in the Danish national cohort with chronic schizophrenia, than in the equivalent first episode cohort (Mortensen & Juel, 1990; 1993).

The mortality of schizophrenic subtypes

I could not aggregate findings about the mortality of different schizophrenic subtypes as each study used different classification systems (Wood *et al,* 1985; Black & Fisher, 1992; Munk-Jørgensen & Mortensen, 1992). The most comprehensive analysis (Munk-Jørgensen & Mortensen, 1992) found a significantly raised SMR in all ICD-8 subtypes except residual schizophrenia, where the increase was non-significant. Within the cohort, simple, hebephrenic, latent and unspecified subtypes had a significantly higher SMR and catatonic, paranoid and schizoaffective subtypes significantly lower. Wood *et al* (1985) found a significantly higher SMR in DSM-III 'other' schizophrenia than in paranoid or chronic undifferentiated disease. Black & Fisher's (1992) analysis of DSM-III-R subtypes had too few deaths for useful comment. It is likely that all subtypes have an increased mortality, the details of which are yet to be determined.

Natural cause mortality (ICD-9 disease categories 001-799)

Eighty four per cent of schizophrenia deaths in this analysis were from natural causes compared to 97% of deaths in the general population (Office of Population, Census and Surveys, 1995). Most schizophrenic suicides occur early (Mortensen & Juel, 1993) so the proportion of natural deaths would probably have been higher if subjects had been followed longer.

The natural cause SMR 134 (CI 131-137) was significantly raised among both males (SMR 123, CI 118-128) and females (SMR 125, CI 120-130). Natural deaths accounted for 1555 (64%) of the 2442 excess deaths in those studies which analysed mortality by ICD category (Table 4.3). The aggregate natural SMR was significantly higher than either of the gender specific rates as it included a large Israeli cohort (Zilber *at al,* 1989) in which mortality was not analysed by gender. This study found an unusually high SMR from natural causes, principally infectious diseases, and low SMR from unnatural causes, possibly because it included recent third world immigrants.

Table 4.3: Natural cause mortality (ICD-9 disease category 001-799)

First author	Male		Female		Total	
(Reference date)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Eastwood (1982)					4	99 (25-216)
Herrman (1983)	25	161 (104-231)	21	163 (101-240)	46	165 (118-212)
Allebeck (1986)					163	184 (157-214)
Black (1988)	6	81 (29-161)	17	227 (132-347)	23	154 (98-225)
Zilber (1989)					780	221 (205-237)
Mortensen (1990)	2084	116 (111-121)	2223	121 (116-126)	4307	118 (115-122)
Newman (1991)	88	162 (130-197)	80	181 (144-223)	168	171 (146-198)
Mortensen (1993)	240	214 (189-244)	225	146 (127-165)	465	175 (159-191)
Total	2443	124 (119-129)	2566	125 (120-130)	6047	134 (131-137)

Natural cause mortality by ICD-9 disease category

The extra deaths were spread over most ICD categories with the exception of cerebrovascular and male neoplastic disease (Table 4.4). The total number of deaths exceeds the sum of the specific categories as I excluded some deaths which Zilber *et al* (1989) aggregated into idiosyncratic categories.

Two major studies (Allebeck & Wistedt, 1986; Zilber *et al*, 1989) did not analyse cause of death by gender, hence in this and subsequent tables the total observed mortality is higher than the aggregate of the gender-specific figures.

Table 4.4: Natural mortality by ICD-9 disease category

ICD-9 disease category	Male		Female		Total	
	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Infectious (001-130)			1	350 (1-1307)	4	400 (104-870)
Neoplastic (140-239)	447	76 (69-83)	591	108 (99-117)	1146	92 (87-97)
Endocrine (240-279)	2	190 (18-546)	3	250 (47-613)	10	244 (116-418)
Mental (290-319)	5	540 (171-1124)	3	630 (118-1532)	11	500 (248-839)
Neurological (320-389)	1	100 (1-329)	2	230 (21-659)	6	187 (231-436)
Cardiovascular (390-429)	1033	112 (105-119)	922	106 (99-113)	2021	111 (106-116)
Cerebrovascular (430-438)	203	82 (71-94)	248	72 (63-81)	471	78 (71-85)
Respiratory (460-519)	308	208 (185-232)	315	246 (220-274)	634	226 (209-244)
Digestive (520-579)	141	210 (177-247)	127	163 (136-192)	278	185 (164-208)
Genitourinary (580-629)	98	181 (147-219)	64	128 (98-161)	168	161 (137-187)
*Other (1-389, 630-799)	356	174 (156-192)	422	190 (144-175)	809	168 (157-180)
All natural causes (001-799)	2443	123 (118-128)	2566	125 (120-130)	6047	134 (131-137)

*disease category used in Danish national cohorts (Mortensen & Juel, 1990; 1993)

Reference: Eastwood *et al* (1982); Herrman *et al* (1983); Brook (1985); Allebeck & Wistedt (1986); Black (1988); Zilber *et al* (1989); Mortensen & Juel (1990); Newman & Bland (1991); Mortensen & Juel (1993).

Relative contribution of ICD-9 disease categories to the overall natural mortality

Table 4.5 shows the relative contribution of each disease category to the overall excess mortality. Studies which did not report results in all the stated categories have been omitted. More than half of the extra deaths were from respiratory or cardiovascular diseases, common diseases in the general population with many known risk factors. Extrapolating the proportions of deaths in two smaller studies (Allebeck & Wistedt, 1986; Newman & Bland, 1991), which published SMRs in categories which were not analysed separately by Mortensen & Juel (1990, 1993) suggests that mental diseases (290-319) account for about 13% of excess natural mortality, endocrine diseases (240-279) for 8%, neurological diseases (320-389) for 4% and infectious diseases (1-139) for 4%. Thus these diseases, though uncommon, may account for about one quarter of the excess natural mortality.

Table 4.5: Relative contribution of each ICD-9 disease category to the overall natural mortality

ICD-9 disease category	Observed deaths	Expected deaths	Observed-expected deaths	Proportion of all excess natural deaths
All natural causes (001-799)	5420	4687	+733	
Neoplastic (140-239)	1146	1247	-101	-14%
Cardiovascular (390-429)	2021	1823	+208	+ 28%
Cerebrovascular (430-438)	471	603	-132	- 18%
Respiratory (460-519)	634	280	+354	+48%
Digestive (520-579)	278	150	+128	+ 17%
Genito-urinary (580-629)	168	104	+64	+ 9%
Other (1-139, 240-389)	702	480	+222	+ 30%

Refs: Allebeck & Wistedt, 1986; Mortensen & Juel, 1990; 1993; Newman & Bland, 1991.

Neoplastic diseases (140-239)

Neoplastic diseases were the most frequently analysed of all categories of death. Considerable variations mortality were reported. The overall male mortality was significantly reduced but the female mortality was non-significantly increased. Most of the reduction in male mortality was due to low rates of lung cancer deaths (Newman & Bland, 1991). These diseases remain a significant cause of death in schizophrenia, accounting for 19% of natural deaths in the meta-analysis coming second in frequency to cardiovascular disease, as in the general population, (Office of Population Census and Surveys, 1995).

Table 4.6: Neoplastic mortality

First author	Male		Female		Total	
(Reference date)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Giel (1978)	26	46 (30-66)	29	66 (44-92)	55	55 (41-84)
Herrman (1983)	4	103 (28-631)	2	67 (6-191)	6	87 (31-170)
Brook (1985)	8	18 (7-32)	15	50 (28-78)	23	31 (20-45)
Allebeck (1985)					34	137 (95-187)
Black (1988)	4	245 (65-555)	3	160 (31-408)	7	201 (79-376)
Zilber (1989)					74	89 (70-110)
Mortensen (1990)	363	85 (76-94)	467	117 (106-128)	830	100 (93-107)
Anderson (1991)	2	46 (5-165)	2	62 (7-233)	4	46 (12-103)
Newman (1991)	13	80 (42-129)	22	140 (88-205)	35	110 (77-149)
Mortensen (1993)	27	81 (54-119)	51	101 (75-133)	78	93 (73-114)
Total	447	76 (69-83)	591	108 (99-117)	1146	92 (87-97)

Cardiovascular diseases (390-429)

Cardiovascular disease, the leading Western cause of natural death in schizophrenia, as in the general population (Office of Population Census and Surveys, 1995), accounted for about a fifth of excess natural deaths. Excess cardiovascular mortality has been found in most, but not all, modern cohort studies. Although significantly raised, the aggregate mortality was only 10% higher than expected.

Table 4.7: Cardiovascular mortality

First author	Male		Female		Total	
	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Giel (1978)	20	53 (32-78)	20	67 (40-99)	40	59 (42-78)
Herrman (1983)	9	180 (81-317)	9	300 (136-528)	18	225 (133-341)
Brook (1985)	66	90 (70-113)	49	65 (48-85)	115	78 (64-93)
Allebeck (1986)					66	173 (134-217)
Black (1988)	2	78 (7-229)	7	329 (132-626)	9	194 (89-344)
Mortensen (1990)	844	113 (106-121)	752	108 (101-116)	1596	111 (105-116)
Anderson (1991)	6	142 (52-309)	7	283 (114-583)	13	194 (103-314)
Newman (1991)	22	130 (81-190)	14	130 (82-240)	36	140 (98-189)
Mortensen (1993)	64	169 (130-216)	64	137 (106-176)	128	151 (126-179)
Total	1033	112 (105-119)	922	106 (99-113)	2021	111 (106-116)

Cerebrovascular diseases (430-438)

Cerebrovascular mortality was reduced in both males and females. This result was principally due to the cohort effect of Mortensen & Juel's (1990) study of elderly institutionalised patients which supplied 70% of subject deaths. Six of the other seven (smaller) studies showed raised cerebrovascular mortality.

Table 4.8: Cerebrovascular mortality

First author	Male		Female		Total	
(Reference date)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Giel (1978)	35	233 (162-317)	17	81 (47-124)	52	144 (108-186)
Herrman (1983)	3	176 (33-432)	2	95 (89-273)	5	131 (41-272)
Brook (1985)	10	43 (21-75)	13	41 (21-66)	23	42 (26-61)
Allebeck (1986)					20	202 (123-300)
Mortensen (1990)	138	70 (59-83)	188	69 (60-78)	326	69 (62-77)
Anderson (1991)	2	287 (27-823)	4	373 (97-829)	6	340 (123-668)
Newman (1991)	3	90 (17-222)	7	160 (63-299)	10	130 (61-223)
Mortensen (1993)	12	164 (85-286)	17	105 (61-168)	29	123 (82-175)
Total	203	82 (71-94)	248	72 (63-81)	471	78 (71-85)

Respiratory diseases (460-519)

Respiratory mortality was increased in all cohorts and was the most significantly increased category of natural death accounting for about one third of all extra natural deaths. About half the excess respiratory mortality was from pneumonia and the rest from chronic obstructive airways disease (Newman & Bland, 1991). Most pneumonia deaths (Weiner & Marvit, 1977; Herrman *et al* 1983; Brook, 1985) were in elderly institutional patients.

Table 4.9: Respiratory mortality

First author	Male		Female		Total	
(Reference date)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Allebeck (1986)					11	240 (119-401)
Mortensen (1990)	271	198 (175-223)	282	246 (218-276)	553	220 (202-239)
Newman (1991)	16	370 (211-574)	11	400 (182-671)	27	380 (250-537)
Mortensen (1993)	21	301 (182-461)	22	217 (136-328)	43	251 (182-332)
Total	308	208 (185-232)	315	246 (220-274)	634	226 (209-244)

Digestive disease (520-579)

Digestive mortality was consistently increased, with significantly raised SMRs from ileus (Mortensen & Juel, 1990), peptic ulcer (Weiner & Marvit, 1977; Newman & Bland, 1991) and cirrhosis (Weiner & Marvit, 1977).

Table 4.10: Digestive mortality

First author	Male		Female		Total	
(Reference date)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Allebeck (1986)					10	240 (113-408)
Mortensen (1990)	115	199 (164-239)	114	163 (135-196)	229	179 (157-204)
Newman (1991)	9	260 (118-458)	6	240 (90-470)	15	250 (139-392)
Mortensen (1993)	17	264 (154-407)	7	127 (50-239)	24	201 (129-290)
Total	141	210 (177-247)	127	163 (136- 192)	278	185 (164-208)

Genitourinary disease (580-629)

All studies reported increased genitourinary mortality with a significantly raised SMR in males and a trend to significance in females. Mortality from pyelonephritis and prostatic hypertrophy was significantly increased in older patients (Mortensen & Juel, 1990).

Table 4.11: Genitourinary mortality

First author	Male		Female		Total	
(Reference date)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Allebeck (1986)					6	420 (154-840)
Mortensen (1990)	93	179 (145-219)	58	126 (96-163)	151	154 (131-181)
Newman (1991)	2	370 (35-1061)	2	370 (35-1061)	4	370 (94- 807)
Mortensen (1993)	3	214 (44-626)	4	151 (41-387)	7	173 (68-325)
Total	98	181 (147-219)	64	128 (98-161)	168	161 (138-187)

Other diseases (1-389, 630-799)

The mortality from other disease categories was consistently increased. Raised SMRs have been reported for diabetes mellitus (Mortensen & Juel, 1990) and 'alcoholism' (Newman & Bland, 1991).

Table 4.12: Mortality from other diseases

First author	Male		Female		Total	
(Reference date)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Allebeck (1986)					14	298 (162-474)
Mortensen (1990)	260	140 (124-159)	362	149 (134-165)	622	165 (144-190)
Newman (1991)	8	250 (197-453)	9	310 (141-546)	17	274 (159-420)
Mortensen (1993)	96	530 (430-468)	60	269 (206-347)	156	386 (328-449)
Total	364	176 (158-194)	431	162 (147-178)	809	188 (176-202)

Unnatural cause mortality (ICD-9 E800-E999)

About 3% of all deaths in England and Wales are from unnatural causes (Office of Population Census and Surveys, 1995). This meta-analysis suggests that in schizophrenia about 16% of all deaths and 46% of excess deaths are unnatural. These proportions would probably fall with longer follow-up as suicide, the principal cause of unnatural death in schizophrenia, falls with length of disease (Mortensen & Juel, 1993) and of follow-up (Black & Winokur, 1988; Newman & Bland, 1991, Mortensen & Juel, 1993).

Every study which has measured the unnatural cause SMR has found this to be raised (Table 4.13), with an aggregate figure of 422 (CI 399-446). There is no direct evidence that overall unnatural mortality changes with age or length of illness.

Table 4.13: Unnatural mortality (E 800-E999)

First author	Male		Female		Total	
(Reference date)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Eastwood (1982)	1	185 (1-726)	2	952 (495-4228)	3	400 (75-981)
Herrman (1983)	7	1000 (396-1878)	4	800 (208-1776)	11	916 (455-1538)
Allebeck (1986)					68	840 (650-1060)
Black (1988)	15	625 (349-981)	7	1272 (504-2390)	22	733 (459-1072)
Zilber (1989)					26	117 (76-149)
Mortensen (1990)	123	147 (122-174)	139	167 (140-196)	262	157 (138-176)
Newman (1991)	102	750 (611-903)	31	790 (540-1099)	133	755 (628-884)
Mortensen (1993)	467	1173 (1069-1282)	168	1226 (1048-1419)	635	1186 (1096-1281)
Total	715	503 (467-541)	351	341 (306-377)	1160	422 (399-446)

Unnatural cause mortality by ICD-9 category

Most of the 1106 unnatural deaths were from suicide 751 (69%) or accidents 330 (30%). Homicide and undetermined death SMRs were greatly increased but accounted for few deaths.

Table 4.14: Unnatural mortality by ICD-9 disease category

ICD 9 disease category	Male		Female		Total	
	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Accidents E800-949	179	225 (194-260)	151	200 (169-233)	330	213 (190-236)
Suicide E950-959	536	998 (915-1084)	200	826 (716-945)	751	981 (913-1053)
Homicide E960-969	7	778 (308-1460)	4	571(146-1268)	11	687 (341-1154)
Undetermined E980-989	6	890 (330-1940)	8	2620 (1130-5170)	14	1430 (960-2130)
All unnatural causes E800-989	728	503 (467-541)	363	341 (306-377)	1106	422 (399-446)

Refs: Pokorny, 1964; Temoche *et al*, 1964; Weiner & Marvit, 1977; Copas & Robin, 1982; Pokorny, 1983; Allebeck & Wistedt, 1986; Nyman & Jonsson, 1986; Black, 1988; Zilber *et al*, 1989; Mortensen & Juel, 1990; Anderson *et al*, 1991; Newman & Bland, 1991; Mortensen & Juel, 1993.

Accident (E 800-E949)

Accidents accounted for 6% (326) of all deaths and 11% (173) of excess deaths in the two Danish national cohorts (Mortensen & Juel, 1990; 1993), with an aggregate SMR of 213 (CI 190-236). These were the only studies to specifically report accidental deaths. Allebeck *et al* (1986) reported that most accidental deaths in elderly schizophrenics were from 'age-related causes such as falls'. Mortensen & Juel (1990) found that two thirds of the excess accidental deaths among older patients were from falls (SMR 166, CI 138-199) and a third from aspiration (SMR 3153, CI 2196-4385)

Suicide (E 950-959)

The weighted mean annual suicide rates, male (46/10,000 population) and female (20/10,000 population), were about 35 times those for the general population of

England and Wales (1.2/10,000 and 0.6/10,000 respectively) (Office of Population Census and Surveys, 1985). Suicide accounted for 10% (564) of all deaths and 32% (497) of excess deaths in the Danish national cohorts (Mortensen & Juel, 1990; 1993), making it the largest single cause of excess mortality. The SMR was raised in all cohorts in the meta-analysis, with an aggregate figure of 836 (CI, 783-890), and was significant at the 5% level in all except Mortensen & Juel's (1990) cohort of elderly chronic patients (Table 4.15). The aggregate male SMR (943, CI 873-1015) was significantly higher than the female figure (673, CI 591-763).

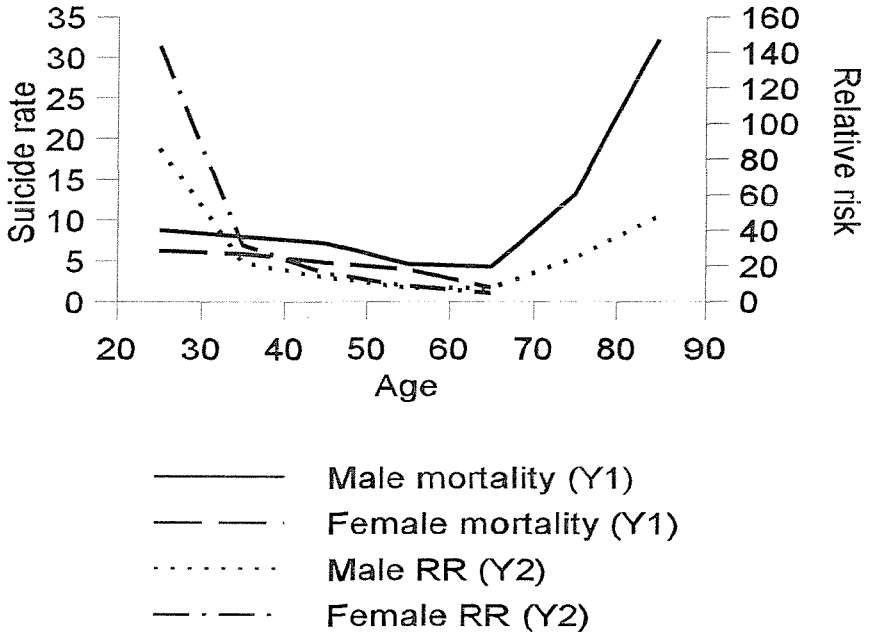
Table 4.15: The suicide mortality of schizophrenia (includes five studies which only examined suicide mortality)

First author	Male		Female		Total	
(Reference date)	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Pokorny (1964)	31	738 (501-1021)			31	738 (501-1021)
Temoche (1964)					8	1210 (488-2072)
Weiner (1977)	13	1300 (689-1954)	4	1000 (261-2220)	17	1214 (706-1860)
Copas (1982)	86	610 (488-746)	30	300 (202-4170)	116	481 (398-573)
Pokorny (1983)	19	1980 (1268-3167)			19	1980 (1268-3167)
Allebeck (1986)	18	1000 (591-1515)	15	1660 (930-2617)	33	1230 (841-1675)
Nyman (1986)	9	3000 (1360-5280)	1	1000 (4-3920)	10	2500 (1190-4290)
Black (1988)	12	3000 (1542-4937).	6	5450 (2159-3465)	18	3600 (2130-5455)
Zilber (1989)					15	320 (178-501)
Mortensen (1990)	37	135 (95-182)	19	136 (76-190)	56	136 (100-170)
Anderson (1991)	5	1950 (526-3448)	2	1280 (1040-3821)	7	1660 (693-3286)
Newman (1991)	81	2076 (1649-2543)	16	1600 (912-3354)	97	2091 (1602-2393)
Mortensen (1993)	370	2067 (1861-2283)	138	2091(1757-2454)	508	2073 (1897-2258)
Total	681	943 (873-1015)	231	673 (591-763)	935	836 (783-890)

Variation of suicide with age

Suicide was increased throughout the course of schizophrenia, being highest in the year following diagnosis and falling thereafter (Mortensen & Juel, 1993). Suicide also declined with length of follow up in mixed stage cohorts (Black & Winokur, 1988; Newman & Bland, 1991).

Figure 4.3: Variation of absolute suicide mortality /1000 person years of risk and relative suicide risk with age.



Mortensen & Juel (1993).

In females both the annual suicide rate and relative risk fell with increasing age (Figure 4.3). In males both variables appeared to have a U-shaped curve, though the peaks in elderly males were calculated from few cases. In the general population the suicide rate increases with age for both genders (Office of Population, Census and Surveys, 1985).

Homicide (E960-969)

Deaths from homicide were increased among both males (SMR 778 CI 308-1460) and females (SMR 511, CI 146-1268), but accounted for less than 1% of the excess unnatural mortality.

Undetermined (E 980-989)

Deaths where it could not be determined whether injuries were accidentally or deliberately inflicted were significantly increased among both males (SMR 890, CI 330-1940) and females (SMR 2620, CI 1130-5170), in the only study in which this was reported (Allebeck & Wistedt, 1986), accounting for 6% of all deaths and 10% of excess deaths.

Chapter 5. Discussion of meta-analysis

Introduction

In this chapter I discuss the possible errors and then the results of the meta-analysis. I include data from studies which were excluded from the meta-analysis where this clarifies the findings.

Sources of error

The results of this meta-analysis have important implications for health service planning and delivery. It is therefore necessary to consider whether the findings might result from methodological error. Errors may be introduced at three points: the original studies, the literature search, and the meta-analysis. The original studies probably underestimated both cohort and disease mortality; the literature search probably did not produce consistent errors; the meta-analysis probably underestimated disease mortality. Thus the overall direction of error in the meta-analysis is probably to underestimate both cohort and disease mortality.

Reasons for variations between different studies

There was considerable variation in the mortality rates reported in the included studies. The analysis of heterogeneity suggests that most of these variations were due to the effects of confounding variables of which phase of illness was probably the most significant. The true disease mortality of schizophrenia is almost certainly higher than the meta-analysis figures most of which were derived from cohorts where subjects had already survived the period of greatest risk. If disease recognition provides the best starting point for analysis of mortality, than Mortensen & Juel's (1993) figures provide the most accurate current measure of schizophrenia mortality. This especially applies to the excess mortality from accidents and suicide, causes of death which are common early in the disease (Mortensen & Juel, 1993).

Length of follow-up, age distribution and the proportion of different subtypes probably also exert significant effects, gender distribution will affect unnatural but not natural SMRs. It is theoretically possible to correct for the effect of confounding variables in the original studies. Unfortunately none included enough subject detail to make this practicable.

Lack of published detail also makes it impossible to sensibly compare the mortality reported in different studies and greatly reduces the possibility of detecting any real differences in mortality which might exist between different countries or services. This is extremely unsatisfactory as it means that it is not currently possible to reliably detect the effect on mortality of any changes in the management of schizophrenia.

Other confounding variables

The validity of an observational meta-analysis is limited by the effects of confounding variables. Some variables which resulted from differences in selection and methodology have been discussed above. Other individual factors will also affect individual mortality risk.

Compared to the general public, people with schizophrenia smoke more (Hughes *et al,* 1986), use more alcohol and illicit drugs (Menezes *et al,* 1996), have a higher prevalence of obesity (Kendrick, 1996), take less exercise and eat a poorer diet (McCreadie *et al,* 1998; Brown *et al,* 1999). They are also more likely to be prescribed neuroleptic drugs (Mortensen & Juel, 1990), are less likely to be employed (Leary *et al,* 1991; Aro *et al,* 1995) or married (Leary *et al,* 1991; Brown & Birtwistle, 1998) and more likely to be poor (Cohen, 1993). These variables influence mortality in the general population (Office of Population Census and Surveys, 1995) and are likely to do so in cohorts with schizophrenia.

Selection bias

Of the studies included in the meta-analysis two (Giel *et al,* 1978; Brook, 1985) were of in-patients, eight (Eastwood *et al,* 1982; Haugland *et al,* 1983; Allebeck & Wistedt, 1986; Black, 1988; Zilber *et al,* 1989; Mortensen & Juel, 1990; Mortensen & Juel, 1993; Hansen *et al,* 1997) of former in-patients and one (Anderson *et al,* 1991) of former in- or day-patients. Six case register studies (Babigian & Odoroff, 1969; Herrman *et al,* 1983; Hassall *et al,* 1988; Newman & Bland, 1991; Amaddeo *et al,* 1995; Baxter, 1996) included an unknown number of subjects who had not received hospital treatment. Wood *et al* (1985) did not discuss recruitment.

Three studies (Giel *et al,* 1979; Brook, 1985; Mortensen & Juel, 1990), of chronic hospitalised patients, followed no later than 1986, provided 26% of meta-analysis subject-years and 54% of deaths. These studies will have skewed results towards the mortality experience of older patients, exposed to different environmental risk factors than their modern counterparts. It may therefore be unsafe to generalise these findings to younger, more recent patients or to different services.

We do not know how many patients with schizophrenia go unrecognised or are never seen by the specialist psychiatric service. Most who are seen do eventually get admitted to hospital (Geddes & Kendell, 1995). Patients who are treated privately or in primary care probably have less severe disease and lower mortality risk. The sole published population based mortality study (Bruce et al, 1994) included only 27 patients with schizophrenia. These subjects had a relative mortality risk of 2.5, which suggests that service contact alone does not explain the raised SMR. The lower aggregate SMR of hospitalised (143, CI 140-147) compared to case register cohorts (183, CI 174-191), suggests that raised mortality is not due to selective hospitalisation of the physically ill (Brook, 1985; Black *et al,* 1985). The net effect of selection bias was probably to underestimate disease mortality.

Cohort effect of Danish national case register studies

The two large Danish national case register studies (Mortensen & Juel, 1990; 1993) provided 49% of total patient-years and 54% of deaths in the meta-analysis and thus had a large effect on the aggregate figures. The effect was larger in analyses of cause of deaths, an area neglected by other authors, where they provided more than 90% of deaths from respiratory, digestive and genitourinary diseases.

Fortunately these two studies are probably the most methodologically sound of all those included in the meta-analysis. Subjects were identified from a long established national database, the record linkage process is clearly described (Dupont *et al*, 1986), attrition was measured and small (Mortensen & Juel, 1990; 1993). Furthermore the mental health systems in Denmark and the United Kingdom are probably similar enough (Munk-Jørgensen & Mortensen, 1992) for results to generalise to this country.

The first episode study (Mortensen & Juel, 1993) is comprehensive, recent and avoids the selection bias of those studies which followed-up prevalence cohorts. The other study (Mortensen & Juel, 1990) gives fewer subject details, most importantly omitting any description of the age distribution of the cohort. The methodology and high mortality however suggest that most subjects were elderly chronically hospitalised patients when recruited in 1957. This study will have skewed aggregate results as described above. The combined effect of these two studies was probably to provide reasonably comprehensive coverage of the lifetime mortality risk in schizophrenia, though the risk factors of the 1990 cohort may have differed from those of more modern patients.

Diagnosis

Successive editions of the International Classification of Diseases (World Health Organisation, 1977) and Diagnostic and Statistical Manual (American Psychiatric Association, 1994) have tightened the diagnostic criteria of

schizophrenia. Some subjects from earlier cohorts would probably not meet modern criteria. Even recent cohorts, with the exception of Anderson *et al* (1991), took diagnoses from case registers and could not verify validity. Some potential subjects will therefore have been lost and inappropriate subjects included through misdiagnosis (Sytema *et al,* 1989). Simpson & Tsuang (1996) found that the use of strictly defined or loosely definitions of schizophrenia did not significantly affect cohort SMR. This is unsurprising as the excess mortality of affective and 'other' psychoses, the conditions most likely to be mistaken for schizophrenia, is similar to that of schizophrenia (Harris & Barraclough, 1998). It is therefore unlikely that differences in diagnostic practice have a large effect on SMRs.

Cause of death

Anderson *et al* (1991) took causes of death from death certificates. Other authors used national or local (Herrman *et al,* 1983; Black, 1988) death registers. Autopsy rates where mentioned (Allebeck & Wistedt, 1986; Mortensen & Juel, 1990; 1993), were higher than in the general population. Causes of death may therefore be more accurate but any effect will be small. Most individual studies analysed too few patient-years of data to reliably detect variations in SMR from specific diseases (Baldwin, 1979). Studies which performed repeated analyses on the same data will have produced some false positive results. Important but uncommon associations between schizophrenia and other diseases may therefore be unrecognised or spurious associations reported. Aggregating SMRs from individual diseases into ICD-9 categories produces large enough groups for statistical analysis but may obscure variations in mortality from different diseases within the same category.

Unnatural mortality

The consistency and size of the SMRs leaves no doubt that schizophrenia has an excess mortality from unnatural causes. The numbers of unnatural deaths in these cohorts are probably accurate. Dramatic deaths are likely to be subject to inquest and to come to the attention of a researcher. A few deaths may be wrongly attributed to natural causes but there is no evidence that this happens more often in schizophrenia than in the general population.

Phase of illness has a particularly large effect on suicide risk (Mortensen & Juel, 1993) hence the predominant use of prevalence cohorts probably caused a significant underestimate of suicide mortality. Suicidal ideation is usually an indication for psychiatric referral, hence subjects with chronic disease were probably at somewhat higher suicide risk than the general population with chronic schizophrenia. Nevertheless the overall direction of error is almost certainly to have underestimated suicide rates.

Classification of unnatural deaths

In England and Wales a suspected unnatural death is referred to the coroner. The coroner's role is to identify the deceased, determine the date, place, manner and cause of death and make recommendations designed to prevent similar deaths. A suicide verdict requires proof 'beyond reasonable doubt' that death resulted from self-inflicted injury and that the deceased intended to take his life (Matthews & Foreman, 1986). Deaths are classified as undetermined when there is insufficient evidence to determine causality. Procedures abroad vary, but have not been systematically studied. In some Western European countries an unnatural death can be registered without reference to the coroner or a verdict reached on the balance of probabilities (Neeleman, 1996). The USA has a mixed system, some counties employing a coroner and others a medical examiner (Hanzlick & Combs, 1998).

Official statistics consistently underestimate the true numbers of suicides

(O'Donnell & Farmer, 1995; Neeleman & Wessely, 1997) misclassifying 20-30% as undetermined or as accidents (Jacobsen & Jacobsen, 1972; Allebeck *et al,* 1986). Undetermined deaths are sometimes included in official suicide figures (Department of Health, 1992) however this is equally unsatisfactory as some undetermined deaths are accidental.

The proportion of violent deaths classified as suicides varies in different countries (Barraclough, 1972) and districts (O'Donnell & Farmer, 1995; Hanzlick & Combs, 1998). An individual decision is likely to be influenced by factors such as the coroner's background and qualifications (Neeleman & Wessely, 1997; Hanzlick & Combs, 1998), the violence of the method (Neeleman & Wessely, 1997) and gender (O'Donnell & Farmer, 1995) and ethnic and cultural background (Neeleman *et al,* 1997) of the deceased.

Crude suicide rates are probably higher and accidental and undetermined death rates correspondingly lower than suggested by this analysis. Under reporting of suicide probably has little effect on SMR as observed and expected deaths are derived from the same certification procedures. The presence of prior mental illness makes no significant difference to the proportion of suicide verdicts (King & Barraclough, 1990).

Statistical and methodological errors in the original studies

Even the best of the original studies will have had errors in data recording, record linkage and loss to follow-up, as previously discussed. These willl in most cases have led to underestimation of mortality.

Literature search

The ideal literature review identifies all potentially relevant articles which are then examined, using pre-determined criteria, to assess the quality of research and conclusions. I chose to search the most readily accessible databases, Medline and BIDS Gateway. Medline is a computerised version of Index

Medicus, a monthly index of articles in medical journals, produced by the U.S National Library of Medicine since 1879. Medline indexes about a quarter of available journals and is biased towards English language publications (Knipschild, 1995). Even with optimal search procedures, it probably identifies only half the relevant papers on a particular topic (Dickersin, 1995). There is an assumption, but no evidence, that indexed journals contain higher quality articles than those which are not. The BIDS Gateway database Embase, owned by Reed Elsevier publishing has similar limitations, but indexes some journals omitted by Medline.

The search will have missed articles published in unindexed journals or before 1966 (Medline) or 1981 (Embase). These losses are unquantifiable but articles good enough to meet my inclusion criteria would probably have been indexed by at least one later author and identified by citation search. More than 80% of psychiatric articles indexed in Medline are in English (Barraclough & Noyes, 1989), hence excluding non-English language articles probably had little additional effect. It is possible that these exclusions led to the omission of relevant articles but unlikely that this affected my conclusions.

Publication bias and multiple publication

The most accurate form of meta-analysis involves the review and analysis of *individual patient data,* and can include unpublished series and data on patients excluded from published analyses (Stewart & Parmar, 1993). This method avoids publication bias, the preferential and earlier publication of studies reporting positive outcomes (Stern & Simes, 1997), but may include data from poorly conducted studies.

I limited this study to an analysis of the literature because the numbers involved made access to individual patient data impracticable and excluded small cohort studies (eg: Wilkinson, 1982; Lesage *et al*, 1990) to reduce an anticipated publication bias in favour of studies reporting wide variations from expected

mortality. Funnel analysis (Dickersin & Berlin, 1992) suggested that publication bias was not an important source of error in the included studies.

Errors may also be introduced by multiple publication (Tramèr *et al,* 1997) where published data is deliberately republished or later incorporated into a larger or longer series. When this occurred, Munk-Jørgensen & Mortensen (1989; 1992) and Mortensen & Juel (1993) and Black *et al* (1985), Black & Winokur (1988), Black (1988) and Black & Fisher (1992), I took data only from the largest cohort.

Length and completeness of follow-up

I excluded studies of less than two years duration because the clustering of suicide around first (Mortensen & Juel, 1993) or subsequent hospital admissions (Allebeck *et al,* 1986; Rossau & Mortensen, 1997) produces a distorted picture of mortality. Nevertheless the fall of SMR with length of follow-up (Newman & Bland, 1991; Mortensen & Juel, 1993) means that the shorter studies in the analysis will have overestimated SMR.

Studies with a high loss to follow-up also distort results if mortality among lost subjects varies from that among those who are traced. Sims (1973) suggests that the mortality is higher in those lost to follow-up. This may depend on the precise tracing sequence used. Record linkage studies which did not measure loss to follow-up (Babigian & Odoroff, 1969; Eastwood *et al,* 1982; Haugland *et al,* 1983; Herrman *et al,* 1983; Allebeck & Wistedt, 1986; Black, 1988; Hassall *et al,* 1988; Zilber *et al,* 1989; Newman & Bland, 1991) were included in the meta-analysis to avoid giving undue weight to in-patient cohorts. These studies will have underestimated cohort mortality. Other errors introduced in the meta-analysis process were probably not systematic.

Overall mortality

Meta-analysis shows a significantly raised SMR from both natural and unnatural

causes. This is probably a lifelong phenomenon (Mortensen & Juel, 1990; 1993). Unnatural mortality was increased four fold and accounted for nearly half of the excess deaths. Natural mortality was increased by a third. Most unnatural deaths were from suicide of relatively young people. The biggest potential for reducing premature deaths therefore lies in reducing suicide in the young. Any gains would however increase the population at risk of premature natural death, hence we need to understand the causes of both the natural and unnatural mortality in order to improve the overall mortality of schizophrenia.

Geographical distribution of studies

Of the 10,351 reported deaths 7,693 (74%) were from Western Europe, 5,991 (58%) Scandinavian, 1,842 (18%) from North America and 816 (8%) from Israel. The only study from outside Western Europe and North America (Zilber *et al,* 1989) found an unexpectedly high natural and low unnatural cause mortality not explained by differences in study method. These differences may reflect different patient characteristics, for example a high prevalence of recent third world immigrants, hence it is probably unsafe to extrapolate my findings to non-Western populations.

The absence of a national database means that we do not know how many UK patients with schizophrenia die prematurely nor if the UK mortality differs from that in other developed countries. UK studies (Herrman *et al,* 1983; Hassall *et al,* 1989; Anderson *et al,* 1991; Baxter, 1996), of local and possibly unrepresentative cohorts, contributed 656 (6%) deaths to the meta-analysis, producing an aggregate SMR of 169 (CI 156-182). This is higher than the overall meta-analysis figure but within the range explained by confounding variables.

Third world mortality

No third world studies met the meta-analysis inclusion criteria. Nevertheless the

available evidence suggests that mortality is probably increased. In Singapore young Chinese patients with schizophrenia had a mortality ten times the general population rate (Tsoi & Wong, 1991) while a diagnostically mixed group of public patients had an SMR of 505, 75% of deaths occuring in patients with schizophrenia (Lim *et al,* 1993). Thara *et al* (1994) reported 10% ten year mortality in a young first episode Indian schizophrenic cohort, and Verghese *et al* (1989) 4% two year mortality in Indian subjects in the International Pilot Study of Schizophrenia (IPSS). Abiodun (1988) reported 1% mortality among mixed diagnostic psychiatric in-patients in Nigeria, with most deaths from infectious diseases.

Comparison with other diseases

Confounding variables make comparison with the mortality of other diseases unsafe. Nevertheless meta-analysis suggests that the mortality of schizophrenia is lower than that of bipolar disease and personality disorder but higher than major depression and neurotic disorders (Harris & Barraclough, 1998). Those SMRs which I could find suggest that schizophrenia mortality is similar to that of chronic physical diseases such as diabetes mellitus (Riley *et al,* 1995) and inflammatory bowel disease (Ekbom *et al,* 1992).

Natural mortality

Any variation in natural mortality might be caused by an association of schizophrenia with particular congenital diseases, changes in exposure to environmental risk factors consequent on schizophrenia or both. A large twin study (Kendler, 1986) suggested that the pattern of natural mortality is best explained by an environmental model, however a link for example with another disease, either in all individuals with schizophrenia or in a subgroup, would probably be obscured by confounding variables such as cigarette smoking.

Symptomatic schizophrenia

A small proportion of excess deaths in schizophrenic cohorts are probably from underlying conditions which produce schizophrenia like symptoms. Such symptoms may be produced by systemic disease, drug or alcohol abuse or may coexist with epilepsy or other cerebral disease as a symptom of shared underlying pathology (Lishman, 1998). There is also evidence that schizophrenia predisposes to dementia (Arnold & Trojanowski, 1996) thereby increasing the risk of dementia related death. Although few deaths in this analysis were from diseases known to produce symptomatic schizophrenia such cases probably make a small contribution to the overall excess mortality.

Neoplastic disease and cigarette smoking

Earlier comments on the apparent low cancer mortality in schizophrenia (Hussar, 1966; Dynes, 1969; Modrzewska & Böök, 1979) were dismissed as artefacts of the proportional mortality method of analysis (Fox, 1978). However reduced male cancer mortality has since been found in every large study which has examined this issue (Table 4.6). The relatively high autopsy rate (Mortensen & Juel, 1990; 1993) and unremarkable female cancer mortality make it unlikely that this is due to under reporting.

It is unrealistic to expect a simple relationship between cancer and schizophrenia as different cancers have different aetiologies. Unfortunately focussing on specific cancers produces too few subjects for useful analysis of any but the most common. Saku *et al* (1995) reported decreased overall mortality and variations in mortality for particular cancers in a large Japanese cohort excluded from meta-analysis because of high loss to follow-up. These findings have not been replicated and some probably represent chance associations. Other authors have reported significant variations in cancer incidence (Dupont *et al,* 1986; Mortensen 1987; 1989; 1992; Gulbinat *et al,* 1992). Some of this probably reflects associations with known risk factors, such

as cervical cancer and sexual activity (Rotkin, 1977) and breast cancer and reduced parity (Ewertz, 1988).

The reduced male cancer SMR is largely explained by a significantly reduced lung cancer mortality (Mortensen & Juel, 1990; Newman & Bland, 1991). This is unexpected as modern cohorts with schizophrenia show a high prevalence of cigarette smoking (Masterson & O'Shea, 1984, Hughes *et al,* 1986). Mortensen & Juel (1990) suggest poverty and hospital cigarette rationing may mean their subjects smoked less than the general population. The reduced lung cancer mortality may therefore reflect exposure. It is however inconsistent to attribute the high respiratory and cardiovascular SMRs to smoking and the low cancer SMR to reduced smoking. Thus it is possible that schizophrenia may in some way protect against cancer, possibly through neuroleptic mediated changes in prolactin secretion (Mortensen, 1987; 1989; 1992).

Cardiovascular disease

All large modern cohort studies show an excess cardiovascular mortality (Wood *et al,* 1985; Allebeck & Wistedt, 1986; Zilber *et al,* 1989; Newman & Bland, 1991; Mortensen & Juel, 1990; 1993), the only exception being in two studies which used in-patient records of case populations with chronic disease (Giel *et al,* 1978, Brook, 1985). It has been suggested that this may be due to the stress of living with mental illness (Saugstad & Ødegård, 1985). A more direct link may be through altered exposure to cardiovascular risk factors.

Here again the relationship is not straightforward (Hayward, 1995). Modern patients have high rates of smoking (Masterson & O'Shea, 1984, Hughes *et al,* 1986), obesity, inadequate exercise and unhealthy diet (McCreadie *et al,* 1998; Brown *et al,* 1999) but we cannot be sure whether these findings also applied to earlier cohorts. There is also evidence of abnormal lipid metabolism (Walker *et al,* 1999) with studies reporting low serum cholesterol (Boston *et al,* 1996) and erythrocyte membrane polyunsaturated fatty acid levels (Horrobin, 1996).

Whatever the complexities of these relationships, it seems appropriate to recommend reduction of known cardiovasular risk factors. Possible associations of cardiovascular deaths and neuroleptic drugs will be discussed later.

Cerebrovascular disease

The impact of schizophrenia on deaths from cerebrovascular disease is less clear than on other disease categories. The overall reduced cerebrovascular mortality, largely due to the cohort effects of two large studies of elderly patients with chronic schizophrenia (Giel *et al,* 1979; Mortensen & Juel, 1990), was not found in other studies (Brook, 1985; Allebeck & Wistedt, 1986; Zilber *et al,* 1989; Newman & Bland, 1991; Mortensen & Juel, 1993). The variability of these findings may well be due to confounding variables and suggests that environmental agents play an important role in cerebrovascular mortality. Modern patients may be exposed to new risk factors or former protective factors may no longer operate, for example supervised medication rounds for older hospitalised cohorts may have led to good compliance with antihypertensive and neuroleptic drugs, and thus to low rates of cerebrovascular disease.

Respiratory disease

Respiratory diseases accounted for nearly half of all excess natural mortality (Table 4.5), about half from chronic obstructive airways disease (COAD) and the rest from pneumonia (Newman & Bland, 1991). There is probably also an increased mortality from asthma (Joseph *et al,* 1996). Cigarettes are the most likely culprits in COAD mortality. High rates of unemployment mean subjects had less exposure to industrial pathogens. Modern patients often live in inner city housing (Dauncey *et al,* 1993), however most of the meta-analysis subjects lived in country asylums with low levels of environmental pollution.
Most pneumonia deaths occurred in elderly institutional patients. The meta-

analysis findings all date from the antibiotic era, though such drugs may not always have been readily available. Pneumonia is an uncommon underlying cause of death (Office of Population Census and Surveys, 1995), but a common terminal event. Institutional conditions such as overcrowding and poor hygiene probably exacerbate the spread and mortality of pathogens, sedative drugs may increase mortality by impairing sputum clearance. A few false positive pneumonia deaths may have been recorded by doctors attributing the death of an uncommunicative patient to a perceived common cause.

Other diseases

There is very little hard evidence about the cause of other excess deaths. Alcohol abuse probably causes many of the digestive deaths, others may be due to the side effects of neuroleptic drugs (Mortensen & Juel, 1990) though mortality from ileus was high in the pre-neuroleptic era (Ødegård, 1952). Some of the excess endocrine and neurological mortality probably reflects misdiagnosed organic psychoses. A few deaths occur from water intoxication (Vieweg *et al,* 1985). The continuing mortality from infectious disease may result from factors such as increased susceptibility due to lifestyle and poor recognition of disease and treatment compliance.

Neuroleptic drugs and schizophrenia mortality

Most people with a diagnosis of schizophrenia receive neuroleptic drugs, usually for many years. These drugs cause many, and occasionally fatal, side effects (Thompson, 1994) but are so established in the treatment of schizophrenia and of such proven benefit that prospective evaluation of their effect on mortality would be both impracticable and unethical. Confounding variables undermine the conclusion of Brill & Patten (1962) and Craig & Lin (1981) that the mortality of psychiatric in-patients was not increased by their introduction.

Mortensen & Juel (1990) found significantly raised SMRs from prostatic disease, pyelonephritis, ileus, diabetes mellitus, falls and aspiration, conditions theoretically caused by side effects of neuroleptic drugs, with an aggregate SMR of 187 (CI 168-206). The aggregate SMR falls however to 97 (CI 168-206) if the reduced SMR from cerebrovascular disease, attributed by the authors to the hypotensive effects of neuroleptic drugs, is factored into the calculation. This might suggest that neuroleptic drugs have little overall effect on natural mortality, however the findings come from a single cohort with chronic disease and may not generalise to other populations.

Neuroleptic drugs have also been implicated in sudden unexpected psychiatric deaths (Simpson *et al,* 1987; Mehtonen *et al,* 1991, Royal College of Psychiatrists, 1997). There is concern that such deaths may occur particularly in black patients and while under restraint (Prins *et al,* 1993; Bannerjee *et al,* 1995). Here again the evidence is indirect. Sudden unexpected deaths occur at a rate of 1/1000 annually in the general population (Levinson & Simpson, 1987) and occurred in psychiatric patients (Bell, 1849) and schizophrenia (Bleuler, 1978) long before the introduction of neuroleptic drugs. The psychological and physiological stress of restraint may itself predispose to sudden death (Royal College of Psychiatrists, 1997).

Most sudden unexpected deaths are associated with ventricular arrhythmias (Brown & Kocsis, 1984). Others are caused by pulmonary embolus secondary to immobility (Bollini *et al,* 1984) and laryngeal dystonia (Brown & Kocsis, 1984). Neuroleptic drugs are toxic in high doses and may cause myocardial depression and cardiac arrhythmias at chronic therapeutic levels (Risch *et al,* 1981; Royal College of Psychiatrists, 1997).

Studies have not to date shown a significant increase in the rate of sudden death in psychiatric patients (Levinson & Simpson, 1987), but this may be due to inadequate sample size. A quarter of all sudden unexpected deaths in Mehtonen *et al's* (1991) series occurred in patients taking low potency phenothiazine

drugs, especially thioridazine. High rates of such deaths have also been reported in patients taking pimozide (Committee on the Safety of Medicines, 1990) and sertindole (Barnett, 1996). Confounding variables such as smoking, diet, obesity and exercise will make it difficult to detect if neuroleptic drugs do increase cardiovascular mortality.

Other neuroleptic drug side effects include the neuroleptic malignant syndrome, a condition characterised by muscular rigidity, pyrexia, autonomic overactivity, rhabdomyolysis and reduced consciousness, which may occur in as many as 2% of treatment episodes and has a mortality of more than 10% (Shalev *et al,* 1989). Impaired temperature regulation may contribute to the excess infectious disease mortality (Giel *et al,* 1978). Some epilepsy deaths may be neuroleptic drug related, through reduced seizure threshold or increased anticonvulsant metabolism (Craig, 1980). Hepatitis (Levinson & Simpson, 1987) and haematological abnormalities (Levinson & Simpson, 1987) are also occasionally fatal. The agranulocytosis associated with clozapine (Anderman & Griffith, 1977) can be largely eliminated by regular haematological monitoring (Krupp & Barnes, 1992) but agranulocytosis due to other agents still causes occasional deaths (Levinson & Simpson, 1987). Mortality also appears to be increased by polypharmacy, possibly through Parkinsonian induced immobility (Waddington *et al,* 1998) and tardive dyskinesia related aspiration and impaired sputum clearance (Yousseff & Waddington, 1987).

Patients with schizophrenia also take antidepressants, minor tranquillisers, anti-Parkinsonian, mood stabilising and other drugs which cause morbidity and mortality. Any attempt to measure their effect on mortality will be hampered by the same factors which apply to neuroleptic drugs.

Preventable mortality and the effectiveness of medical treatment

Advances in medical science mean that effective treatments are now readily available for many previously lethal conditions. Success in treating such

conditions is sometimes used as a marker for the effectiveness of medical services (Department of Health, 1994). This approach was pioneered by Rutstein *et al* (1976) who produced a concensus list of diseases for which effective treaments were widely available and proposed that a high mortality from these diseases was a useful proxy measure for the effectiveness of medical treatment in a particular population. It should be noted that this procedure does not identify an absolute number of preventable deaths. Furthermore deaths are coded by ICD guidelines, which attribute death to the underlying disease, hence those deaths where the immediate cause might have been preventable (eg: surgical error in an individual with cancer) are not included in the analysis. The procedure is used in the annual reports of the Chief Medical Officer (Department of Health, 1994), albeit with a smaller list of diseases than in Rutstein *et al's* (1976) original paper, and has previously been used to assess the treatment of medical diseases in a psychiatric population (Dupont & Mortensen, 1988).

Kraepelin (1919) suggested that schizophrenia mortality may be exacerbated by late presentation and poor compliance with treatment for coincident medical conditions. Mortensen & Juel (1990; 1993) identified a significantly raised aggregate SMR (135, 95% CI 110-163) from diseases regarded as 'treatable' by (Rutstein et al, 1976), and argue that this implies patients with schizophrenia receive worse medical treatment than the general population.

Effective treatment requires that a disease is recognised and appropriate treatment delivered. Increased pain tolerance (Dworkin, 1994), possibly exacerbated by neuroleptic drugs (Patt *et al,* 1994), poor insight (Jeste *et al,* 1996), negative symptoms (Jeste *et al,* 1996), isolation and lack of a telephone, may impair the schizophrenic patients' recognition and communication of new symptoms. Physicians frequently miss co-morbid medical disease in the mentally ill (Koran *et al,* 1989), psychiatrists more often than general physicians (Koranyi, 1979). Other carers probably share this reduced awareness of physical

disease (Jeste *et al,* 1996).

This analysis suggests that there is significant excess mortality from chronic medical diseases such as COAD asthma and diabetes mellitus. Chronic diseases require regular monitoring of efficacy of treatment. This is particularly difficult to achieve in itinerants or others who are not registered with a GP. Patients with schizophrenia are also poor at keeping appointments and complying with medication (Weiden *et al,* 1991), sometimes because of cognitive deficits (Davidson & Haroutinian, 1995; Goldberg & Berman, 1995) which may be exacerbated by drugs both therapeutic, particularly anticholinergic and sedative (Jeste *et al,* 1996), and recreational.

Needs assessment of the physical health in patients with schizophrenia

A considerable literature has built up around the concept of met and unmet need in psychiatric patients. These terms are somewhat ambiguous (Brewin *et al,* 1987) but generally refer to measures of whether psychiatric patients are receiving the services required for optimal function. Need, variously defined, is regarded as met if it has attracted the most effective intervention and no more effective intervention is available and unmet if it has not. The levels of met and unmet need give a measure of the effectiveness of services received by a particular population. Schedules such as the Needs for Care Assessment Schedule (Brewin *et al,* 1987) and the Camberwell Assessment of Need (Phelan *et al,* 1995) include questions about physical health but only identify needs which are recognised by the subject or informant. A comprehensive schedule for the assessment of physical health needs in the severely mentally ill, which included basic physical investigations, might be an effective way of promoting effective health care of this group.

Other Proposed Environmental Factors

It would be surprising if environmental risk factors which affect general

population mortality did not also influence schizophrenia mortality. Such factors include diet (de Groot *et al,* 1996), exercise (Paffenbarger *et al,* 1986; Lee *et al,* 1997), obesity (Durazo-Arvizu *et al,* 1997; Solomon & Manson, 1997), airborne pollution (Verhoeff *et al,* 1996, Borja-Aburto *et al,* 1997), social class (Smith *et al,* 1997; Wannamethee & Shaper, 1997) and marital status (Kaprio *et al,* 1996).

All have been theoretically linked with raised schizophrenia mortality, none have been examined systematically. Giel *et al* (1978) and Saugstad & Ødegård (1979) proposed that in-patient mortality might be increased by immobility secondary to negative symptoms, institutionalisation, sedation and poor diet. Mortensen & Juel, (1990) speculated that the location of asylums in the countryside might protect against the effects of environmental pollution and unemployment reduce exposure to work related toxins. Poor housing (Cohen, 1993) in the inner city (Dauncey *et al,* 1993) probably increases exposure to airborne pollution. However Babigian & Odoroff (1979) found that residential area was not associated with mortality while Baxter (1996) found that social class explained only a small part of the excess mortality, both in mixed diagnostic cohorts.

Health promotion

Improving the health of the mentally ill is an explicit government aim (Department of Health, 1992). People with schizophrenia have a high mortality from diseases with known risk factors and are therefore an appropriate target group for health promotion interventions. GPs currently make little effort to modify physical risk factors (Kendrick, 1996). Scattered reports (Byrne *et al,* 1994) suggest that people with serious mental illness value health promotion advice but there is little evidence that this is being systematically attempted or evaluated.

Future directions

The results of this study reflect the experience of a previous generation. New risk factors continue to appear, old ones re-emerge. Reduced sexual activity (Gupta *et al,* 1997) may offer some protection against HIV and other blood bourne infections but drug users who share needles will be at risk. TB is re-emerging as a major threat to public health (Crompton & Haslett, 1995). People with schizophrenia will be at special risk because of their over representation among the homeless (Scott, 1993). New therapeutic drugs may be less toxic but idiosyncratic reactions may appear. It is therefore important that the natural cause mortality of schizophrenia continues to be monitored in order to identify and address changing risk factors.

Unnatural mortality

The large excess suicide mortality of the meta-analysis supports Kendler's (1986) twin study conclusion that the unnatural SMR of schizophrenia is largely intrinsic to the disease. The excess accident and homicide mortality and wide range of reported suicide rates suggest environmental factors are also involved.

Accidental deaths

A high accidental death rate has been found in most cohorts large enough for this to be detected. The pattern appears to differ from that seen in the general population, with fewer workplace and road traffic accidents but more home accidents (Edlund *et al,* 1989). Most accidental deaths in elderly schizophrenics are from falls or aspiration (Allebeck *et al,* 1986; Mortensen & Juel, 1990), both theoretically associated with neuroleptic drug side effects. Allebeck *et al* (1986) and Mortensen & Juel (1993) concluded that about 20% of accidental schizophrenia deaths were probably misclassified suicides and a further 20% related to drug or alcohol intoxication. Suicides are more likely to be misclassified if they involve a less inherently lethal method such as drug

overdose (Neeleman & Wessely, 1997). Psychoactive drugs double the rate of falls in the elderly (Mustard & Mayer, 1997; Cumming, 1998), while neuroleptic drugs may cause aspiration through dystonia and impaired gag reflex (Mortensen & Juel, 1990).

Road traffic accidents are the most common form of accidental death in the general population and the most common cause of all deaths in males under thirty five (Office of Population Census and Surveys, 1995). People taking depot medication for schizophrenia show significant impairment on driving simulator tests (Wylie *et al,* 1993) with concentration likely to be impaired both by psychotic experiences and antipsychotic drugs (Cremona, 1986). Sedative drugs are implicated in a quarter of fatal road traffic accidents in both drivers and pedestrians (Cremona, 1986). Antipsychotic drugs also impair concentration, visual acuity and co-ordination (Metzner *et al,* 1993). The impairment of driving performance is recognised by the UK Driver and Vehicle Licensing Authority's (DVLA) twelve month driving ban following an acute psychotic episode. Nevertheless, while people with schizophrenia have double the accident rate per mile of the general population, they are less likely to drive, drive fewer miles and overall are involved in fewer accidents (Edlund *et al,* 1989).

Suicide

Suicide, the most common cause of excess mortality in schizophrenia, accounts for nearly half of all excess deaths. The size and consistency of reports of excess suicide mortality make it extremely improbable that these are due to bias or statistical error. Reducing suicide is therefore the biggest single challenge in reducing schizophrenia mortality.

Data about the characteristics of schizophrenic suicides come from three main types of study, prospective cohort follow-up, interview with unsuccessful suicide attempters and informant interviews about completed suicides. These

methods have limitations and have produced sometimes contradictory results. Schizophrenic suicide is uncommon enough to make it difficult to collect a large enough prospective series for useful analysis. Survivors of suicide attempts are a different group from completed suicides. Informant interviews are retrospective and thus unreliable.

Sociodemographic factors

Schizophrenic suicides share many characteristics with general population suicides. These include unmarried status and living alone (Drake *et al,* 1984; Allebeck *et al,* 1987; Heilä *et al,* 1997), unemployment (Roy, 1982; Heilä *et al,* 1997) and social isolation (Roy, 1982; Drake *et al,* 1984; Nyman & Jonsson, 1986; Modestin *et al,* 1992; Heilä *et al,* 1997). Caldwell & Gottesman, (1990) report suicide as more common in whites, though this American finding may not generalise to other countries.

Suicide is more common among males in schizophrenia as in the general population, with suicides accounting for nearly half of excess male schizophrenic deaths but about one eighth of excess female deaths. Thus schizophrenia and male gender appear to have an additive effect on the risk of suicide. This may be due to the generally earlier onset (Loranger, 1984; Angermeyer & Kuhn, 1988), and more severe course (World Health Organisation, 1979) of male schizophrenia. Schizophrenic suicide occurs earlier in males (Roy, 1982) and may be more common in early onset illness (Cohen *et al,* 1990).

General population suicides are most common in middle and old age (Office of Population Census and Surveys, 1995). In contrast, schizophrenic suicide is most common in the young (Anderson *et al,* 1991; Newman & Bland, 1991; Mortensen & Juel, 1993), with a mean age at death of 33 (Roy, 1982), probably because of an association with early illness rather than directly with age (Rossau & Mortensen, 1997).

The lifetime suicide risk of schizophrenia

The lifetime population suicide risk is approximately 0.9% (Caldwell & Gottesman, 1990). The most frequently quoted lifetime risk in schizophrenia (10%) comes from Miles' (1977) meta-analysis, which plotted suicides as a proportion of all cohort deaths, against length of follow-up. Inskip *et al* (1998) repeated this analysis using modern data and computer technology and found a best fit lifetime risk of 4%. Both these meta-analyses were of mixed stage of illness cohorts and hence probably underestimated suicide. In Mortensen & Juel's (1993) first episode cohort 5.5% of subjects had died from suicide when censored at 1-18 years. Adding this figure to the suicide rate (0.9%) in the same authors' (1990) cohort with chronic schizophrenia, produces a combined figure of about 6.5%, probably the best current estimate of lifetime risk.

Trends in suicide mortality

Suicide was identified as a possible outcome of schizophrenia by both Kraepelin (1919) and Bleuler (1911). The suicide rate in schizophrenia in the asylums of the first half of the century was higher than in the general population (Ødegård, 1936; Alström, 1942). Contemporary follow-up studies also reported an increased suicide rate (Rennie, 1939; Johanson, 1958; Kay & Lindelius, 1970; Tsuang, 1978; Stephens *et al,* 1997). Evidence from Denmark suggests that the suicide rate in first episode schizophrenia doubled between 1970 and 1987 (Mortensen & Juel, 1993), a time when Denmark had similar deinstitutionalisation policies to the UK and the incidence of schizophrenia was either stable (Folnegović *et al,* 1990) or falling (Eagles *et al,* 1988; Der *et al,* 1990; Munk-Jørgensen & Mortensen, 1992). Deinstitutionalisation may therefore have increased schizophrenic suicide.

Methods of suicide

The method of suicide varies with the location. Drug overdose is the most

common method of suicide in schizophrenia as in the general population (Heilä *et al,* 1997; Rossau & Mortensen, 1997), with three quarters of overdose deaths caused by low potency neuroleptic drugs (Heilä *et al,* 1997). Violent methods are more common than in the general population (Heilä *et al,* 1997) and are more common in hospital than at home (Rossau & Mortensen, 1997), possibly because of lack of access to drugs.

Biological markers

Psychotic patients with a history of suicidal behaviour have altered REM sleep patterns (Keshavan *et al,* 1994; Lewis *et al,* 1996). Dexamethasone suppression testing has shown both raised (Kaplan & Harrow, 1996) and normal (Lewis *et al,* 1996) cortisol levels in schizophrenic patients showing suicidal behaviour. Meltzer (1998) suggests that if depressive symptoms result from reduced levels of serotonin (Holden, 1995) they may respond better to atypical antipsychotic drugs than to conventional neuroleptics.

Course of illness

Suicide is most common in the first year of illness (Mortensen & Juel, 1993). In patients who survive the first year, suicide is associated with chronic severe illness (Nyman & Jonsson, 1986; Modestin *et al,* 1992; Heilä *et al,* 1997), multiple hospital admissions (Rossau & Mortensen, 1997), repeated exacerbations and remissions (Roy, 1982; Wilkinson, 1982; Breier & Astrachan, 1984; Drake *et al,* 1984; Barner-Rasmussen, 1986; Nyman & Jonsson, 1986) and residual impairment (Lindelius & Kay, 1973; Dingman & McGlashan, 1986). Late suicides, though often planned, follow specific life events less often than non-schizophrenic suicides (Nyman & Jonnson, 1986; Rich *et al,* 1988). About half of schizophrenic suicides occur in individuals who have previously attempted suicide (Heilä *et al,* 1997), completed suicide occurring in about the same proportion as in other parasuicides (Wilkinson & Bacon, 1984). Eventual

suicide is predicted by suicidal ideation (Drake *et al,* 1984; Allebeck *et al,* 1987) and by previous attempts (Wilkinson, 1982; Breier & Astrachan, 1984; Dingman & McGlashan, 1986; Allebeck *et al,* 1987; Rossau & Mortensen, 1997).

Co-morbidity

In the general population suicide is increased by substance misuse (Harris & Barraclough, 1997) and particular medical diseases (Harris & Barraclough, 1994). A number of studies have suggested that substance misuse increases the risk of suicide in schizophrenia (Dassori *et al,* 1990; Bartels *et al,* 1992; Heilä *et al,* 1997), however Drake *et al* (1984) and Bartels *et al* (1992) found that the excess risk was small when controlled for depressive symptoms. Rossau & Mortensen's (1997) multivariate analysis showed that the excess suicide risk associated with substance misuse was non-significant but that suicide was increased in patients with co-morbid physical disease.

Mental state

Suicide appears to be more common in DSM-III-R active than residual phase of illness (Heilä *et al,* 1997) and in patients with prominent delusions and suspiciousness than in those with marked negative symptoms (Fenton *et al,* 1997). Earlier failures to find an association with positive symptoms (Roy, 1982; Breier & Astrachan, 1984; Drake *et al,* 1984 Cheng *et al,* 1990) may have been due to inadequate sample size. Command hallucinations, though seen in a proportion of suicides (Heilä *et al,* 1997), are relatively common in schizophrenia and rarely lead to completed suicide (Zisook *et al,* 1995). Increased agitation is sometimes noted prior to suicide (Drake *et al,* 1985). Suicide is associated with depressed mood (Roy, 1982; Drake & Cotton, 1986; Heilä *et al,* 1997), depressive symptoms on previous hospital admissions (Wilkinson, 1982; Roy, 1982; Rossau & Mortensen, 1997) and related

symptoms such as psychomotor disturbance and guilt (Drake & Cotton, 1986). Depressive symptoms occur in about half of all patients with schizophrenia (Markou, 1996). These may be intrinsic to the acute schizophrenic process, may occur when positive symptoms have remitted (post-psychotic depression) or may be caused by the mood altering effects of neuroleptic drugs, probably acting through subcortical systems (Azorin, 1995). Drake & Cotton (1986) concluded that while schizophrenic suicides often appear depressed, only a minority experience major depressive episodes. Multivariate analysis of controlled studies suggests that depressive symptoms are not increased when controlled for hopelessness (Beck *et al,* 1985; Drake & Cotton, 1986). Schizophrenic suicide can be viewed as a rational response to a devastating disease, an interpretation supported by the high rates of suicide after hospital discharge. Drake *et al* (1984) found increased suicide was associated with awareness of current disabilities, fear of future deterioration and was more likely in well educated people with high career expectations and awareness of their loss. These subjective findings have not been replicated or subjected to multivariate analysis. Amador *et al* (1996) used validated scales to show that suicidal behaviour was associated with awareness of delusions and negative symptoms but not with general awareness of having a mental illness.

Treatment

The proportion of suicide victims with schizophrenia in community series varies between 2 and 8% (Robins, 1986; Arato *et al,* 1988; Rich *et al,* 1988; Cheng *et al,* 1995). The proportion in hospital series varies from 20% (Modestin *et al,* 1992) to 35% (Copas & Robin, 1982; Proulx *et al,* 1997). In the recent UK National Confidential Inquiry into suicide and homicide by people with mental illness, 26% of suicides had a diagnosis of schizophrenia (Royal College of Psychiatrists, 1996).

About a third of schizophrenic suicides occur in hospital (Barner-Rasmussen,

1986; Heilä *et al,* 1997). In-patient suicide is most common early in the course of a hospital admission (Copas & Robin, 1982; Rossau & Mortensen, 1997) or during leave (Cohen *et al,* 1990, Rossau & Mortensen, 1997) but may still occur after more than a year in hospital (Barner-Rasmussen 1986). Suicide is also common in the first weeks after hospital discharge (Roy, 1982; Wilkinson, 1982; Pokorny, 1983; Drake *et al,* 1984; Allebeck *et al,* 1986). Typically 30% of suicides occur within a month and 50% within three months of hospital discharge (Roy, 1982). Rossau & Mortensen (1997) found that the suicide risk in the 28 days after discharge was as high as during the first week in hospital, when psychotic symptoms are presumably at their height, and that risk increased with the number of hospital admissions in the year before death.

Most schizophrenic suicides are in contact with psychiatric services at the time of death (Heilä *et al,* 1997). About half of out-patient suicides saw a psychiatrist in the week before death (Cheng *et al,* 1990; Heilä *et al,* 1997). Suicidal intent is usually communicated but this is often oblique and may be missed (Breier & Astrachan, 1984; Nyman & Jonnson, 1986; Rich *et al,* 1988). The evidence linking neuroleptic medication and suicide is inconsistent, different authors reporting suicides to have been receiving higher (Cheng et al, 1990; Awad, 1993) or lower (Roy, 1982; Taiminen & Kujari, 1994) doses than controls at the time of death. These findings probably reflect differences in severity of illness rather than direct drug effects (Cheng *et al,* 1990; Taiminen & Kujari, 1994). Conventional neuroleptic drugs may produce depressive symptoms in as many as 40% of patients (Awad, 1993; Taiminen & Kujari, 1994; Voruganti *et al,* 1997). Suicidal behaviour is reduced and suicide rare in patients taking Clozapine (Meltzer & Okayli, 1995), but this may reflect patient selection and closer supervision.

Homicide

Schizophrenia is associated with a significantly increased mortality from

homicide (Newman & Bland, 1991; Mortensen & Juel, 1993; Ruschena *et al,* 1998). Schizophrenia probably puts people at risk through living in poorer (Dauncey *et al,* 1993), more dangerous neighbourhoods and through increased contact with other mentally disordered people (Ladds, 1995). In the USA and probably elsewhere people with schizophrenia are among those killed by the police (Wilson *et al,* 1998).

Undetermined deaths

Deaths are classified as undetermined when investigation fails to establish whether injuries were accidental or deliberate. Schizophrenia increases the risk of accident and suicide hence it is unsurprising that undetermined deaths are also increased. Many of these are suicides with insufficient evidence of intent (Allebeck *et al,* 1989). In other cases sophisticated psychological autopsy cannot confidently determine cause (Allebeck *et al,* 1989). Social isolation and delayed finding of the body may also impede diagnosis.

Summary

This review demonstrates that a diagnosis of schizophrenia is associated with a significantly increased SMR from both natural and unnatural causes. It suggests that about two thirds of the excess deaths are from natural and one third from unnatural causes. The excess natural deaths probably occur across all disease categories. The variation from general population rates is best explained by a model of differential exposure to environmental risk factors (Kendler, 1986). Confounding variables mean that we cannot prove or disprove a direct link with other medical conditions.

Different authors have suggested possible aetiological factors for the variations from general population rates. None of these have been systematically studied. We therefore know very little about the reasons for the extra natural deaths and lack an evidence base for interventions.

Suicide is greatly increased in schizophrenia, is probably intrinsic to the disease and is most common in young males. Schizophrenic suicide has been extensively studied but many studies are methodologically unsound. Apparently contradictory results may therefore be due to differences in methodology. Suicide remains an uncommon event. It is therefore difficult to assemble a large enough cohort to undertake the kind of prospective study which would answer many of the outstanding questions. Multivariate statistical analysis has resolved some of the apparent contradictions and provided a partial evidence base for interventions. The excess mortality from accidents has not been studied systematically.

Chapter 6: Method

Subjects

A District General Hospital (DGH) based psychiatric service started in Southampton in 1979, replacing previous services based at the county asylum, Knowle Hospital. Contemporary concern about the effectiveness of community based psychiatric services (Creer & Wing, 1974) prompted Gibbons *et al* (1984) to identify all patients aged 16-65 with schizophrenia, living outside hospital, who had contact with the Department of Psychiatry at the Royal South Hants Hospital between 1.02.81 and 31.01.82 (N=370). Forty seven patients with chronic schizophrenia, living long-term in Knowle Hospital, were excluded as the study was specifically of patients receiving community services. Potential subjects were identified from the Southampton case register and at points of service entry (out-patient clinics, in-patient wards, general hospital, domiciliary and forensic consultations) and were included in the study if they had at least one of the following, in the absence of organic brain disease, drug or alcohol abuse:

- a 'firm diagnosis of schizophrenia' by the responsible consultant
- case note evidence of first rank symptoms of schizophrenia
- persistent non-affective delusions
- persistent non-affective auditory hallucinations.

These criteria were selected by Gibbons *et al* (1984) to identify a cohort who met the broad contemporary clinical definition of schizophrneia, .

Follow-up

Subjects were traced through hospital, Family Health Service Authorities (FHSA) and NHS Central records, family, friends or information in the 1981 research records, and classified as alive, dead or untraced on 31.12.94. Alive means unambiguous evidence from clinical records, professional staff, relatives or patient; dead, sight of death certificate or other official document confirming

death; untraced neither of these. The untraced were included in the analysis until the date they were lost.

Medical, psychiatric and smoking history, personal circumstances, account and cause of death came from: the 1981 research record, hospital case notes, relatives, professional staff and coroner's record. Cause of death was taken directly from the death certificate, following the procedure laid down in ICD-9, where death is attributed to the underlying disease (World Health Organisation, 1977). Twenty eight (35%) were signed by a doctor and 49 (62%) by the coroner, 29 (37%) after post mortem examination and 20 (26%) after inquest.

Statistical methods

I calculated:

- Expected mortality using the person years method (Breslow & Day, 1987) and the mortality experience of England and Wales (Office of Population Census and Surveys, 1981-94).
- SMR by dividing the observed by expected mortality and multiplying the result by 100 and confidence intervals from the Poisson distribution (Gardner & Altman, 1989).
- The effects of smoking and social disadvantage using Chi squared analysis to compare the SMR of dichotomous groups, dissimilar at outset for factors known to increase general population mortality. Subjects with incomplete data were omitted from the pertinent part of the analysis.
- Predictors of suicide or natural death by logistic regression analysis of six predetermined factors known to increase mortality in the general population. The particular variables were chosen because of the availability of high quality data in original study details or case notes. Those variables which were significant at the 10% level in bivariate logistic regression were included in a multiple regression analysis using forward selection based on likelihood ratio.

- The effectiveness of medical care (Rutstein et al 1976) by calculating a SMR for diseases, where effective treatment is widely available (Department of Health, 1994)

Case note audit

I examined medical and psychiatric case notes to determine the circumstances of death and identify those deaths where available effective treatment was not delivered. This audit was designed to identify cases where the immediate, but not underlying, cause of death might have been prevented by better treatment. Such cases would be missed by analysis based on death certificate codes. I also looked for patterns which might suggest underlying mechanisms of excess mortality. Interpretation of the case notes was subjective and based on clinical experience, as data were too complex to fit pre-determined criteria.
Salient details of each natural death are given in Appendix I and each unnatural death in Appendix II.

Chapter 7: Results

Subjects

When recruited in 1981 the cohort of 370, ill for a mean of 12 years (range 0-39), comprised 213 males, mean age 39 years (range 19-64) and 157 females, mean age 45 years (range 16-65). The unmarried, the unemployed and the manual worker were over-represented ($P<0.001$) compared to the general population (Table 7.1). Eighty percent of males and 64% of females smoked, compared with 38% of males and 33% of females in the general population (Office of Population Census and Surveys, 1984).

Status at follow-up

I established vital status at census date for 357 (96%) subjects (Table 7.2). Four of the twelve (4%) untraced subjects were documented as having left the country. Another disappeared suddenly, after discontinuing long-term medication but was not declared legally dead until after the census date. Seventy nine (21%) subjects had died, a crude annual mortality rate of 164 deaths/10,000 population and ten year survival of 83.6%. Fifty eight (73%) deaths were from natural and 19 (24%) from unnatural causes. Two deaths abroad were from unknown causes. Schizophrenia was mentioned as a contributory factor to one suicide and two natural deaths.

Table 7.1: Demographic characteristics at outset of 370 subjects with schizophrenia, compared to the general population of England and Wales

Demographic characteristic	Males (N=213)	*Males 16-64 general population	Females (N=157)	*Females 16-64 general population
Age				
16-25	22 (10%)	25%	11 (7%)	25%
26-35	69 (32%)	21%	33 (21%)	21%
36-45	58 (27%)	20%	39 (25%)	20%
46-55	41 (19%)	17%	33 (21%)	17%
56-65	23 (11%)	17%	41 (26%)	17%
Marital status				
single	139 (65%)	28%	40 (26%)	21%
married/cohabiting	26 (12%)	66%	67 (43%)	61%
widow	1 (0.5%)	4%	7 (4%)	14%
divorced/separated	23 (11%)	3%	30 (19%)	4%
unknown	24 (11%)		13 (8%)	
Social class **				
I/II	33 (16%)	27%	29 (18%)	28%
III	75 (35%)	48%	49 (31%)	49%
IV	39 (18%)	18%	30 (19%)	18%
V	38 (18%)	7%	29 (18%)	5%
unknown	28 (13%)		20 (13%)	
Employment status				
unemployed and	144 (68%)	16%	61 (39%)	8%
retired	38 (18%)	70%	21 (13%)	59%
working	0	0	62 (39%)	27%
housewife	6 (3%)	4%	1 (1%)	5%
student	25 (12%)		12 (8%)	
unknown				

*Office of Population Census and Surveys (1984a). **determined from occupation of head of household.

Table 7.2: Vital status by gender of 370 subjects on 31.12.94

Vital status	Males (N=213)	Females (N=157)	Total (N=370)
Alive	154 (72%)	125 (79%)	279 (75%)
Dead	51 (24%)	28 (18%)	79 (21%)
Untraced	8 (4%)	4 (3%)	12 (4%)

All cause mortality

The all cause SMR was 299 (CI, 236-372), three times that expected. The male SMR was higher than the female, though not significantly so (chi squared=2.96, df=1, P=0.09). The mean male age at death (54 years, CI 50-58 years) was lower (t=2.07, df=77, P=0.04) than the female figure (60 years, CI 56-64 years). The SMR of first episode subjects was 248 (95% CI, 30-896), based on two deaths among 27 subjects. Deaths were spread over most ICD-9 categories (Table 7.3)

Table 7.3: Mortality by ICD 9 category of 370 subjects with schizophrenia

ICD-9 disease category	Male		Female		Total	
	Observed	SMR (95% CI)	Observed	SMR (95% CI)	Observed	SMR (95% CI)
Infectious (001-139)	0	(0-5796)	1	1527 (24-5864)	1	629 (16-3503)
Neoplasms (140-239)	11	243 (121-435)	3	60 (12-174)	14	146 (80-246)
Endocrine (240-279)	1	466 (12-2597)	4	1869 (486-4148)	5	1166 (368-2416)
Nervous (320-389)	3	1224 (253-3578)	0	0 (0-1517)	3	615 (127-1796)
Circulatory (390-459)	17	262 (152-402)	9	206 (93-362)	26	239 (156-340)
Respiratory (460-519)	2	208 (25-753)	4	430 (112-955)	6	423 (183-833)
Digestive (520-579)	1	217 (6-1207)	1	232 (6-1293)	2	224 (27-809)
*Natural Deaths (0-799)	36	271 (189-366)	22	269 (168-393)	58	232 (176-296)
Unnatural Deaths (E800-999)	13	1179 (628-2016)	6	1540 (565-3351)	19	1273 (767-1988)
†All Causes (0-999)	51	354 (264-465)	28	232 (154-336)	79	299 (236-372)

* Includes one death coded 799 (cause unknown) after inquest. † Includes two deaths from unknown causes.

Variation of SMR with age

The SMR was raised in all age groups, but fell with increasing age (Figure 7.1). Most unnatural deaths were in young and most natural deaths in older subjects (Figure 7.2).

Figure 7.1: Variation of observed and expected deaths and SMR with age

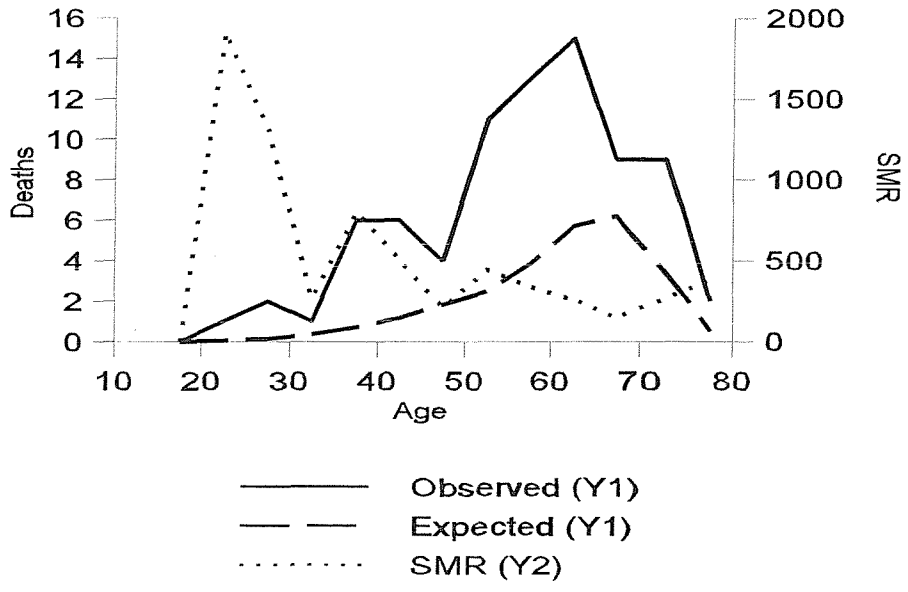
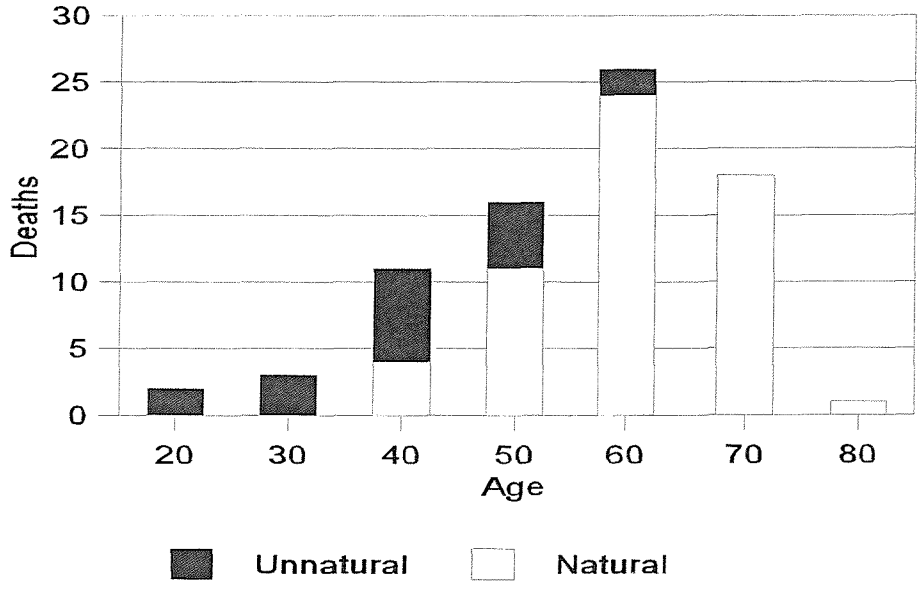


Figure 7.2: Distribution of deaths by age.



Variation of SMR with length of follow-up

The SMR fell during the first six years of the study, plateauing thereafter (Figure 7.3). Most unnatural deaths occurred at the beginning of the study, natural deaths were more evenly distributed (Figure 7.4).

Figure 7.3: Survival analysis and variation in SMR with length of follow-up

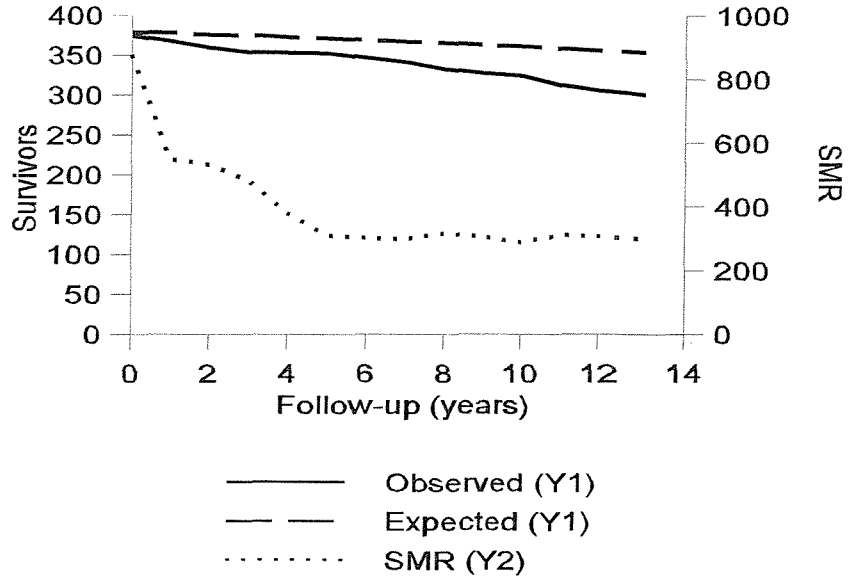
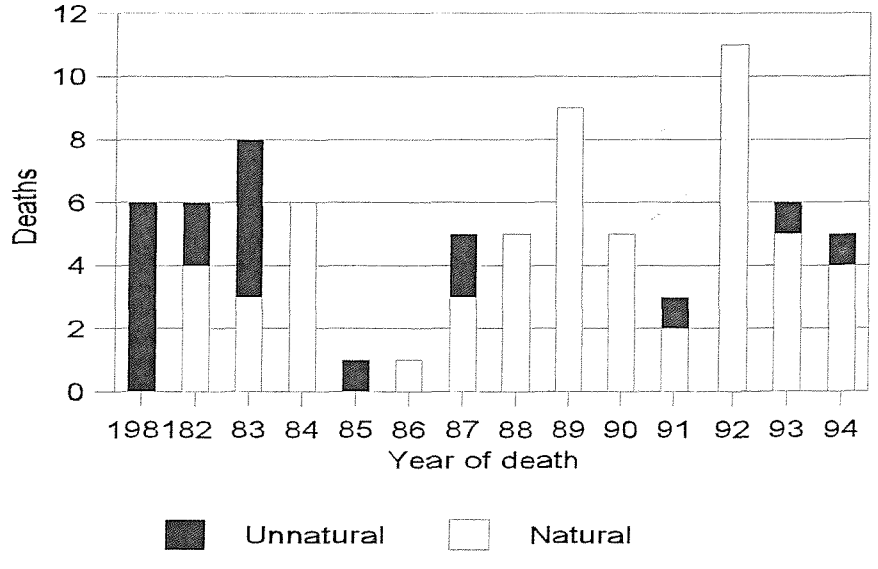


Figure 7.4: Distribution of deaths by year of death



Sociodemographic variables

Mortality was higher in the unmarried, the unemployed and in manual workers, as predicted by general population studies. None of these differences reached statistical significance (Table 7.4).

Table 7.4: SMR in dichotomous subgroups dissimilar for characteristics associated with increased general population mortality

Characteristic	Observed Deaths	SMR (95% CI)	χ^2 difference paired SMRs
Married (N=93)	18	252 (150-399)	P>0.2
Unmarried (N=240)	54	335 (252-437)	
Employed (N=121)	25	275 (178-405)	P>0.5
Unemployed (N=212)	47	333 (245-442)	
Social class I,II,IIIN (N=114)	18	179 (165-441)	P>0.5
Social class IIIM,IV,V (N=210)	50	323 (240-426)	

Subjects with incomplete data were omitted from the pertinent part of the analysis

Cigarette smoking

Eighty per cent of male and 64% of female subjects smoked cigarettes, twice the contemporary general population rates (38% and 33%, Office of Population Census and Surveys, 1984a). The all cause mortality was significantly raised among the smokers (SMR 360, CI 270-471) but not among the non-smokers (SMR 178, CI 85-328). Nineteen subjects died from smoking related conditions (Royal College of Physicians, 1971), an SMR of 181 (CI 112-275).

Table 7.5: SMR in smokers compared to non-smokers

Characteristic	Observed Deaths	SMR (95% CI)	χ^2 difference paired SMRs
Cigarette Smokers (N= 224)	53	360 (270-471)	P=0.051
Non-smokers (N=82)	10	178 (85-328)	

Natural cause mortality (ICD-9 disease categories 001-799)

The natural cause SMR (232, CI 176-296) did not change significantly during the follow-up period, natural deaths accounting for two-thirds (63%) of the excess mortality. Eighty per cent of natural deaths were from circulatory, neoplastic or respiratory disease, the same rank order as in the general population (Office of Health Economics, 1992).

Table 7.6: SMR for causes with more than two deaths.

ICD-9 Cause of death	Observed deaths	SMR (95% CI)
Lung cancer (162)	5	208 (68-485)
Diabetes mellitus (250)	3	1,214 (228-2,978)
Epilepsy (345)	2	2,620 (317-9,464)
Cardiovascular Disease (390-429)	14	187 (102-298)
Cerebrovascular disease (430-438)	9	481 (218-847)

Predictors of natural death.

Multivariate logistic regression analysis identified age as a predictor of natural death, with a trend towards significance for cigarette smoking (Table 7.7)

Table 7.7: Predictors of natural death

Variable	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Probability
Male gender	1.37 (0.77-2.44)		N/S
Age	1.12 (1.09-1.16)	1.14 (1.08-2.00)	<0.001
Age at onset schizophrenia	1.05 (1.02-1.09)	0.99 (0.94-1.04)	0.71
Cigarette smoking	0.37 (0.14-1.01)	0.33 (0.10-1.09)	0.071
Employment	1.19 (0.53-2.67)		N/S
Single	0.95 (0.54-1.66)		N/S
Social class IIIm, IV,V	0.52 (0.29-0.94)	0.81 (0.34-1.94)	0.64

Preventable natural mortality

Six deaths, all in patients aged under 65, were from causes designated as 'preventable' by the Chief Medical Officer (Department of Health, 1994), an SMR (468, CI 172-1020) more than four times the expected value. Four of these six 'avoidable' deaths, in people aged 35-64, were from cerebrovascular disease (Nos. 17, 28, 30, 36) and two from surgical disease (Nos. 32, 35). Case note audit suggested six deaths from causes not included in the CMO's list might also have been prevented. The causes of these deaths were: diabetic keto-acidosis (No. 14), hypothyroidism (No. 18), dehydration (No. 47), lobar pneumonia with congestive heart failure (No. 3) and septicaemia with lobar pneumonia (Nos. 21, 57).

Unnatural cause mortality (ICD-9, E800-999)

The unnatural cause SMR (1273, CI 767-1988) was twelve times that expected. Unnatural deaths accounted for a third (33%) of the excess mortality (two subjects died abroad from unknown causes hence 4% of deaths could neither be classified as natural nor unnatural). Fourteen of the nineteen unnatural deaths were by suicide (SMR 2803, CI 1532-4703), three accidental and two from undetermined causes. The unnatural deaths were clustered in the early years of the study with six (32%) in the first year and eleven (58%) the first three years (Figure 7.4).

Table 7.8: Unnatural cause morality.

ICD-9 Cause of death	Observed deaths	SMR (95% CI)
Accidents (E800-949)	3	379 (71-931)
Suicide (E950-959)	14	2803 (1532-4703)
Undetermined (E980-989)	2	990 (120-3580)
Total	19	1275 (606-1900)

Accidental deaths

Three out-patient deaths were recorded as accidental. One, from benztropine poisoning (No. 67), was probably not an accident. Schizophrenia probably contributed to two deaths from asphyxia (No. 71) and hypothermia (No. 77).

Suicide

Of the fourteen suicides, five (36%) died in the first year and twelve (86%) in the first five years. Eleven (79%) of the suicides were in contact with the psychiatric services at the time of death, seven (50%) were in-patients, one (7%) a day-patient and three (21%) out-patients. One other man had been discharged from hospital without follow up, two weeks before death. The remaining three subjects had rejected psychiatric contact. Ten (71%) subjects were receiving antipsychotic drugs at the time of death.

Of the variables included in the bivariate analysis of suicide prediction the only trend towards significance was for manual social class status. No multivariate analysis was therefore performed (Table 9.7).

Table 7.9: Predictors of suicide

Variable	Unadjusted odds ratio (95% CI)	Probability
Male gender	1.72 (0.64- 4.66)	0.28
Age	0.99 (0.96-1.04)	0.94
Age at onset schizophrenia	1.02 (0.96-1.09)	0.51
Cigarette smoking	0.39 (0.05-3.29)	0.38
Employment	0.98 (0.27-3.49)	0.96
Single	0.57 (0.21-1.54)	0.27
Social class IIIm, IV, V	0.35 (0.12-1.00)	0.05

Undetermined deaths

One undetermined death, of a man who died from amitryptilline poisoning after absconding from hospital, was probably a misclassified suicide (No. 75). There was insufficient evidence to determine the exact circumstances of death of a man who died in a fall or jump from his flat (No. 69).

Unknown deaths

Two subjects died abroad. The fact of death was confirmed by a UK government department but I was unable to discover the cause. A 55 year old male with severe Parkinson's disease died shortly after returning to India. A 66 year old Englishman died in the Phillippines where he moved after his new Filipino wife had been refused entry to the UK.

Chapter 8: Discussion

Introduction

I will first discuss the probable effects of errors in the study and then discuss the findings and their importance.

Confounding variables and selection bias

Subjects were not representative of the local population with schizophrenia as the original study criteria excluded people living in long stay psychiatric wards; those who did not have any contact with psychiatric services during the index year, those whose symptoms were exacerbated by drugs or alcohol and those with unrecognised schizophrenia. Subjects were mostly middle aged. Males were over represented, probably because of the greater male morbidity in schizophrenia (World Health Organisation, 1979), and hence the greater need for secondary service contact.

The study describes the mortality of a prevalence cohort with schizophrenia, in which the 343 (93%) non-first episode subjects had already survived the period of greatest excess mortality (Mortensen & Juel, 1993). This procedure almost certainly produced an underestimate of mortality as measured from disease onset. This is probably the most important error in the study hence it is likely that the overall direction of error is to underestimate the excess disease mortality of schizophrenia.

Of those groups excluded from the study, long stay patients have a relatively low SMR (Giel *et al,* 1978; Brook, 1985). Most patients who avoid contact with specialist psychiatric services for a year will be well and presumably at lower risk of premature death. This may not apply to a few who are itinerant or otherwise difficult to engage. Most people with unrecognised schizophrenia are probably young, have early disease and hence a high SMR (Mortensen & Juel, 1993).

People who misuse drugs and alcohol have a high mortality (Harris & Barraclough, 1998). The exclusion of potential subjects with significant substance misuse, common in psychiatric research in order to obtain a 'pure' cohort, probably reduced the number of poor outcome subjects. The meta-analysis suggests that the male excess probably increased suicide risk but not natural mortality.

Some members of the cohort have since been rediagnosed as suffering from non-schizophrenic psychoses, others excluded from the original cohort have been confidently diagnosed with schizophrenia. Misdiagnosis however, probably has little effect on mortality rates (Simpson & Tsuang, 1996).

How representative was the Southampton cohort of the general population with schizophrenia?

Subjects were originally identified through a detailed census of points of entry to the local psychiatric services in 1981-2. Recruited for a study of the effectiveness of local community based services, inclusion criteria were chosen to meet broad contemporary clinical definition of schizophrenia (Gibbons *et al,* 1984). This mortality study was therefore undertaken using a cohort chosen fifteen years before for a different purpose. These criteria were not ideal but the practicalities of this mortality analysis dictated the use of a retrospectively identified cohort.

Subjects were not wholly representative of the general population with schizophrenia as discussed above. There is no reason to think that contemporary patterns of psychiatric contact in Southampton differed from those in the rest of the country. It is therefore likely that subjects were representative of UK patients, with clinically broadly diagnosed schizophrenia, living outside hospital and in contact with psychiatric services. Results should generalise to similar settings though possibly not to younger, more recent patients or to those

countries with different patterns of service provision or mortality.

Follow-up

Vital status, established by record linkage through FHSA and NHS central records, was verified with GPs, other health professionals, family or friends. Matched death certificates were checked for full name, date and place of birth, place of death and NHS number where I knew it. The amount of detail makes it very unlikely that matches were incorrect.

Completeness of follow-up was unexceptional compared to other recent studies (Mortensen & Juel, 1990, 1993; Newman & Bland, 1991), and much better than in the only comparable UK study (Anderson *et al,* 1991). Mortality among the 12 (4%) untraced subjects may have been increased, if they were missed because itinerant or living in the third world. If all were dead, the all cause SMR would be 344, if alive 294.

The death certificate causes of death should be more accurate than in the general population, as the rates of post mortem examination (62% compared to 22%), and coroner's inquest (26% compared to 3.5%) were many times higher than the national average (Home Office Statistical Bulletin, 1994). These high rates are explained partly by the unnatural deaths (N=19), and partly by a large number of deaths referred to the coroner because the medical officer had not seen the deceased in their final illness. One death certificate (No. 41) was incorrect by ICD-9 guidelines (World Health Organisation, 1977) as it omitted serious underlying pathology.

Statistical methods

Local mortality rates are lower than average for England and Wales (Office of Population Census and Surveys, 1996a), hence the use of national reference population data will have underestimated cohort mortality. The SMRs,

calculated by Dr Hazel Inskip, a local epidemiologist, using a standard computer programme and statistical analysis (Breslow & Day, 1987), were subject to the same errors as comparable studies. SMRs were checked by computer and hand calculations. Some of the differences from previous results may reflect the better Southampton follow-up rate.

Calculation of an 'avoidable' natural SMR followed the procedure used in the CMO's annual report (Department of Health, 1994). Designed to give a rough measure of quality of medical treatment this analysis is based on deaths from selected common diseases for which effective treatment is available. It misses potentially preventable deaths from rare causes and deaths where the immediate though not the underlying cause of death was treatable, thereby probably underestimating avoidable mortality. The study probably followed general population surveys in underestimating the prevalence of cigarette smoking (Bennett *et al,* 1995) and thus its effect on mortality.

Care assessment

I obtained relevant hospital case notes on all but the two patients who died abroad. Audit was retrospective and subject to recorder and investigator bias. Designation of individual deaths as preventable was subjective and conservative. Vignettes were chosen to illustrate particular points rather than as measures of the prevalence of particular mechanisms. It is impossible to tell retrospectively whether any of these individuals would have survived with better treatment or whether the prevalence of these events differed from that in the general population. It is also impossible to identify an absolute number of preventable deaths.

Summary of main positive and negative findings

The overall results and patterns of mortality were broadly in line with those in the literature, with an excess mortality from both natural and unnatural causes. Excess deaths were distributed much as expected but mortality was high and remained so when comparison was limited to studies of similar cohorts and methodology. Reference studies do not include enough subject details to be sure that differences are not due to confounding variables. The results would however fit with the trend to increasing mortality observed by Munk-Jørgensen & Mortensen (1992). Other important positive findings include the association between cigarette smoking and mortality and the excess mortality from treatable diseases.

Power calculation (Altman, 1997) suggests that the main negative findings, the absence of significant sociodemographic effects on mortality, the non-significant excess lung cancer mortality and the failure to identify predictors of suicide probably reflect inadequate sample size. The small cohort makes it difficult to comment meaningfully on other unexpected findings such as the high mortality from infectious, nervous and endocrine diseases.

The case note audit, a method not previously used in this context, suggests that the mechanisms underlying the excess natural mortality include altered exposure to known risk factors, especially cigarette smoking, poor recognition and treatment of acute medical disease and inadequate treatment of chronic medical disease. Audit of suicides produced findings in line with the recent literature (Royal College of Psychiatrists, 1996). The audit results will be discussed in detail later in the thesis.

Overall mortality

This study confirmed an association between schizophrenia and premature death. The SMR was higher than in any previous non-first episode cohort, but the cohort was relatively small and some SMRs have wide confidence intervals. There is no national standard with which to compare results. Other UK studies (Herrman *et al,* 1983; Hassall *et al,* 1988; Anderson *et al,* 1991; Baxter, 1996) give too few subject details to be certain whether the present high mortality might be due to confounding variables. I have no reason to suspect that schizophrenia mortality is higher in Southampton than in the rest of the UK or the developed world, but cannot exclude this possibility. Alternatively schizophrenia mortality may be increasing, for reasons as yet unknown (Munk-Jørgensen & Mortensen, 1992). Increasing national mortality would be an indictment of mental health policies, a high local rate an indictment of local services. Either way, these results underline the need for continued monitoring.

Sociodemographic factors

The results of the analysis of marital, employment and social class effects, though not statistically significant, lay in the direction predicted by general population figures (Office of Population Census and Surveys, 1990a). Power calculation (Altman, 1997) suggests that the failure to demonstrate significance was probably due to small cohort size. Many subjects suffered social decline during the course of follow-up, thus outset measurements probably underestimated subsequent disadvantage. Nevertheless the results confirm previous findings from mixed diagnosis cohorts that social disadvantage only explains a small part of the excess mortality of mental illness (Babigian & Odoroff, 1969; Baxter, 1996).

Cause of death

As in the meta-analysis, about two thirds of extra deaths were natural and one third unnatural. Most natural deaths were from similar causes to those seen in the general population (Office of Health Economics, 1992). The immediate causes of death were similar to those reported in other schizophrenic cohorts where these data have been listed (Lesage *et al,* 1990; Anderson *et al,* 1991).

Infectious diseases

Death from infectious disease is now uncommon in the UK, hence a single case, merits discussion. An elderly woman died in hospital after physicians refused life support treatment citing poor quality of life (No. 57). Her husband found her agitation difficult to manage and kept her in bed, inactive and under stimulated. Community Psychiatric Nurse (CPN) and psychiatrist were unable to intervene effectively. Bed sores progressed to septicaemia and multiple organ failure.

Neoplastic diseases

Cancer mortality was increased in males but reduced in females, results which fell within the range of previous studies. Five (36%) of 14 cancer deaths were from lung cancer and one from oesophageal cancer, all in smokers, the others from different common cancers. The SMR from lung cancer was unexceptional when expected mortality was weighted for the smoking prevalence of the cohort. The cohort was too small to advance the argument about whether schizophrenia protects against cancer.

Five cancers (Nos. 5, 15, 29, 34 and 55) were already disseminated at presentation. Two cases, of malignant melanoma (No.5) and lymphoma (No.15), in itinerants unregistered with GPs, were detected during coincidental psychiatric hospital admissions. A sixth subject died a year after refusing potentially curative surgery for bowel cancer (No. 27). Psychiatrists found no

evidence of psychosis.

Recent treatment advances make early detection of cancer increasingly important and delayed presentation a plausible explanation of increased mortality. I cannot say whether these cancers were detected later than in the general population or whether earlier detection would have made any difference to outcome.

Endocrine diseases

Mortality from endocrine diseases was unexpectedly high and probably a real finding. Three of five deaths from endocrine diseases were from causes which at first sight appear preventable. A 57 year old male, in regular psychiatric contact, became increasingly confused over two weeks and was eventually admitted to hospital, stuporous and hypothermic (No. 18). He died the same day after a cardiac arrest. Tests returned after death showed severe hypothyroidism.

A 55 year old female, diabetic, itinerant, unregistered with a GP and refusing of psychiatric contact, collapsed in the street and died in hospital from diabetic keto-acidosis. Deemed not detainable at a Mental Health Act assessment nine months ealier she had no further psychiatric contact.

An elderly woman fell and fractured her femur (No. 47). She was treated and discharged to a nursing home where she refused food and drink. She died from bronchopneumonia and dehydration two months later, five days after re-admission to hospital, an outcome which might have been prevented by earlier or more aggressive medical intervention.

Two other subjects died from the complications of diabetes (Nos. 31, 56). I could not find reliable information about their treatment compliance but this, possibly exacerbated by smoking and the effects of neuroleptic drugs, is a plausible explanation of the high SMR (Mortensen & Juel, 1990).

Nervous diseases

The SMR from nervous diseases was also high and was largely due to two deaths from epilepsy, one from asphyxia (No. 1) the other from status epilepticus (No. 4). Both subjects were relatively young, known epileptics, neither were alcohol or drug dependent. I could not find whether they were compliant with anticonvulsant medication. These cases highlight importance of epilepsy control in patients taking medication which reduces seizure threshold, and were the only instances where the clinical picture or cause of death suggested symptomatic schizophrenia. The third death, from motor neuron disease (No. 37), appears unremarkable.

Circulatory diseases

Cardiovascular SMR was increased consistent with previous findings. It is very likely that this was partly due to the subjects' smoking. Poor diet, inadequate exercise (Brown *et al,* 1999) obesity and hypertension (Kendrick, 1996) probably also contributed. Most deaths occurred at home in the middle aged and elderly, and were largely undocumented. None were associated with neuroleptic doses above British National Formulary (1999) limits.

The improved outcome associated with early intervention in acute cardiac disease (Boon & Fox, 1995), suggests that delayed recognition and treatment may contribute to the excess cardiovascular mortality. I could however only identify one death where an opportunity for intervention was missed: A 41 year old male collapsed in the street and died from acute pulmonary oedema (No. 2) after leaving the casualty department without waiting to see a doctor.

The reasons for the high cerebrovascular mortality are unclear. I could not find useful data about these patients' health and risk factors before the CVA. Some of the excess mortality was probably smoking related but it is inconsistent that

this would increase cerebrovascular mortality nearly five times but only double cardiovascular mortality. The nursing home death from aspiration pneumonia of a 62 year old female (No. 30) merits further comment. This subject had underlying cerebrovascular disease and was also taking a neuroleptic drug. Similar deaths were reported by both Lesage *et al* (1990) and Anderson *et al* (1991), a large number of deaths from a generally uncommon cause, raising questions about the role of neuroleptic drugs.

Respiratory diseases

Respiratory mortality was high compared to previous schizophrenic cohorts, though there were too few deaths for reliable statistical comparison. Two deaths from asthma (Nos. 20, 48) and one from bronchopneumonia (No. 10) in subjects with chronic respiratory disease, appear unremarkable. Death certification of bronchopneumonia (No. 41), which omitted underlying cerebrovascular disease, diabetes, arteriopathy and resulting amputation was incorrect by ICD-9 guidelines (World Health Organisation, 1977).

Two deaths of long stay psychiatric patients with post mortem diagnoses of lobar pneumonia, followed missed diagnosis by psychiatrists: A 41 year old female died from lobar pneumonia with underlying 'congestive cardiomyopathy' (No. 3). She became acutely dyspnoeic, was examined and prescribed a diuretic. She died two days later at home, nurses having thought her well enough to take leave from the hospital.

A 58 year old female died from septicaemia secondary to lobar pneumonia (No. 21). She became non-specifically unwell three days before death, was examined but received no firm diagnosis or treatment. Subsequent nursing notes described her as 'chesty', apyrexial and not particularly unwell.

This analysis may underestimate the importance of respiratory disease as bronchopneumonia was recorded as the immediate cause of 14 (24%) natural

deaths, most in patients with other serious physical disease, cerebrovascular disease (N=7), skull fracture, motor neuron disease, carcinomatosis, COAD, congestive cardiac failure. I do not know whether these numbers are significant as reference mortality statistics are based on the underlying rather than the immediate cause of death (World Health Organisation, 1977).

Digestive diseases

Two deaths from acute intestinal obstruction were potentially preventable by surgical intervention: A 63 year old woman with chronic schizophrenia, learning difficulties and poor communication skills who died suddenly in a rest home (No. 32), was found at post mortem to have developed acute intestinal obstruction secondary to old surgical adhesions.

A 63 year old divorced male with residual schizophrenia, died alone at home from acute intestinal obstruction secondary to an inguinal hernia (No. 35). He had been admitted to hospital when the hernia obstructed four months earlier, was managed conservatively and placed on a waiting list for elective surgery.

Mechanisms of excess mortality

These vignettes suggest a number of mechanisms which may contribute to the excess natural mortality of schizophrenia. These can broadly be divided into three categories: altered exposure to known environmental risk factors, failure to recognise or adequately treat acute physical disease and failure to adequately treat chronic physical disease. The excess mortality thus appears explicable by known mechanisms and thus should be susceptible to available interventions.

Opportunities were missed in all the selected vignettes but it is impossible to put a precise figure on how many deaths might have been prevented by optimal interventions. The descriptive analysis suggests that some would have been very difficult to prevent.

Environmental risk factors

Subjects had different sociodemographic characteristics to otherwise similar members of the general population, with an excess of the unemployed, single and manual workers. They also had increased rates of other risk factors, notably smoking. No subject deaths were directly caused by intoxication, withdrawal or use of other drugs, though alcohol was probably a factor in some cases of late presentation (Nos. 5, 15) and poor treatment compliance. Statistical analysis was not feasible because of the small cohort size, exclusion of known alcohol and drug abusers and the unreliability of data about substance use.

Similar problems prevented testing of the effects of diet, self-care and exercise however survivors ate a poorer diet and took less exercise than the general population, when interviewed in 1996 (Brown *et al,* 1999). These differences remained when results were adjusted to reflect social class distribution. If survivors were selected for health, it is likely that the deceased also had unhealthy lifestyles. One death (No. 57) was directly related to bizarre lifestyle.

Smoking related mortality

These results suggest that most of the excess natural mortality of modern community samples is caused by cigarette smoking. Subjects who were non-smokers also had a raised SMR, however smoking is almost certainly the largest potentially preventable cause of premature death. The high prevalence of smoking, seems to be due to low rates of quitting rather than to particularly high rates of starting smoking (Brown, 1991). Smoking cessation programmes can be effective in schizophrenia (Ziedonis & George, 1997; Addington *et al,* 1998) but psychiatrists rarely discuss smoking with patients (Lawrie *et al,* 1995). Indeed staff may use cigarettes to reinforce desired behaviour (Mester *et al,* 1993). Developing and evaluating strategies to help patients stop smoking should therefore be a high priority for health service planners and will require changes

in the attitudes of mental health workers as well as action by individual clinicians.

Psychiatric treatment

No cohort deaths were unequivocally due to psychiatric treatments, however neuroleptic drugs may have contributed to a death from aspiration pneumonia (No. 30). Neuroleptic drugs may also have exacerbated diabetes, epilepsy and chronic respiratory disease (Mortensen & Juel, 1990). It is important not to overstate this case. Treatment can be life-saving in a psychiatric emergency. Earlier treatment of subjects who were refusing physical treatment (Nos, 14, 47) might have prevented death. Effective treatment of negative symptoms may improve patients' self care and health management. Possible side effects should therefore be carefully monitored but it is important that patients are not denied effective psychiatric treatment.

Chronic physical disease

Four of the six deaths in the statistical analysis of preventable diseases were from cerebrovascular disease, considered preventable by effective hypotensive treatment. The raised SMRs from epilepsy, diabetes and respiratory disease may also reflect inadequate treatment, possibly exacerbated by the effects of neuroleptic drugs. Inadequate treatment may result from poor clinical practice or because the patient rejects or is poorly compliant with quality treatment.
Poor clinical practice can be addressed by audit, clinical governance and continued education, though it is difficult to target this effectively at poor performers. We do not know whether psychiatrists or GPs provide the best routine medical treatment for people with serious mental illness, though the GP is the professional most likely to be in contact with the 25-40% of patients who lose contact with the psychiatric services (Brown & Birtwistle, 1998).
Intervention studies have shown improved care delivery by GPs but have not

shown health gains (Burns & Kendrick, 1997). The respective Royal Colleges (1993) advocate a shared model of care but there is little evidence of how this works in practice.

One subject death, from diabetic keto-acidosis (No. 14), was directly due to patient non-compliance. Patients are often reluctant to take psychotropic medication (Corrigan *et al,* 1990). Compliance with treatments of physical disease is probably also poor. Some interventions, such as providing clear explanations of the rationale for treatment, clear written instructions and simple dose regimes are common sense. Specific compliance therapy (Kemp *et al,* 1998) may also be helpful.

Two subjects died after rejecting treatment (Nos. 27, 47). A third died after treating doctors refused life support treatment (No.57). There is no suggestion that these decisions were improper. A competent person may choose to reject optimal medical treatment. It is however important that competence is assessed and incompetent patients receive optimal psychiatric treatment to give them the best opportunity to make informed decisions. Similarly doctors should base decisions about ceasing treatment on all available evidence about quality of life.

Acute physical disease

Serious physical co-morbidity is common in psychiatric disease (Jeste *et al,* 1996). Effective treatment of acute physical disease requires that the disease is recognised and appropriate treatment delivered. Study subjects died after acute disease went unrecognised by subjects (Nos. 2, 35) carers (No. 32) and doctors (Nos. 3, 18, 21). Failed recognition of disease may also have contributed to the raised cardiovascular and cancer mortality as previously discussed.

It is unrealistic to expect to improve illness recognition by patients and carers but important that doctors are alert to the possibility of serious physical disease, particularly when patients become non-specifically unwell or suffer an unexplained change in mental state.

Unnatural mortality

The unnatural mortality of the Southampton cohort was significantly increased. As in other series most unnatural deaths were from suicide, though deaths from other causes were also increased. Most of these deaths were potentially preventable, some by simple measures. Most unnatural deaths in the general population are also potentially preventable, however a certain level is accepted as the price of participating in risky activities. Such mortality may be reduced by measures such as wearing seat belts.

Accidental deaths

Of the three accidental deaths one by benztropine poisoning (No.67), would have been better classified as undetermined as it is unlikely that a fatal dose would be taken accidentally. Death might have been prevented by closer supervision or dispensing smaller quantities of medication.

Two other deaths were probably accidental but causally related to schizophrenia:

A 48 year old male living with elderly parents died of asphyxia in a bedroom fire (No. 71). Depot anti-psychotic medication had been stopped after years of stability in an attempt to relieve a severe drug induced extra-pyramidal syndrome. Readmission because of disorganised conduct was followed by self-discharge against advice a week before death.

A 64 year old male with mainly negative symptoms, compliant with medication and living quietly in a group home, was found dead from hypothermia twenty miles away in the New Forest where he had apparently walked (No. 77).

Suicide

Fourteen (6%) local suicide deaths is a high but not exceptional figure for such a cohort. Ten (71%) victims had previously attempted suicide. These numbers are too small to draw statistically significant conclusions but the characteristics of the victims and circumstances of the deaths fit broadly with previous findings.

The choice of mostly violent methods (Heilä *et al,* 1997; Rossau & Mortensen, 1997) probably represented opportunity. Six hospital suicides all used violent methods. Two out-patient suicides poisoned themselves with prescribed and two with or over the counter drugs. Four used violent methods. The preponderance of early hospital suicides may reflect problems of ward design and clinical practice in a new psychiatric unit or simply clustering around psychiatric contact. Four hospital suicides had no recent risk assessment, one died shortly after relaxation of observation and one despite close observation. Most hospital suicides could be prevented by close monitoring, however best practice requires that staff balance security needs against patient autonomy. The resultant risk management issues can and should be addressed by training.

Three of four suicides, who were not in contact with psychiatric services when they died, had rejected treatment and follow-up. The case notes suggest that one of these (No. 71) might have been re-engaged by a more assertive approach. The other two (Nos. 68, 76) had explicitly refused treatment. The discharge from hospital without follow-up of the fourth man (No. 69) should not happen under the Care Programme Approach (CPA) policy. It is unrealistic to expect to prevent all schizophrenic suicides as some occur without warning (Nos. 64, 66, 73, 74), or in patients who actively reject psychiatric contact.

Undetermined deaths

One undetermined death was probably suicide, potentially preventable by better supervision and prescription of low toxicity medication (No. 75). A 55 year old male with treatment resistant schizophrenia and a history of substance misuse and attempted suicide died from a self-administered overdose of amitryptilline, which he took at home after absconding from hospital.

There was insufficient evidence of intent to determine the cause of death of a 40 year old male who died from injuries sustained in a fall or jump from the flat where he resided (No.69). He defaulted from follow-up, moved away from

Southampton and died two years later without further psychiatric contact.

Predictors of natural and unnatural deaths

Analysis of predictors of outcome was undertaken in order to examine whether cross sectional data could be used to identify individuals at high risk of premature death. I sed logistic regression analysis rather than a proportional hazards model, on statistical advice, as this method identifies predictors of outcome while proportional hazard analysis compares survival times.
These analyses identified age and possibly cigarette smoking as predictors of natural death and lower social class as a predictor of suicide. The predictors of natural death are unsurprising, The failure to demonstrate a gender effect may reflect confounding by the female subjects' greater age, the failure to show effects of other variables may be due to inadequate sample size. This analysis reinforces the importance of smoking as a risk factor for natural mortality and suggests that clinicians should pay particular attention to the physical health of older people with schizophrenia.

Can observational studies lead to recommendations for mental health care delivery?

Evidence based practice demands that clinical decisions are based on the best available evidence. While the gold standard of evidence remains the well conducted RCT (Sacker *et al*, 2000), this level of evidence is often unavailable and its collection unethical or impracticable. Thus service planners and clinicians will sometimes need to base decisions on observational evidence, a practice with a sound historical basis (Doll & Peto, 1976).
Particular problems in measuring mortality data in schizophrenia arise from the relative infrequency of death which means that cohorts need to be large and follow -up long. A RCT assessment of the impact of an intervention, such as smoking cessation would probably not yield results for ten years. Planners and

clinicians have an ethical responsibility to base decisions on a balance of the quality of available evidence against the possible harm of awaiting better evidence. Individuals will need to make their own decisions about the quality of evidence in this thesis.

Suggested actions for service providers and commissioners

Health care providers and commissioners should aim to reduce premature death in identifiable groups with high mortality rates. Improving the health of the mentally ill is a specific government target (Department of Health, 1992).

The results of this study in respect of natural deaths suggest that mental health service planners should place greater emphasis than currently on health promotion. Cigarette smoking is almost certainly the largest preventable cause of premature death in this group. Developing and evaluating strategies to reduce patients' smoking should therefore be a high priority for health service planners. Other issues would include the promotion of healthy eating, exercise and weight loss. Such activities would take staff from their normal work and thus have implications for staffing levels. Institutions also have a responsibility to provide a healthy diet and environment for who are not in a position to make such choices themselves. Any such changes should be properly evaluated and effective practice disseminated.

Whether GPs or psychiatrists are best placed to treat medical disease in the seriously mentally ill is uncertain and merits further investigation, meanwhile service planners should ensure that responsibility for such treatment and monitoring of individual patients is explicitly allocated and accepted. Service planners also need to ensure that clinicians have adequate facilities and training to maintain their diagnostic skills and that they have ready access to appropriate investigations and second opinions. They should also consider how best to deliver assertive health care to itinerants who are not registered with GPs. Finally they need to ensure the continued measurement of mortality in these

vulnerable patients in order to monitor the effect of any service developments or changes in treatment. Services should also consider auditing natural patient deaths, as many now audit unnatural deaths, in order to identify deficiencies and recommend improvements in local services.

With respect to unnatural deaths, issues identified in this study include the assertive provision of treatment to patients who lose contact with ordinary services, better staff training in suicide risk management, considering policies on the use of toxic drugs and improving ward design to reduce obstacles to patient observation. Some of these issues can be addressed through clinical governance. Follow-up may have been improved by the introduction of the CPA process and supervised discharge. Service managers certainly have a responsibility that these mechanisms operate effectively. Service planners and politicians however need to recognise that it is unrealistic to expect to prevent all schizophrenic suicides as some occur without warning or in patients who exercise their right to refuse psychiatric contact.

Other suggestions for suicide reduction are comprehensively addressed in the National Confidential Inquiry into suicide and homicide by the mentally ill (Department of Health, 1999). The principal recommendations of that report include improving the skills of 'front-line' staff, improving administration and information exchange, making available optimal drug and psychological interventions and developing special services to address particular high risk groups (Department of Health, 1999).

Implications for clinical practice

Good practice demands that clinicians regularly review their own performance. This study suggests that some deaths from acute diseases should be preventable by better recognition and treatment by clinicians. This will require psychiatrists to ensure that their medical diagnostic skills are up to date. Non-psychiatric specialists should take care to ensure that the mentally ill not only have the

capacity to understand and consent to treatment but also that they have the capacity to react appropriately if predictable complications develop.

All doctors should be alert to the possibility of medical disease in patients who develop new symptoms or show unexplained changes in mental state and should recognise that a psychotic patient may not complain of symptoms which would cause distress in the mentally well. They should also consider invoking the Mental Health Act when a patient's mental state is seriously jeopardising their physical health.

Clinicians, especially psychiatrists should be attach a higher priority to patients' lifestyles, especially to cigarette smoking, the more so that there is now evidence that smoking cessation programmes are effective in schizophrenia (Ziedonis & George, 1997). This may require a considerable change in attitude (Mester *et al,* 1993; Lawrie *et al,* 1995).

Clinicians should ensure that routine screening and the monitoring of chronic medical disease is as effective in this group as in the general population and should also consider the merits of needs based assessment and regular physical examination of patients who might fail to recognise that they were ill. They should also monitor and where necessary take measures to improve compliance with medical treatments. Finally they should audit their practice to ensure that these aims are met.

With respect to unnatural deaths, individual clinicians have a responsibility for ensuring safe practice themselves and by their subordinates in relation to risk assessment, positive decisions about the need for follow-up and caution in the prescription of toxic drugs. A general strategy of awareness of high risk periods in the disease and provision of a consistently high standard of treatment to all patients may be a more effective strategy than targeting treatment at particular individuals (Rossau & Mortensen, 1997).

Recommendations for further Research

Mortality is the most objective measure of disease outcome and the effectiveness of medical treatment. It is vital that this continue to be monitored in order to assess the impact of national policy changes and the performance of local units. Further large, prospective cohort studies are needed to test hypotheses about aetiology and examine mortality from specific causes. These should use incident cohorts. Further individual follow-up studies are needed to provide more statistically powerful evidence, to identify treatment deficiencies and to suggest changes in treatment. Such studies need to look in detail at the circumstances of individual deaths and will often necessarily take a qualitative approach. This approach should be extended to GP notes.

Prospective cohort studies are needed to evaluate new approaches to health care delivery including the use of needs based assessment tools, the provision of routine physical screening and the evaluation of specific interventions such as smoking cessation and weight reduction. These should be RCTs wherever feasible.

Chapter 9: Conclusions

Gains in knowledge resulting from this project

This project has increased understanding of the excess mortality of schizophrenia by integrating findings from previous research studies and by original research into the circumstances of individual patient deaths. It confirms that there is a significant excess mortality from both natural and unnatural causes. It also demonstrates that the excess natural deaths occur in most but not all ICD-9 disease categories, a finding which supports Kendler's (1986) proposal that the excess natural mortality reflects differential exposure to environmental risk factors. The confirmation of a normal or reduced mortality from neoplastic diseases highlights the need for further research in this area. These are important advances as the findings of individual studies were often contradictory or lacking in statistical power.

The original research provided the first quantitative evidence of the relative roles of cigarette smoking and sociodemographic variables in the excess mortality of schizophrenia. It also identified a significant excess mortality from potentially treatable diseases and suggested some of the underlying mechanisms. These include unhealthy lifestyle, failed recognition and poor medical treatment of medical disease and poor treatment compliance. Possibly the most optimistic finding is that most of the excess natural mortality is explicable by known mechanisms and hence should be susceptible to currently available interventions.

Summary of findings

Schizophrenia has an increased mortality from natural and unnatural causes. Many of the excess natural and accidental deaths are potentially preventable by addressing known risk factors, especially cigarette smoking, or by better treatment of medical disease. In practice, some risk factors are not susceptible to medical intervention and some patients will reject optimal treatment. Natural and accidental mortality will probably remain raised. Schizophrenic suicide is well

recognised and may be increasing (Mortensen & Juel, 1993).

Psychiatry, as a branch of medicine, should aim to treat disease and promote health. Mortality is the most fundamental measure of disease outcome and hence of the effectiveness of medical treatment and should continue to be monitored. We will not be able to prevent all premature deaths in schizophrenia but should aim to prevent as many as possible.

Addendum: Recent developments in the literature about schizophrenia mortality

There have been few relevant publications since this thesis was first submitted. The most important study, describes time trends in schizophrenia mortality between 1976 and 1995 (Ösby *et al,* 2000). This paper used record-linkage to measure SMRs for all causes, natural deaths, cardiovascular deaths, suicide and 'unspecified violence' in successive five year cohorts identified from the Stockholm in-patient register. The study found a highly significant increase in SMR in each category among both males and females. The SMRs for the period 1981-95, which most closely match the period of this thesis, were higher than in previous cohorts and compatible with the results described in this thesis. These findings support previous evidence that the mortality of schizophrenia is increasing (Munk-Jørgensen & Mortensen, 1992; Mortensen & Juel, 1993), a finding that should be of great concern to clinicians and service planners alike. A more specific paper examining the prevalence of cardiac abnormalities in patients taking psychotropic drugs (Reilly *et al,* 2000) has led to the withdrawal of two drugs particularly associated with ECG abnormalities.

Appendix

Appendix 1: 58 deaths from natural causes

Case No.	Personal Details	Place of Death	Smoke	Cause of Death *
1	m 37	home	?	asphyxia, epileptic fit
2	m 41	street	Y	acute pulmonary oedema, left ventricular hypertrophy
3	f 41	home (leave from long stay ward)	?	lobar pneumonia, congestive cardiomyopathy
4	m 42	home	Y	status epilepticus
5	m 46	hospital (NFA)	Y	liver metastases, malignant melanoma
6	m 49	home	Y	congestive cardiac failure, myocardial infarction, coronary thrombosis
7	m 50	hospital	Y	dissecting aortic aneurysm
8	m 52	home	Y	carcinoma bronchus
9	m 52	home	Y	acute cardiac failure, coronary atheroma
10	m 54	long stay ward	Y	bronchopneumonia, chronic obstructive airways disease
11	m 54	hospital	?	ischaemic heart disease
12	m 54	long stay ward	Y	carcinoma lung
13	f 54	home	Y	carcinomatosis, carcinoma lung

Case No.	Personal Details	Place of Death	Smoke	Cause of Death
14	f 55	hospital ICU	Y	diabetic coma, diabetes mellitus
15	m 56	hospital (NFA)	Y	lymphoma
16	m 56	home	Y	cause unknown (inquest)
17	m 57	hospital	?	pneumonia, intra-cerebral haemorrhage
18	m 57	hospital ICU	?	hypothyroidism
19	m 57	home	Y	ischaemic heart disease, coronary atherosclerosis
20	f 58	home	?	asthma, chronic bronchitis, emphysema
21	f 58	long stay psychiatric ward	N	septicaemia, lobar pneumonia
22	f 58	nursing home	N	bronchopneumonia, multiple cerebro-vascular accidents, atherosclerosis.
23	f 58	hospital	Y	carcinomatosis, carcinoma breast
24	m 58	group home	?	myocardial infarction, coronary thrombosis, atheroma
25	f 59	hospital	Y	carcinomatosis, carcinoma oesophagus
26	m 59	hospice	N	renal carcinoma
27	m 61	home	?	carcinoma of sigmoid colon

Case No.	Personal Details	Place of Death	Smoke	Cause of Death
28	m 61	hospital	?	cerebro-vascular accident
29	m 61	home	Y	carcinoma lung
30	f 62	nursing home	Y	aspiration pneumonia, cerebro-vascular disease
31	f 62	home	N	hypertensive heart failure, diabetes mellitus
32	f 63	rest home	Y	acute intestinal obstruction, adhesions
33	f 63	group home	?	myocardial infarction, coronary artery thrombosis
34	m 63	hospital	Y	cardiac failure, carcinomatosis, carcinoma colon
35	m 63	home	Y	acute intestinal obstruction, scrotal hernia
36	m 63	hospital	Y	cerebro-vascular accident
37	m 63	nursing home	Y	bronchopneumonia, motor neuron disease
38	f 64	hospital	Y	cardiac failure, coronary thrombosis, coronary atherosclerosis
39	m 64	rest home	Y	acute heart failure, myocardial infarction, coronary atheroma
40	m 66	hospital	Y	carcinoma bronchus
41	m 67	hospital	N	bronchopneumonia

Case No.	Personal Details	Place of Death	Smoke	Cause of Death
42	f 67	hospital	N	bronchopneumonia, cerebral haemorrhage
43	m 68	home	Y	myocardial infarction, coronary thrombosis
44	m 68	group home	Y	intra-cerebral haemorrhage
45	f 69	home	Y	myocardial infarction, coronary atheroma
46	m 69	nursing home	Y	coronary artery atherosclerosis, chronic obstructive airways disease
47	f 70	hospital	Y	bronchopneumonia, hyponatraemia, dehydration
48	f 70	hospital	Y	asthma, chronic obstructive airways disease
49	m 70	nursing home	Y	cardiac failure, myocardial degeneration
50	f 71	hospital	Y	stroke
51	f 71	home	Y	cerebral haemorrhage
52	m 71	rest home	Y	generalised atherosclerosis
53	m 72	hospital	?	bronchopneumonia, disseminated adenocarcinoma caecum
54	m 72	hospital	Y	septicaemia, gangrene, vasculitis
55	m 72	hospital	N	obstructive jaundice, disseminated carcinoma

Case No.	Personal Details	Place of Death	Smoke	Cause of Death
56	f 75	hospital	?	congestive cardiac failure, ischaemic heart disease, diabetes mellitus
57	f 75	hospital	?	lobar pneumonia, septicaemia
58	f 76	hospital	Y	bronchopneumonia, cerebro-vascular haemorrhage

* Cause of death as written on death certificate. Deaths were coded following standard WHO procedure (World Health Organisation, 1977).

Appendix 2: Nineteen deaths from unnatural causes

Case No.	Personal Details	Place Of Residence / Fatal Act	Cause Of Death
59	m 22	hospital	jumped from bridge
		Itchen bridge	suicide
60	m 25	hospital	crushed by train
		railway track	suicide
61	m 27	hospital	drowned in wash basin
		hospital	suicide
62	m 31	hospital	set fire to self in toilet
		hospital	suicide
63	m 35	homeless hostel	jumped from building
		homeless hostel	suicide
64	f 36	hospital (on leave)	crushed by bus wheel
		bus station	suicide
65	f 37	home	aspirin poisoning
		home	suicide
66	m 39	group home	cut throat
		group home	suicide
67	f 39	home	benztropine poisoning
		home	accident
68	m 40	hospital	crushed by train
		railway track	suicide
69	m 40	home	fall/jump from flat
		home	undetermined
70	m 41	home	crushed by train
		railway track	suicide
71	m 48	home	asphyxia in bedroom fire
		home	accident

Case No.	Personal Details	Place Of Residence/Fatal Act	Cause Of Death
72	m 52	home	amitryptilline poisoning
		home	suicide
73	f 52	home	paracetamol poisoning
		home	suicide
74	f 54	residential hotel	asphyxia by plastic bag
		residential hotel	suicide
75	m 55	hospital	amitryptilline poisoning
		home	undetermined
76	f 58	home	distalgesic poisoning
		home	suicide
77	m 64	group home	hypothermia
		New Forest	accident

Appendix 3: Two deaths from unknown causes

Case No.	Personal Details	Country Of Residence	Cause Of Death
78	m 55	India	unknown
79	m 66	Phillipines	unknown

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