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A Six Year Follow-up of the Cavan/Monaghan First Episode Psychosis Study

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Summary

Aspects of outcome in first episode psychosis require clarification. In doing so, boundaries between diagnoses within the psychosis spectrum of disorders may be better understood, thus contributing to improvement in operational diagnoses of psychotic disorders. In addition, the place within the spectrum of psychotic disorders of lesser studied diagnoses, such as major depressive disorder with psychotic features, is unclear. This study is a six year follow-up of the Cavan/Monaghan First Episode Psychosis Study, and investigates outcomes in a cohort characterised by substantive ethnic and socioeconomic homogeneity and stability. This study examines key aspects and predictors of outcome, including diagnostic stability, psychopathology, social and occupational functioning, quality of life and service-engagement. Three major diagnostic nodes, schizophrenia, bipolar disorder and major depressive disorder with psychotic features emerge from the data. Schizoaffective disorder appears to inhabit the territory between these three nodes. Schizophreniform disorder appears primarily a progenitor of schizophrenia, while delusional disorder appears primarily a variant progenitor of schizophrenia and schizoaffective disorder. Brief psychotic disorder appears to be related prospectively to bipolar disorder and major depressive disorder, while substance-induced psychosis and psychosis not otherwise specified appear to be related prospectively to schizophrenia and schizoaffective disorder. Follow-up data on psychopathology, functioning, QOL and service engagement result in an overall picture of SZ having the most adverse outcome of all the diagnoses within the psychotic spectrum. Systematic comparisons are made with SA, BD and MDDP. Additionally, the study illuminates rarely considered aspects of SF, DD, BrPsy, PNOS, SIP, SIM, PGMC and MGMC. Extent of psychopathology has a notably adverse effect on outcome for all diagnoses, whereas an ability to maintain social integration and a more 'normal' life course appears to have a positive effect on outcome. These findings have implications for the approach to treatment across psychotic disorders: broader symptom management, whether via pharmacological or psychotherapeutic approaches, may prevent particularly adverse outcomes, and interventions that promote occupational and social integration are key in raising outcomes beyond the level achievable by symptom management alone.

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Acronyms

AIMS	Abnormal Involuntary Movement Scale
Alz	Alzheimer's disease
ARMS	At risk mental states
ATPD	Acute and transient psychotic disorder
BD	Bipolar disorder I
BD II	Bipolar disorder II
BDNF	Brain derived neurotrophic factor
BrPsy	Brief psychotic disorder
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness Study
CBT	Cognitive behaviour therapy
CNE	Condensed Neurological Evaluation
CNV	Copy number variation
COMT	Catechol-O-methyl-transferase
CPN	Community psychiatric nurse
DA	Dopamine
DAOA	D-amino acid oxidase activator
DD	Delusional disorder
DSM	Diagnostic and Statistical Manual
DUI	Duration of untreated illness
DUP	Duration of untreated psychosis
EE	Expressed emotion
EPPIC	Early Psychosis Prevention and Intervention Centre
ERP	Event-related potential
ETD	Eye tracking dysfunction
EXIT	Executive Interview
FE	First episode
FEP	First episode psychosis
fMRI	Functional magnetic resonance imaging
FUFEP	Follow-up first episode psychosis
GABA	Gamma-aminobutyric acid
GAF	Global Assessment of Functioning
GP	General practitioner
HoNOS	Health of the Nation Outcome Scale
IPSS	International Pilot Study of Schizophrenia
IQ	Intelligence quotient
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MDD	Major depressive disorder
MDDP	Major depressive disorder with psychotic features
MMSE	Mini-Mental State Examination
MPA	Minor physical anomaly
NART	National Adult Reading Test
NEHB	North Eastern Health Board

NEMESIS	Netherlands Mental Health Survey and Incidence Study
NES	Neurological Evaluation Scale
NIMH	National Institute of Mental Health
NMDA	N-methyl D-aspartate
PANSS	Positive and Negative Syndrome Scale
PANSS pos	Positive and Negative Syndrome Scale positive subscale
PANSS neg	Positive and Negative Syndrome Scale negative subscale
PANSS gen	Positive and Negative Syndrome Scale general subscale
PANSS tot	Positive and Negative Syndrome Scale total score
PAS	Pre-morbid Adjustment Scale
PC	Principal component
PCP	Phencyclidine
PNOS	Psychosis not otherwise specified
PTSD	Post traumatic stress disorder
QOL	Quality of life
QLS	Quality of Life Scale
RIP	Deceased
SA	Schizoaffective disorder
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SCID	Structured Clinical Interview for DSM diagnosis
SE	Service engagement
SES	Service Engagement Scale
SF	Schizophreniform disorder
SLE	Systemic lupus erythematosis
SLOF	Specific Levels of Functioning
SNP	Single nucleotide polymorphism
SPSS	Statistical Package for the Social Sciences
SSRI	Selective serotonin reuptake inhibitor
SUMD	Scale to Assess Unawareness of Mental Disorder
SZ	Schizophrenia
TD	Tardive dyskinesia
TIPS	Early Treatment Intervention in Psychosis Study
VCF	Velo-cardio-facial syndrome
WHO	World Health Organisation
WHOQOL-Bref	World Health Organization Quality of Life-Bref Scale

Neurobiology and epidemiological risk factors for psychosis

Concept of psychosis

From the beginning of our efforts to conceptualise and understand psychotic illness there have been attempts to classify these disorders. This has led to identification of commonalities between individual patients but also to confusion as to the reliability of our efforts to categorise them and the boundaries between these categories. One of the first authors to attempt to place a structure on such disorders, which Locke (1959) may have been describing in those 'under the power of an unruly Passion', was Griesinger. He believed that there were 'primary' disease processes involving what would now be termed affective and schizoaffective disorders, from which a 'secondary' disease process, involving what would now be termed residual schizophrenia (SZ), might evolve. However, in later life he acknowledged that it was possible to have a primary, non-affective psychosis (Griesinger, 1861). Kraepelin (1896) subsequently differentiated between dementia praecox, characterised by chronic deterioration in mental functioning, and affective psychosis, characterised by a more periodic form of illness. However, later in his career he came to believe that these two manifestations of disease could coexist and that a single concept of psychosis might be more useful (Kraepelin, 1920). Bleuler (1911) first used the term 'schizophrenia' and divided it into subcategories. Whilst he held to the idea of two illnesses, SZ and affective psychosis, he also believed that they could co-exist. Subsequent years saw a focus on descriptive psychopathology (Jaspers, 1946,1963; Schneider, 1959). In modern times, systems for objective classification provided by the International Classification of Disease (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM) have provided a structured and reliable but inadequate system. According to the DSM classification system, which will be used in this study, SZ is defined by the presence of at least one first rank symptom of psychosis or two other psychotic symptoms, in association with duration and exclusion criteria. Schizophreniform disorder (SF) is distinguished primarily by its shorter duration, with brief psychotic disorder (BrPsy) having an even shorter duration and more variable symptoms. Delusional disorder (DD) is usually characterised by

monosymptomatic delusions with little or no other significant symptomatology. Bipolar disorder (BD) is diagnosed following an episode of mania, which may or may not include psychotic symptoms that will resolve when mood symptoms settle. In contrast, schizoaffective disorder (SA) may be diagnosed where psychotic symptoms occur both with and without prominent affective symptoms. Major depressive disorder (MDD) is diagnosed following a significant episode of depression, which may or may not also involve contemporaneous psychotic symptoms that will later resolve with resolution of affective symptoms; in this thesis, MDDP refers only to those cases of MDD characterised by psychotic symptoms. Psychosis or mania may also occur secondary to a general medical condition (psychosis/mania due to a general medical condition; PGMC/MGMC) or secondary to substance abuse (substance induced psychosis/mania; SIP/SIM). The diagnosis of psychosis not otherwise specified (PNOS) is reserved for psychotic symptoms that fail to meet the criteria for any other psychotic disorder. However, a number of facts point to the inadequacy of this classification system: diagnostic shifts in an individual patient over time are common; different disorders cluster within families; and symptoms considered to be most typical of one disorder are commonly found in other diagnoses. Our understanding of psychotic disorders and of their sub-classification is incomplete and a fuller understanding is likely to be gained by combining an epidemiological, clinical and neurobiological approach.

Neurobiology of schizophrenia and the psychotic disorders

Despite the fact that SZ is the seventh costliest illness worldwide (Freedman, 2003), progress in revealing the neurobiological processes underlying SZ has been frustratingly slow during recent decades, compared to that in other neuropsychiatric disorders such as Parkinson's disease and Alzheimer's disease. The development of understanding of the causes of these latter disorders has been accelerated by the discovery of pathological lesions, as well as their possessing less phenotypic heterogeneity (Ross & Margolis, 2005). In contrast, SZ is operationalised in terms of symptom clusters in the absence of any pathognomonic substrate, as one of a group of phenotypically overlapping psychotic disorders, including BD. However, recently there has been more rapid advancement in our understanding of SZ as a disorder of brain development, due to advances in the fields of neuroimaging, genetics,

phenotypic analysis and molecular pathology. Understanding of psychotic spectrum disorders in terms of symptom and cognitive dimensions has also contributed to this process (Ross et al., 2006).

Neuropsychological abnormalities

Neurocognitive abnormalities are of interest in psychosis for several reasons: firstly, because they are increasingly seen as a core clinical feature contributing to the functional impairment seen in the illness (Bowie & Harvey, 2005); secondly because they may, in addition, prove to be useful endophenotypic markers for SZ and other disorders in the psychotic spectrum (Snitz et al., 2006); and thirdly, because they may help in the process of identifying regions or systems in the brain that are subject to dysfunction in these disorders. Cognitive deficits occur in the areas of attention, working and episodic memory, executive function, learning, verbal fluency and motor speed. Poor working memory in SZ, for example, has been found to be related to dorsolateral prefrontal cortex dysfunction (Goldman-Rakic, 1999). One study showed that, typically, there are circumscribed abnormalities of executive function, attention and memory but that a subgroup of patients demonstrates a more global pattern of cognitive dysfunction (Weickert et al., 2000). The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) is a National Institute of Mental Health (NIMH) initiative which is developing a standardised range of assessments of cognitive function in SZ in the domains of speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving and social cognition (Nuechterlein et al., 2004).

Whilst patients with BD demonstrate less neurocognitive dysfunction than individuals with SZ (Krabbendam et al., 2005), the affective psychoses also exhibit a degree of impairment.

Neuroimaging studies

The use of new imaging techniques such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), and of improved automated image analysis techniques,

have all been important contributors to the advancement of our understanding of psychotic disorders. The structural abnormalities that have been most consistently replicated by research in SZ are: enlargement of the lateral and third ventricles; reduction in the volume of medial temporal lobe structures (hippocampal formation, subiculum, parahippocampal gyrus) and of the superior temporal gyrus. The prefrontal cortex and orbitofrontal region of the frontal lobe have also been found in some studies to have reduced volumes. The parietal lobe has been the subject of less study; however, there is also evidence of structural abnormalities in this region. Other areas where abnormality has been reported include cavum septi pellucidi, basal ganglia, thalamus, cerebellum and corpus callosum. MRI imaging of individuals with an at risk mental state (ARMS) has shown that some of these abnormalities are evident prior to the onset of frank psychosis (Lymer et al., 2006). When these abnormalities emerge is not entirely clear but it is probable that some emerge during a period of early abnormal neurodevelopment, with some later additional progression, possibly associated with environmental stressors (Rapoport et al., 2005; Pantelis et al., 2005). FMRI studies of brain functioning during cognitive tasks indicate that networks, rather than regions, underlie functional abnormality, suggesting that abnormality resides in dysconnectivity between brain regions rather than dysfunction within any single region (Ross et al., 2006).

MR research on patients with BD show that abnormalities in prefrontal cortical areas, striatum and amygdala are present early in the course of illness and may even antedate illness onset. Later in the course of illness abnormalities in the cerebellar vermis, lateral ventricles and other prefrontal regions may be evident.

Neuropathology

Abnormal neuropathological findings have been noted in SZ, despite no evidence having been found for a gross neurodegenerative process. These include a reduction in cortical neuropil volume, in the absence of comparable neuronal loss, cytoarchitectural abnormalities and abnormalities of neuronal processes and abnormalities of synaptic connectivity, including many of the areas implicated in neuroimaging studies (Harrison, 2005).

Pathophysiology

The dopamine hypothesis of SZ was one of the earliest and still enduring formulations of pathophysiology. It was founded on the knowledge of the mechanism of action of medications found to reduce psychotic symptoms, namely dopamine (DA) 2 receptor blockade, in addition to the finding that drugs which increased levels of DA could induce or exacerbate psychosis. Recent neuroimaging studies have indicated increased subcortical release of DA in living patients (Guillin et al., 2007). A recent finding of relevance to this hypothesis is that DA plays a role in cognitive function mediated via the prefrontal cortex (Ross et al., 2006). A role for glutamate has also been inferred from knowledge about the pharmacology of drugs such as ketamine and phencyclidine (PCP) and their potential to cause or exacerbate psychotic symptoms (Coyle, 2006). Reduced gamma-aminobutyric acid (GABA) neurotransmission in SZ appears to be indicated by neuropathological findings relating to chandelier neurons, a type of GABA interneuron (Lewis et al., 2005).

Neurotransmitters implicated in pharmacological studies in BD include noradrenaline and serotonin, with evidence for this coming from the efficacy of antidepressant drugs, brain imaging studies and genetic association studies. However, not all studies have supported the roles of serotonin and noradrenaline in BD. The DA system has also been implicated on the basis of drug efficacy, post-mortem analysis of gene expression, neuroimaging and genetic association studies. The GABA and glutamate systems may also play a role, again based on evidence from pharmacological, neuroimaging and gene expression and association studies (Shi et al., 2008).

Genetic factors in schizophrenia

Linkage analysis and association studies are the main methodologies used in efforts to identify genes associated with risk for diseases such as SZ. It appears that multiple genes of small effect may interact to confer risk for SZ (Allen et al., 2008).

Disrupted-in-schizophrenia-1 (DISC-1)

Some of the strongest evidence in the search for a genetic aetiology to SZ relates to the DISC-1 gene. A balanced translocation between chromosomes 1 and 11 in a large Scottish pedigree study of SZ resulted in association of the DISC-1 gene with the disorder (Porteous & Millar, 2006). The DISC-1 locus has also been found to be a risk factor in a number of studies of different populations, including both SZ and affective disorders (Porteous et al., 2006). Cognitive endophenotypes of SZ have also been found to be associated with DISC-1 polymorphisms. Postulated functions of the gene include cytoskeletal and nervous system functions related to development, including synaptic plasticity and neuronal migration (Chubb et al., 2008)).

Dysbindin

The finding of chromosome 6p linkage in SZ resulted in the identification of dysbindin (dystrobrevin binding protein 1) as a gene conferring risk for SZ (Straub et al., 2002). It co-localises with dystrobrevin in brain tissue and is found pre- and post-synaptically, as well as elsewhere in the body (Williams et al., 2005). While its functional significance in SZ is not yet understood, there is some evidence that it plays a role in regulating glutaminergic function in prefrontal cortex (Jentsch et al., 2009). Reduced expression is found in brain tissue in SZ (Bray et al., 2005) and there appears to be an association between dysbindin risk haplotypes and increased rates of negative symptoms in SZ (Fanous et al., 2005; De Rosse et al., 2006).

Neuregulin 1

Chromosome 8p was alsofound to be linked to SZ. Finemapping of a locus on this chromosome resulted in the identification of neuregulin 1 (NRG1) as associated with risk for SZ (Stefansson et al., 2002; Harrison, 2005). Due to existence of multiple potentially relevant alleles and haplotypes, it has been difficult to establish the role of this gene in SZ. However, recent post-mortem studies implicate regulation of the NMDA receptor, consistent

with the hypothesised involvement of glutamate (Hahn et al., 2006). More recently, research in mice indicates that it plays a role in growth of neuronal dendritic spine growth, with emergence over time of behavioural abnormalities analogous to those found in SZ. Interestingly, these spine abnormalities are reversed by treatment with clozapine (Barros et al., 2008).

Chromosome 22 and catechol-O-methyl-transferase

Chromosome 22 has been shown in many linkage studies to be associated with SZ (Harrison, 2005) and patients with SZ have an increased frequency of a deletion in chromosome 22q11 (Karayiorgou et al., 1995). Its relevance is strengthened by research on the same deletion in velo-cardio-facial Syndrome (VCFS), a developmental disorder in which up to 30% of cases exhibit psychotic symptoms (Murphy et al., 1999). As yet, which gene in this area might be associated with risk for SZ remains unclear. However, the catechol-O-methyl-transferase (COMT) gene has been the subject of considerable research. Considering the DA hypothesis of SZ, the fact that the product of this gene is an enzyme which inactivates DA in the synapse (Tunbridge et al., 2006) makes it a plausible candidate. However, evidence indicates that polymorphisms associated with distinct effects on synaptic DA may mediate the putative relationship with SZ via effects on cognitive function (Egan et al., 2003). Other genes present in this region which have been implicated include the proline dehydrogenase (PRODH) gene, a variant of which impacts on synaptic availability of glutamate (Owen et al., 2005).

Copy number variation

An area that has been the focus of much recent study is that of the rare copy number variation (CNV) in SZ. A series of copy number variants such as 1q21, 15q11.2, 15q13.3, 16p11.2, 22q12 and Neurexin 1 loci have been found to be associated with SZ. These mutations, though rare, have high penetration and confer risk for other disorders such as autism and intellectual disability, in addition to SZ. Reduced fertility rate in SZ keeps their frequency low and, to date, it appears that each of these mutations may be responsible for only small

numbers of cases. It appears likely that many such rare mutations will be discovered in the years to come (St Clair, 2009).

Genetic factors in bipolar disorder

There is considerable overlap between genes conferring risk for SZ and BD, including DISC1, NRG1 and DTNBP1 (Seretti & Mandelli, 2008). Additional genes of particular interest in BD include DAOA(G72), BDNF, SLC6AF and TPH2 (Barnett & Smoller, 2009). Additionally, risk for BD may be conferred by CNVs associated with risk for SZ (Alaerts & Del-Favero, 2009).

Epidemiological and biological risk factors in schizophrenia

In addition to the above genetic risk factors, there is a wealth of research pointing to neurodevelopmental factors in the pathobiology of SZ. The neurodevelopmental hypothesis postulates that SZ is the result of disrupted brain development (Weinberger, 1987; Lewis & Murray, 1987). This has been elaborated as genetic factors have been uncovered, resulting in a 'developmental risk factor' model which hypothesises a series of early and late risk factors which interact to increase deviance from normal brain development (Welham et al., 2009). 'Social' risk factors such as childhood adversity and social isolation have been the subject of increasing research (Oliver, 2008).

Minor physical anomalies

Minor physical anomalies (MPAs) are indicators of abnormal foetal development and include morphological variations of the head, face, mouth, fingers, hands and toes, as well as dermatoglyphics, i.e. finger and palm prints. They may be caused by genetic factors or by developmental disruption due to environmental causes. That some MPAs are associated with a particular stage of development provides clues to the timing of the disruption. Facial dysmorphology is closely linked embryologically to brain development, giving biological plausibility to the hypothesis that this is a marker of disrupted brain development

(Waddington et al., 1999). Most, but not all, studies have found an excess of MPAs in SZ (Weinberg et al., 2007). Similarly, dermatoglyphics have been found to show qualitative and quantitative differences in SZ compared to normal populations (Bramon et al., 2005).

Season of birth

It has been repeatedly shown that there is a small excess of late winter and spring births in SZ in the northern hemisphere (Davies et al., 2003). A meta-analysis in the southern hemisphere, however, showed no overall effect (McGrath, 1999). A meta-analysis of data from the northern hemisphere showed a greater season of birth effect in deficit than in non-deficit SZ (Messias et al., 2004). Perinatal viral exposures and nutritional deficiencies are some of the hypothesised mediators of this effect (Torrey et al., 1988).

Place at birth

Urban birth has been associated with risk for SZ in a number of large studies (Kelly et al, 2009). However, it has not been possible to separate urban birth from growing up in an urban setting as the risk factor (see below).

Pregnancy and birth complications

There is a large body of research which indicates an increase in risk for SZ among offspring delivered following a history of pregnancy and/or birth complications (Cannon et al., 2002). Individual complications found to be associated with SZ include low birth weight, prematurity, pre-eclampsia, prolonged labour, ante-partum haemorrhage, rhesus incompatibility, multiparity, foetal distress, infection, hypoxia, inflammation and nutritional deficiency. However, the complexity of foetal development creates difficulties in the attempt to identify an individual cause.

Prenatal infection

Contradictory evidence exists regarding a putative association between SZ and prenatal infection. Positive findings with regard to influenza, toxoplasmosis and rubella all exist (Brown, 2006). An association between elevated maternal cytokines in offspring who later develop SZ has been found in some studies (Buka et al., 2001). An interest in prenatal infection persists due, in part, to the potential for primary prevention.

Prenatal nutrition

Evidence for maternal nutrition being a risk factor for SZ is largely indirect. There is an increased rate of SZ in the offspring of women exposed to famine (Susser et al., 1996; St Clair et al, 2005). Low maternal pregnancy body mass index has also been found to be associated with SZ (Wahlbeck et al., 2001). It has been hypothesised that pre-natal vitamin D deficiency might be a candidate risk factor for SZ; this may be related to findings in SZ of an excess of late winter-spring births and of increased rates in urban environments (McGrath, 1999).

Early environment

Evidence regarding the environment in which a child is reared point to an interaction between genetic risk and environmental adversity (Mirsky et al., 1995; Wahlberg et al., 1997). In a more recent Swedish study, socioeconomic adversity measures in childhood were shown to interact with genotype to increase risk for SZ (Wicks et al., 2005).

Urban living, migrant status and social capital

For some time it has been clear that there is an association between urban birth/upbringing and SZ (Harrison et al., 2003 ; Kelly et al, 2009) and that there is a dose response relationship between amount of time spent in an urban environment over childhood/adolescence and risk for SZ (Pedersen & Mortensen, 2001). Factors hypothesised

to mediate this relationship are diverse and include stress, adversity, traffic pollution, low income and poor education. There is also strong evidence for an association between migrant status and SZ (Cantor-Grae & Selten, 2005). There is interest in the idea that social stress might link these two risk indicators. It appears that individuals living in areas with lower social capital (Kirkbride et al., 2008) may be at greater risk for SZ. This mirrors findings in Chicago 80 years ago (Faris & Dunham, 1939) that rates of SZ were highest in the most disorganised neighbourhoods, more so than in working class areas with greater social cohesion.

Cannabis misuse

Over past decades there has been much research into cannabis consumption as a risk factor for SZ. This issue has been confounded by the possibility that individuals with prodromal SZ may be more likely to self-medicate with cannabis, giving rise to a non-causal association. However, a recent large meta-analysis showed that those who had ever used cannabis were at increased risk of developing SZ, with a dose-response relationship (Moore et al., 2007)

Epidemiological and biological risk factors in bipolar disorder

There is considerable overlap in epidemiological and biological risk factors for BD and SZ. Birth seasonality, abnormal dermatoglyphics, prenatal infection and increased perinatal complications have all been found to convey risk for BD, as well as for SZ (Höschl & Stopková, 2009). However, urban birth has not yet been confirmed as a risk factor for BD (Soares & Young, 2000). Lower socioeconomic status may confer increased risk for BD. However, rates of BD are increased in higher income countries, with some cultural subgroups showing increased risk for BD, such as Native Americans, Maori and Pacific Island inhabitants (Merikangas & Pato, 2009).

Epidemiology

Introduction

The epidemiology of disease is the basis from which much of our understanding flows. This is particularly the case when dealing with a disease, or a group of diseases as may be the case here, whose diagnostic boundaries are only partially understood. If distinct epidemiological patterns are reliably reproduced between different studies across the various diagnoses included under the general concept of psychotic illness, we may infer some degree of validity for the individual diagnoses; we can then be more confident that we have a good working concept of the disorder at issue. However, if this is not the case, a revision of the prevailing conceptual framework may be necessary.

The Cavan/Monaghan First Episode Psychosis Study, which provides the basis for this thesis, is an epidemiological study and it is therefore important to understand the current scientific context in which it resides. Studies looking at incidence and prevalence rates for different disorders will be considered in this section. These vary in their methodologies. Incidence designs include both first episode psychosis (FEP) studies, where an effort is made to detect all new cases of psychosis within a given time period and specified geographical area, and cohort studies, such as birth cohort studies or studies which follow-up military conscript cohorts assessed at a particular age. Prevalence studies are based on identifying cases within an established clinical population or, more rigorously, by door-to-door population surveys of either entire populations or representative samples of the population.

The other crucial issue in epidemiological study design is the selection of appropriate diagnostic instruments to ensure that cases found are 'true' cases (specificity) and that as few cases as possible are not diagnosed (sensitivity). A number of different instruments have been in common use over past decades. Results from studies that have focused on the extent to which the use of different instruments changes rates of diagnosis have been extremely varied: on the one hand, Jablensky et al. (1993) indicate that there is a high correlation

between Kraeplin's diagnostic system, as used by him in 1904, and the CATEGO classification (88.6%); on the other hand, Brockington et al. (1978) found that there was an 11-fold difference in the rates of SZ detected when ten different instruments were used in relation to the same clinical cases.

In view of the differences highlighted above in terms of methodology, it is not surprising that differences in rates for the various diagnoses are found between studies. It is therefore of great importance to take these factors into account when seeking putative reasons for differences in rates.

The epidemiology of schizophrenia

Schizophrenia - incidence

Calculations of the incidence of SZ have varied from 0.04 – 0.58/1000 (Eaton, 1999) an almost 15-fold difference. However, when meta-analysis considers only the central 80% of studies, a five-fold difference (0.08 – 0.43) is seen (McGrath, 2005). Whilst the factors described above are likely involved in the generation of such differences, observed geographical and temporal variations in rate are not likely to be entirely methodological artefacts and give plenty of opportunity to speculate on aetiological factors. Table 1 indicates representative studies completed over recent decades in different parts of the world.

Schizophrenia – prevalence

Prevalence estimates for SZ are markedly higher than for incidence, as is usual for a chronic disease often starting early in life. Values quoted for prevalence, like those for incidence, vary considerably from 1.2 to 7.1/1000 (point prevalence). The majority of studies cluster within a narrower range of 1.4 – 4.6/1000 (Jablensky et al., 2000). This range of results may be attributable in part to methodological factors similar to those described above in relation to incidence, but also to differences in rates resulting from real population differences. Table 2, adapted from Jablensky et al. (2000), indicates representative studies.

Table 1: Incidence studies of schizophrenia

Study	Country	Methodology	Annual rate per 1000
Ødegaard 1946	Norway	National FEP	0.24
Helgason 1964	Iceland	National first admission	0.27
Häfner & Reimann 1970	Germany	Local case register	0.54
Raman & Murphy 1972	Mauritius	National first admission	0.9 (Indian Muslims) 0.14 (Indian Hindus) 0.24 (Africans)
Lieberman 1974	Russia	Retrospective prevalence	0.20
Lin et al., 1989	Taiwan	Household survey	0.17
Bamrah et al., 1991	UK (urban)	Case register/GP survey	0.19
Castle et al 1991	UK (urban)	Case register	0.08 (DSM-III) 0.25 (ICD)
Iancono & Beiser 1992	Canada (urban)	FEP local	0.08
Jablensky et al., 1992	Russia (urban) Denmark (urban) Ireland (urban) Honolulu (island) India (urban) India (rural) Japan (urban) UK (urban)	International first contact	0.02[a] 0.07[a] 0.09[a] 0.09[a] 0.09[a] 0.11[a] 0.10[a] 0.14 [a]
Nicole et al.,1992	Canada (urban)	Local first admission	0.09 (DSM III) 0.32 (ICD)
D'Arcy et al., 1993	Canada (Saskatchewan)	FEP local	0.10

Rajkumar et al., 1993	India	Door to door survey	0.41
Hickling & Rodgers-Johnson 1995	Jamaica	National FEP	0.21 (restrictive) 0.24 (broad)
Vazquez-Barquero et al., 1995	Spain	FEP local	0.19
Bhugraet al., 1996	Trinidad	FEP local	0.16
Bhugra et al., 1997	UK (urban)	FEP local	0.39
Goater et al., 1999	UK (urban)	FEP local	0.22
Mahy et al., 1999	Barbados	FEP national	0.28
Hanoeman et al., 2002	Surinam	National first admission	0.16
Proctor et al., 2004	UK (semirural)	FEP local	0.03
Hickling 2005	Jamaica Trinidad Barbados	FEP	0.21 0.22 0.29
Hamada et al., 2006	Japan (Tsushima island)	FEP	0.23
Fearon et al., 2006	UK	FEP	0.71 (Afro-Caribbean) 0.40 (Black African) 0.11 (Asian) 0.07 (White British)
Herrell et al., 2006	US military data	FEP	0.16
Menezes et al., 2007	Brazil (urban)	FEP	0.06

[a] restrictive criteria (CATEGO S+)

FEP First episode psychosis

GP General practitioner

Table 2: Prevalence studies of schizophrenia

Study	Country	Methodology	Rate per 1000
Brugger 1931	Germany	Census	2.4
Strömgren 1938	Denmark (rural)	Census	3.9
Lemkau et al., 1943	USA	Census	2.9
Essen-Möller et al., 1956	Sweden	Census	6.7
Rin & Lin, 1962	Taiwan	Census	2.1
Hagnell 1966	Sweden	Census	4.5
Bash & Bash-Liechti 1969	Iran (rural)	Census	2.1
Crocetti et al., 1971	Croatia	Household sample	5.9
Dube & Kumar 1972	India	Census	2.6
Rotstein 1977	Russia	Census	3.8
Padmavathi et al., 1987	India (urban)	Census	2.5
Indian Council of Medical Research 1988	India (urban)	Census	2.2
Lin et al 1989	Taiwan	Census (repeat of Rin & Lin, 1962)	1.4
Bøjholm & Strömgren 1989	Denmark (island)	Census (repeat of Strömgren 1938)	3.3
Robins & Regier 1991	USA	Sample survey	7.0
Lee et al., 1990	Korea (urban/rural)	Census	3.0/4.0

Char-Nie et al.,1993	Hong Kong	Community survey	1.2 (male), 1.3 (female)
Kendler & Walsh 1995	Ireland (rural)	Register-based family study	5.4 (male), 4.3 (female)
Jeffreys et al., 1997	UK (urban)	Census	5.1
Waldo 1999	Micronesia	Key informants, clinic records	6.8
Kebede et al.,1999	Ethiopia	Door-to-door	7.1
Jablensky et al., 2000	Australia (4 geographical areas)	Census	3.1-5.9
Ran et al., 2003	China (rural)	Door-to-door	4.1
Scully et al., 2004	Ireland (rural)	Clinical records	3.9
Barrett et al., 2005	Malaysia (rural)	Clinical records	5.0 (ICD-10) – 10.0 (RDC)
Wu et al., 2006	US	Register	6.3 (male), 2.3 (female)
Hamada et al., 2006	Japan (Tsushima island)	Clinical records	5.8
Perala et al., 2007	Finland	Population survey	8.7
Chang 2008	South Korea	Register	4.0

ICD-10 International Classification of Disease 10

RDC Research Diagnostic Criteria

Geographical differences in incidence/prevalence of schizophrenia

Given that the location of the present study is geographically and demographically distinct, it is important to note such factors when considering geographical variation in rate of SZ. As can be readily seen from the above tables, there are considerable differences between rates of illness calculated at different sites. However, it is difficult to draw conclusions from this. Much of the similarity or difference may be attributed to the fact that researchers use similar

or different methodologies. Differences such as sample size, sampling process, age of the population, rate of substance misuse, diagnostic biases at different sites and diagnostic tools used, among others, will all impact on rate. From this perspective, one of the most useful studies is the WHO Ten Country Study as reported by Sartorius et al (1986) and Jablensky et al (1992). Because methodology used in this incidence study was standardised over the different sites, differences vs. similarities in rate may be interpreted with more confidence. Bresnahan (2003) suggests that any conclusion drawn by researchers that narrowly defined SZ, believed to be related to the CATEGO S+ diagnosis, shows little variation across sites is mistaken. This is because the S+ diagnosis demonstrates a low correlation with ICD-10 or DSM-IV diagnoses of SZ (Mason et al., 1997). Therefore, it is more helpful to consider variation in ICD-9 rates across sites, which range from 0.13 – 0.43/1000. Follow-up study at sites in the UK (Nottingham) and India (Chandigarh) confirms that ICD-10 diagnosis correlates best with broadly defined rates of SZ (ICD-9) calculated in the original study (Brewin, 1997; Bresnahan, 2003). A comparison of 94 incidence studies (Saha et al., 2006a) indicated incidence of SZ to be increased in males at higher latitude but not over the population as a whole.

Differences between rates of schizophrenia in developed vs. developing countries

The possibility that there might be a difference between developed and developing countries in terms of incidence and prevalence of SZ has been the subject of much speculation. It is probably more relevant to consider incidence rather than prevalence rates, as prevalence figures will also reflect course and outcome that appear across most studies to be better in developing countries. The overall range for the incidence of broadly defined SZ (e.g. ICD-9 criteria), as may be observed in Table 1, is 0.03 – 0.54/1000. The range of values found in studies carried out in developing countries is 0.09 – 0.41/1000 vs. 0.03 – 0.54/1000 in developed countries. Given the variation in methodology between the studies included, it is difficult to draw any conclusions about difference in incidence based on these ranges. An analysis of 52 studies of incidence of SZ in least developed, emerging, and developed countries found that although rates in developed countries were highest, apparent differences did not reach statistical significance (Saha et al., 2006b). Whilst there are clearly outlier

populations with very high rates (e.g. population isolates in Finland; Hovatta, 1999) and very low rates (Hutterites of South Dakota; Nimgaonkar, 2000), there does not appear to be a clear distinction in incidence rate according to a country's level of development.

Difference in rates of schizophrenia between urban and rural populations

The finding of higher rates for SZ among urban relative to rural populations has been repeatedly replicated (Kelly et al, 2009). The Swedish conscript study (Lewis et al., 1992) showed that even after controlling for cannabis use and psychiatric disorder at inception, urban upbringing remained a risk factor for SZ. A birth cohort study carried out in Holland (Marcelis, 1998) showed a similar pattern and also indicated that the effect of urbanicity to increase likelihood of SZ was stronger in males than in females. A Danish study (Mortensen et al., 1999) also controlled for family history and showed that the association endured; additionally, urban upbringing was a stronger risk factor for SZ (population attributable risk 34%) than having a mother with SZ (9%). Sundquist et al (2004) found that increasing incidence of SZ with urbanicity in Sweden showed a dose-response relationship. Kirkbride et al (2006) found a similar pattern of increased incidence in larger, more densely populated urban areas (South-East London) than in smaller urban areas (Nottingham, Bristol). A Danish study looking at time trends in incidence of SZ from 1910 to 1986 showed that increased rate of SZ in urban compared to rural settings has existed since the first such studies and that the magnitude of this effect has not increased over time (Pedersen & Mortensen, 2006).

The epidemiology of schizophrenia in Ireland

It is worth considering the studies that have been carried out in Ireland in more detail, in order to evaluate the results of the present study. The Irish arm of the World Health Organization (WHO) ten-country incidence study (Jablensky et al., 1992) was carried out in Dublin. The methodology of this study was to ascertain and assess all first contact cases of SZ in the area. Different rates were calculated, depending on the restrictiveness of the criteria used to diagnose SZ. Three different diagnostic practices were used. The

computerised reference classification CATEGO S+ was the more restrictive, focusing on the presence of first-rank positive symptoms for a one month period prior to assessment; ICD-9 was the broadest classification system used, where groups of first and second rank symptoms were combined to reach a diagnosis. The various values calculated were 0.09/1000 (CATEGO S+), and 0.21/1000 (ICD-9). As can be seen from the 2.3 fold difference, considering diagnostic practice is key when comparing rates calculated in different studies. A prevalence study was carried out in Roscommon (Kendler, 1995). Here, a point-prevalence figure of 5.4/1000 population was seen in males and 4.3/1000 in females. The initial 8-year results from the Cavan/Monaghan First Episode Psychosis Study reported an incidence rate for SZ of 0.07/1000 using DSM-IV criteria. The broader definition of SZ-spectrum disorder including SA and SF yielded a figure of 0.1/1000 (Baldwin, 2005).

The epidemiology of bipolar disorder

Bipolar disorder – incidence

Estimates of incidence of BD are subject to the same methodological sources of variation as for SZ, namely sampling strategies and diagnostic procedure. Particularly relevant for BD is the issue of whether or not to include bipolar disorder II (BD II) in estimates and the studies listed below have taken different approaches in this regard. A second issue is that of whether to confine studies to BD 'with psychotic features' or to include all BD, as in the present study. Estimates vary from 0.017/1000 in Bristol (Lloyd et al., 2005) to 0.200/1000 in the US military (Herrell et al., 2006). However, if the two outlying studies are removed, the range narrows to 0.026/1000 in England and Denmark (Leff et al., 1976) to 0.123/1000 in Finland (Räsänen et al., 1998). This is a five-fold difference, similar to that found in the incidence of SZ. The studies are represented in Table 3 below.

Bipolar disorder – prevalence

Estimates of lifetime prevalence of BD range from 0.26% in Cavan/Monaghan (Scully et al., 2004) to 5.1% in Hungary (Szadoczky et al., 1998), giving a 20-fold difference in rates of

BD. However, when studies including BD II are excluded, this range narrows to 0.26% to 1.8% (Fekadu et al., 2004), a 7-fold difference. Estimates are summarised in Table 4 below.

Table 3: Incidence of bipolar disorder

Study	**Country**	**Methodology**	**Annual rate per 1000**
Leff et al., 1976	Aarhus, Denmark London, England	First admission mania	0.026
Hunt et al., 1993	Various sites in urban UK	Casenote search	0.061 – 0.087
Daly & Walsh, 1995	Dublin, Ireland	Treatment-based study	0.045
Räsänen et al., 1998	Finland	Hospital register study	0.123
Baldwin et al., 2005	FEP	FEP study	0.052
Lloyd et al., 2005	London, UK Nottingham, UK Bristol, UK	FEP study	0.062 0.030 0.017
Herrell et al., 2006	US military	FEP study	0.200

FEP First episode psychosis study

Table 4: Prevalence studies of bipolar disorder

Study	**Country**	**Methodology**	**Rate per 1000**
Fogarty et al., 1994	Canada	Household survey	6
Weissman et al., 1996	10 countries	Population-based study	3 – 15*
Kessler et al., 1997	USA	Probability sample	4 13
Szadoczky et al., 1998	Hungary	National survey	51
Angst 1998	Switzerland	Prospective cohort study	55
ten Have et al., 2002	Holland	Population sample	24 10
Judd & Akiskal 2003	USA	Household survey	8 (BD I) 5 (BD II alone)
Fekadu et al., 2004	Ethiopia	Survey	18 (narrow)
Scully et al., 2004	Ireland	Casenote survey	2.6 3.5*
Negash et al., 2005	Ethiopia	Door-to-door survey	5 (I)
Goldney et al., 2005	Australia	Random population sample	2.5*
Perala et al., 2007	Finland	Population survey	2.4%
Merikangas et al., 2007	US	Population survey	10%

*Figure includes BD I and II

Differences in incidence of bipolar disorder across study sites

There are no marked differences between developed and developing countries in terms of rates of BD, which mirrors the findings in SZ. However, urbanicity does seem to have an impact. The studies that are easiest to compare in this regard are those carried out in the UK and Ireland. The early study of Leff et al (1976) shows a relatively low rate for London (0.026/1000); however, the study of Lloyd et al (2005) showed a much higher rate for London (0.062/1000) than for the smaller cities of Nottingham (0.030/1000) and Bristol (0.017/1000). The two studies carried out in Ireland indicate for the urban site of Dublin a rate of 0.045/1000 (Daly & Walsh, 1995) vs. 0.052/1000 in rural Cavan/Monaghan (Baldwin et al., 2005).

Incidence and prevalence of major depressive disorder with psychotic features

The majority of studies of both incidence and prevalence of MDD include the full spectrum of the disorder from mild episodes of depression to severe episodes with psychotic features. For the purposes of this section, only studies concerning major depressive disorder with psychotic features (MDDP) are included. There are relatively few, most of which have been carried out in the context of FEP studies. The Suffolk County FEP study, carried out on Long Island, New York, showed that MDDP was the third most common psychotic presentation after SZ and BD, with 11% of participants receiving this diagnosis (Bromet et al., 1992). Another FEP study carried out in Northumberland revealed an incidence rate of 0.056/1000 (Proctor et al., 2004). The Cavan/Monaghan FEP has reported a rate of 0.064/1000 at 8 years (Baldwin et al., 2005). An FEP study carried out in the North of England calculated MDDP to make up 19% of FEP, compared to 13% for SZ (Crebbin et al., 2008).

A study comparing prevalence rates for MDDP in New South Wales, Australia, with rates in England and Wales found it to be lower in Australia, with a rate of 2.8% of all cases of FEP; this compared with a rate of 6.5% in England and Wales (Parker, 1975). A telephone survey of approximately 19000 individuals was carried out in five countries (UK, Germany, Italy, Portugal, Spain) and revealed point prevalence rate of 0.4% (4/1000) (Ohayon & Schatzberg,

2002). Probably the most complete study to date is a Finnish general population survey combined with a national mental illness register examination of over 8000 people, which found a lifetime prevalence for MDDP of 0.35% (Perala et al., 2007)

Incidence and prevalence of schizoaffective disorder

The incidence of schizoaffective disorder has been the subject of less attention. Bromet et al (1992) found that of all cases of FEP in the Suffolk County study, 4.8% had SA. A study in the US found an incidence of 'schizomania' of 0.017/1000 and 'schizodepression' of 0.040/1000 (Tsuang, 1995). Baldwin et al (2005) established an incidence rate of 0.02/1000 in the Cavan/Monaghan FEP study. Prevalence studies of SA are limited to those estimating the prevalence of the disorder in treated samples. Marneros et al (1990) found that in the Cologne Longitudinal Study, 28.5% of those with psychosis met DSM-III-R criteria for SA.

Incidence and prevalence of schizophreniform disorder

In the Suffolk County FEP study, Bromet et al (1992) found SF to comprise 3.2% of all FEP. Baldwin et al (2005) calculated an incidence rate for SF of 0.018/1000 in the Cavan/Monaghan FEP study. Prevalence studies are probably less common due to the assumption that the majority of cases of SF will evolve into more disabling psychoses such as SZ.

Incidence and prevalence of brief psychotic disorder

Baldwin et al (2005) found that 5.2% of cases of FEP in Cavan/Monaghan were BrPsy. Again, one might suppose that prevalence studies of BrPsy are not undertaken frequently due to assumptions regarding prospective diagnostic instability.

Incidence and prevalence of delusional disorder

The only data on incidence of DD are again from the Suffolk County and Cavan/Monaghan FEP studies, the former estimating that it constitutes 4.0% of cases of psychosis (Bromet et al, 1992) and the latter estimating this at 4.6% (Baldwin et al, 2005). No prevalence data on this disorder could be found.

Conclusions

Although substantive data exist in relation to the incidence and prevalence of SZ, there is much less for other disorders. BD is relatively well covered, but MDDP, SA, SF, BrPsy and DD are poorly covered in the literature; for other diagnoses, such as SIP, PGMC and PNOS, there is little in the way of systematic, comparative data. To a large extent, information on these less well investigated diagnoses relies on diagnostically inclusive FEP studies, such as the Cavan/Monaghan FEP study. Excluding methodological differences is perhaps easier for SZ than for BD and MDDP, as there may be less consistency in diagnostic protocols for BD, MDDP and other conditions. However, differences in methodology between studies, relating particularly to case identification remain an enduring problem in the research carried out on the incidence of psychosis. There is no consistent evidence for any geographical difference in rates for psychotic diagnoses, with the exception of a probable urban excess in SZ. Additional research looking at incidence of the full spectrum of psychotic diagnoses will be of considerable benefit in terms of adding to our understanding of these conditions and service planning. Future work should also evaluate geographical differences in important variables which may impact on outcome, such as duration of untreated illness (DUI) and DUP.

Diagnostic Stability

Introduction

The impact of Kraepelin was to propose patterns in territory characterised by heterogeneity. The scientific method was implemented more slowly in psychiatry as a result of this heterogeneity, which is compounded by interaction with many other individual differences that impact on the clinical manifestations of psychiatric disorders. The concepts of dementia praecox and manic depressive psychosis began to impose order on the chaos of psychopathology as displayed in the asylums of his time. These concepts have remained substantially unaltered over 100 years and are only recently being re-evaluated.

Despite considerable advances in the field of psychiatry over the past century, diagnoses are still made on the basis of the clinical assessment of psychopathology. Symptoms and signs have been factor analysed to an extent that has yielded relatively reproducible diagnoses but their validity is unclear. A categorical system of classification has persisted but increasingly the opinion has been voiced that a dimensional model may be more accurate (Helzer et al., 2008). As the field of psychiatric genetics has evolved, the idea that the symptoms of psychosis have some unifying validity has emerged. By close examination of the symptoms and prognostic variables that exist within this group of diagnoses, we may learn more than by considering the individual disorders having such symptoms in common. Much progress has been made in searching for the aetiology of psychotic disorders but the picture is far from complete. What is clear is that, in general, psychotic disorders are multifactorial in origin. This multifactorial model probably involves final common pathways which lead to the clinical manifestation of psychotic symptoms. Whilst psychiatric genetics is making considerable progress in looking for the biological roots of this model, it is necessary to continue epidemiological work that attempts to establish the validity of diagnostic categories. One important contribution to this is the study of diagnostic stability.

Given that psychotic disorders have overlapping and multiple but incompletely understood aetiologies, pathologies and outcomes, examination of diagnostic stability should help clarify

the validity of our current diagnostic classification and hopefully move it forward to a more accurate system.

Diagnostic stability has been the subject of considerable research effort over the past 20 years and in isolated studies prior to that. Whilst the primary assumption in looking at diagnostic (in)stability is that the reason for change is the inadequacy of the system, there are several other reasons why diagnosis might change over time. First, the clinical picture may in reality change over time, with new symptoms or symptom clusters becoming prominent. Second, new information may come to light over time which may cause the diagnosis to be reconsidered. Third, the original data collected on an individual may be considered in a new light. The above reasons were listed in the context of a 6 month diagnostic stability follow-up study of first admissions for psychosis (Fennig et al., 1994a). Another possibility to be considered is that the use of different classification systems may yield different diagnoses. However, it has been suggested that this is not the case and that switching between these systems does not cause any substantive change in diagnosis (Amin et al., 1999a). There have been other studies that have looked at changes in diagnostic practices and biases over time, depending on available treatments, and have shown the influence of such changes on diagnostic stability (Kendell et al., 1993).

Diagnostic stability has been studied using a variety of methodologies over past decades. The most satisfactory method is by prospective FEP studies, which reduce the danger of selection bias. Another type of prospective study that has been commonly used is that based on an index admission for psychosis. The third common type of study, and the least satisfactory, is that based on retrospective examination of casenotes; this is susceptible to several forms of bias.

Psychosis

Before looking at studies which have attempted to clarify the diagnostic stability of different psychotic disorders, it is worth mentioning a number of studies which have taken a broader view of the stability of the diagnosis of psychosis. A case register study was carried out in

Switzerland of 1442 patients across the psychiatric diagnostic spectrum. Over 45 years, the diagnosis of psychosis was the most stable of all (Huguelet et al., 2001). Another register based study undertaken in Denmark (Jorgensen & Mortensen, 1988) showed that of all first admission psychoses, 40% overall had their diagnosis changed over 2-year follow-up. Some prospective studies have also considered the broader stability of a psychotic diagnosis. The EPPIC (Early Psychosis Prevention and Intervention Centre) study in Australia (Schimmelmann et al., 2005) found that when 492 patients were followed up at 18 months, 69.9% of them had the same diagnosis compared to inception. Some small studies, with insufficient numbers to draw meaningful conclusions, quote overall figures for diagnostic stability. One carried out in Washington (McClellan & McCurry, 1999) followed up 51 cases of early onset psychosis over a period of two years. They found overall diagnostic stability to be 50%. Another early onset study in India followed 28 patients over five years and found overall diagnostic stability to be 86% (Srinath et al., 1997). A third, small study of 24 individuals with early onset FEP found an overall diagnostic stability over the 2-year follow-up period of approximately 52% (Fraguas et al., 2008).

Two recent studies have looked for non-diagnostic correlates and predictors of diagnostic stability. A study carried out in California looked at cross-sectional diagnostic stability comparing individuals with a recorded diagnosis of either SZ or MDDP across different treatment settings. There was less diagnostic stability among those with a reference diagnosis of SZ and diagnoses were most unstable in forensic and emergency psychiatric settings compared to inpatient and outpatient settings (Folsom et al., 2006). Another study, taking a different approach, looked for predictors of diagnostic stability in a population with non-organic psychosis and found that the only significant predictor was number of hospitalisations, leading to two potential hypotheses: first, that diagnostic variability reflects a more fluctuant and pathological disease course; second, that rigidity of diagnostic criteria is exposed by increased contact between the patient and their healthcare provider (Jakobsen et al., 2007).

Schizophrenia

Many studies have compared diagnostic stability across various diagnoses. Of these, a large proportion has shown that SZ is the most stable diagnosis, with representative studies indicated in Table 5. Of the retrospective studies, the largest was carried out in Edinburgh (Forrester et al., 2001) and looked the casenotes of 204 patients with a diagnosis of psychosis who had multiple admissions. They found diagnostic stability for SZ ranged from 58% (clinically defined schizophrenia) to 98% (operationally defined SZ), greater than for any other psychotic disorder. Another study looked at the casenotes of patients over the course of one year and again found that SZ was the most stable of the diagnoses (96%; Kuruoglu et al., 2001). A study carried out in Norway (Hoye et al., 2000) looked at 151 patients who had multiple admissions between the years 1980 – 1995 and showed a diagnostic stability of 90%.

Prospective studies have yielded similar results. The studies to be discussed followed up patients for periods ranging from one to 11.5 years, and show diagnostic stabilities ranging from 80 to as high as 97%. The results are summarised in Table 5. The largest of these studies was part of the EPPIC trial, carried out in Australia, and looked at 492 patients over a period of 18 months (Schimmelmann et al., 2005). It yielded a diagnostic stability of 97%. Another FEP study was carried out in New York and compared the diagnostic stability of SZ and SF (Naz et al., 2003). Here, 628 individuals were followed up for two years and indicated diagnostic stability for SZ to be 92%. An FEP five year follow-up study in Hong Kong found SZ to have a prospective diagnostic stability of 100% (Chang et al., 2009). A population-based incidence cohort study carried out in Holland had a follow-up period of 2.5 years for 181 individuals (Veen et al., 2004); this showed a diagnostic stability of 91%. Another FEP study carried out in Dublin (Whitty et al., 2005) had a high diagnostic stability of 97% when 161 patients were followed up over four years. One of the lower figures, 80%, was produced by a FEP study in the UK when 168 individuals were followed up at three years (Amin et al., 1999a). A study with a particularly long follow-up period of 11.5 years examined an early onset psychosis cohort (Hollis, 2000). This study yielded a diagnostic stability for SZ of 80%, another of the lower figures.

Table 5: Diagnostic stability in schizophrenia

Type of study	Location	N	Follow-up period	Diagnostic stability	Reference
FEP study	UK	168	3y	80%	Amin et al., 1999a
Casenote based	Norway	151	Up to 15 y	90%	Hoye et al., 2000
Early onset FEP study	UK	110	11.5y	80%	Hollis, 2000
Casenote based	Scotland	204	8y	58% (clinically defined SZ) 98% (operationally defined SZ)	Forrester et al., 2001
FEP study	USA	628	2y	92%	Naz et al., 2003
Population-based incidence study	Holland	181	2.5y	91%	Veen et al., 2004
FEP study	Ireland	161	4y	97%	Whitty et al, 2005
FEP study	Australia	492	1.5y	97%	Schimmelmann et al., 2005
FEP study	Hong Kong	166	5y	100%	Chang et al., 2009

SZ Schizophrenia

FEP First episode psychosis

We learn more about the deficits of the current classification system when we consider cases of diagnostic instability, where there is less diagnostic clarity and where diagnosis over time is more fluid. An interesting point is that changes towards a diagnosis of SZ appear more common over time than a change away from that diagnosis. One study that points to this is the population-based incidence study carried out by Veen et al (2004). Here, it was noted that when all initial cases of psychosis were considered, 49% received an ultimate diagnosis of SZ. The reverse, i.e. a change away from SZ, was uncommon. A similar observation was made in an Irish-based FEP study (Whitty et al., 2005) and another study adds that more men than women move into the category of SZ at follow-up (Chaves et al., 2006). A case register study carried out in Denmark also points to similar findings, in that more individuals received a diagnosis of reactive psychosis at onset whereas a diagnosis of SZ was more common in the later phase of the illness (Weeke, 1984). More recently, the notions of prospective and retrospective validity have been introduced. This helps to conceptualise the finding that high levels of diagnostic stability reported over time in SZ conceal the finding that the category appears often more populated at follow-up than at onset of illness. An FEP

study (Rahm & Cullberg, 2007), making use of this idea, looked at 146 individuals at baseline and at 3-year follow-up and divided them into three diagnostic super-groups: SZ spectrum disorders, affective disorders and PNOS. It was found that the first two groups had prospective validity and that, within the individual diagnoses, SZ has the greatest degree of stability. PNOS was markedly less stable, generally moving towards the SZ spectrum group over the follow-up period.

The above two findings (i.e. that whilst a diagnosis of SZ is stable over time, other psychotic diagnoses commonly turn out to be early manifestations of a later diagnosis of SZ) relate to the finding that SZ as a diagnosis has a high positive predictive value but a relatively low sensitivity. This latter finding is highlighted by Amin et al's FEP study (1999a), which shows high specificity for the diagnosis but low sensitivity.

Another well-replicated finding is that the SZ/affective disorder dichotomy has good positive predictive value over time. In the FEP study of Whitty et al (2005) this is calculated to have 80% diagnostic stability over the follow-up period. Another study, which followed up 88 cases of early onset psychosis, found a positive predictive value of the SZ/affective disorder dichotomy of 87% at six months and 80% at 10 years (Jarbin & von Knorring, 2003). Another study followed diagnosis in 154 people from onset to two years and found that SZ spectrum disorders (SZ, SA, SF) had greater stability (87%) than the affective disorders (BD, MDDP), for which diagnostic stability was 55% (Subramaniam et al., 2007).

Bipolar disorder

BD has also been shown to have a high degree of diagnostic stability over time, with representative studies indicated in Table 6. The casenote-based study carried out by Forrester et al (2001) calculated this to be within the range of 24-80%. A casenote-based study looked retrospectively at diagnosis in 500 individuals over a period of 30-40 years and showed, as in all the above studies, that affective disorders had a high degree of diagnostic stability, slightly below that of SZ (Tsuang et al., 1981).

Prospective studies have yielded similar results. The Long Island FEP study found BD to have diagnostic stability of 86% (Fennig et al, 1994a). The EPPIC study (Schimmelmann et al., 2005) calculated a positive predictive value of 83%. Amin et al's FEP study (1999a) calculated a figure of 91% for mania over 3 years. An FEP five year follow-up study carried out in Hong Kong gave a prospective diagnostic stability for BD of 96% (Chang et al., 2009). The study of Hollis (2000) also makes a broader distinction between affective disorders and SZ and yields a figure of 83% for BD in this early onset population. At four years, the study of Whitty et al (2005) yielded a figure of 80%. A very high figure of 100% is quoted by an Indian study that followed up 28 individuals with early onset psychosis over a period of 5 years (Srinath et al., 1997).

Table 6: Diagnostic stability in bipolar disorder

Type of study	Location	N	Follow-up period	Diagnostic stability	Reference
Casenote based	US	500	30-40y	56%	Tsuang et al., 1981 (BD and affective disorders)
FEP	US	278	6 months	86%	Fennig et al., 1994a
FEP early onset	India	28	5y	100%	Srinath et al., 1997
FEP	UK	168	3y	91%	Amin et al., 1999a
Casenote based	Scotland	204	8y	24% (clinically defined BD) 80% (operationally defined BD)	Forrester et al., 2001
FEP	Australia	492	1.5y	83%	Schimmelmann et al., 2005
FEP	Ireland	161	4y	80%	Whitty et al., 2005
FEP	Hong Kong	166	5y	96%	Chang et al., 2009

A Spanish study took a different perspective on diagnostic stability, looking at routine clinical practice. Here, they examined the prospective and retrospective consistency of clinical diagnosis in those who had received a diagnosis of BD on at least one occasion. In the study, only 23% of patients received the diagnosis at 75% or more of assessments (Baca-Garcia et al., 2007).

Major depressive disorder with psychotic features

Relatively few studies have addressed diagnostic stability for MDDP. One of these is a prospective study which followed-up two groups of individuals over a period of seven years (Maj et al., 1990). One group had major depression with mood congruent psychotic features, while the other had major depression without psychosis. It was found that the group without psychotic features was actually slightly less stable than the other group; the authors conclude this to be evidence against MDDP being a separate nosological entity and for it being a more severe manifestation of MDD in general. Another perspective on MDDP views it as coming under the umbrella of BD. Here, it is assumed that all individuals with MDDP have the capacity to become manic, given a long enough follow-up period. A prospective study followed up patients with MDD with and without psychotic features over a period of 15 years. It was found that 27% converted to BD II and 19% converted to BD I (Goldberg et al., 2001).

Schizoaffective disorder

SA shares some diagnostic features of both SZ and BD and therefore might be expected to show more diagnostic instability. Changes in rates for this disorder may therefore indicate a change in diagnostic practice rather than a real change in rate, more so than for SZ or BD. Also, a reciprocal change might be seen in either SZ or BD where SA varies over time. One study looked at diagnoses made in a private university hospital over a 12-year period from 1981 to 1993. It showed that the diagnosis of SA accounted for 1.4% of psychotic diagnoses at the beginning and for 8.7% at the end of the period. Rates of BD, however, remained more or less constant over the same period. The authors suggest that some of the reasons for this shift over time might be changes in diagnostic criteria, treatment orientated diagnostic bias and indirect effects of sharply falling lengths of stay (Zarate et al., 1997).

Two casenote studies examined the diagnostic stability of SA. The study by Forrester et al (2001) quotes a figure of 5-39% stability over a period of eight years. The study of Kuruoglu et al (2001) indicated diagnostic stability of 46% over a one year period.

Prospective studies have generally shown similar, relatively low rates of diagnostic stability for SA, with the notable exception of a figure of 94% (Schimmelmann et al, 2005). This exception was found in the EPPIC study in Australia, which followed individuals over 18 months. Other studies looking at diagnostic stability for SA show lower figures, such as 36% in a study with a follow-up period of two years (Schwartz et al., 2000) and "low" in a study by Hollis (2000) where follow-up was over an 11.5 year period. Overall, it may be concluded that SA has generally been found to have a lower rate of diagnostic stability, over a range of follow-up periods, compared to SZ and BD. As suggested at the outset, this is one of the areas that might be expected to be most sensitive to changes in diagnostic practice.

Schizophreniform disorder

Another diagnosis that is often assumed to be an early manifestation of a more longitudinally robust diagnostic category is that of SF. In both ICD-10 and DSM-IV, the only aspect that differentiates SF from SZ is the time for which symptoms have been present. It might be argued that where the onset of positive symptoms has been preceded by a long prodrome of negative symptoms, SZ is quite a different entity to SF, where the onset will have been more acute. However, in general, the following studies indicate otherwise.

All of the studies mentioned below are prospective in design. The first concentrates on the overall stability of the diagnosis, whereas the remainder provide additional information in terms of how the diagnosis of SF evolves. The EPPIC study quotes an overall diagnostic stability figure for this diagnosis of 40% over 18 months (Schimmelmann et al., 2005). A study carried out by Naz et al (2003) compared baseline diagnoses of SZ vs. SF over a follow-up period of two years. It was found that 50% of SF were re-diagnosed with SZ at follow-up, 13% with affective disorder and 19% retaining a diagnosis of SF; this compares to the diagnostic stability of 92% for SZ over the same period. A study carried out in Israel (Iancu et al., 2002) followed up individuals for an average of 12 years post index hospitalisation with SF. It was found that 84% of individuals had experienced subsequent psychotic episodes and 70% had a diagnosis within the SZ spectrum, which they consider to

include SZ or SA. Another study followed up individuals who had received a diagnosis of SF at inception into an FEP study. At 4-18 years, 81% of the total number of 48 individuals had a diagnosis of SZ (Chinchilla Moreno et al., 1996). A study following up 56 people diagnosed with SF at the first episode found that 46% had evolved into SZ by seven years (Marchesi et al., 2007). Two other smaller studies are also notable. The first followed up 27 FEP individuals with SF for five years and found that 60% had a diagnosis of SZ, while 26% retained their original diagnosis (Egea et al., 2004). Finally, Zarate et al (2000) followed up 12 patients who had an initial diagnosis of SF and found that ten of these were now diagnosed as having SZ at two years.

Brief psychotic disorder

BrPsy is another diagnosis within the psychosis spectrum that has been found generally to be less stable. Because the episode on which a diagnosis is made is, by definition, short and allows for a wide range of affective and psychotic symptoms, none of which need predominate, it is not surprising that it can be a starting point for a number of different longer-term diagnoses. The exception to this appears to be in developing countries, where the diagnosis may have much greater diagnostic stability, indicating the possibility of a separate pathological entity.

Retrospective and prospective studies have yielded similar results. An early study carried out in Norway (Opjordsmoen, 1985) looked retrospectively at individuals who were admitted for treatment of psychosis 30 years ago; it was found that what they termed 'reactive psychosis' and 'acute delusional reactions with remission', which may be considered diagnostically congruent with BrPsy, had relatively low levels of diagnostic stability. Another retrospective study was carried out on a total of 351 individuals who had early onset psychosis; of those who received a diagnosis of transient adolescent psychosis, 66% were found to have a diagnosis of SZ 15 – 19 years post onset (Valevski et al., 2001). A shorter period of one year follow-up was applied in a prospective study of first admissions with a diagnosis of acute and transient psychotic disorder (ATPD); it found that 52% retained the same diagnosis, with 28% changing to a diagnosis of affective psychosis and 15% receiving an ultimate diagnosis of SZ

(Jorgensen et al., 1997). A study carried out in Nottingham found that 19% of cases of FEP were diagnosed with ATPD; it was found that the diagnosis was notably more stable in women than in men (Singh et al., 2004). In another FEP study, 45 individuals with 'acute polymorphic psychotic disorder' were followed up at 3 years; 33 retained this diagnosis, 10 changed to a diagnosis of BrPsy and the rest had unspecified diagnoses (Sajith et al., 2002). An FEP study carried out in Iran (Amini et al., 2005) followed up 60 individuals with FEP over one year; BrPsy was found to have a similar level of diagnostic stability to affective psychosis and SZ.

Delusional disorder

There is less focus on DD in studies of diagnostic stability. An Indian study of 150 patients with DD found that 80 of these individuals retained the same diagnosis at 2-year follow-up (Debnath et al., 2006).

Substance-induced psychosis

There is little literature on the diagnostic stability of SIP. However, a one year follow-up study of 319 individuals with early-phase psychosis presenting to an emergency department found that of those diagnoses with SIP, 25% had evolved to a diagnosis of primary psychosis at follow-up (Caton et al., 2007).

Conclusions

Within the spectrum of psychotic disorders, some show markedly higher degrees of stability than others. SZ and BD appear to show substantial stability over time. SF, MDDP and DD show intermediate levels of stability, although these disorders have been the subject of considerably less attention than SZ or BD. Of note, SF shows the expected high degree of transition to SZ while MDDP shows a moderate degree of transition to BD I and II. SA and BrPsy have also received less systematic study with regard to diagnostic stability and results have been somewhat contradictory. One important outcome in any diagnostic stability study,

which obscures the specific data at issue but which is an indicator of the potentially tragic consequences of these disorders, is suicide. Some prospective studies have provided important data that contribute to awareness of risk management as a key consideration in the treatment of psychosis. One study of 22 adolescents with an onset diagnosis of affective psychosis and a follow-up period of 10 years found that four of these individuals died by suicide during the period of follow-up (Strehlow & Piesiur-Strehlow, 1985). Another study by Whitty et al (2005) of 147 individuals found that four had died by suicide at 4-year follow-up. Substance abuse is a factor which might influence results of studies examining diagnostic stability; however, it is often poorly specified and research in this area would benefit from further clarification of the issue. Further prospective studies, such as that described in this thesis, will add to understanding of current diagnostic categorisation and its shortcomings, particularly with regard to defining disorders other than SZ and BD.

Functioning

Introduction

Since the origins of the concept of psychosis there has been an appreciation of the importance of long-term outcome. The inclusion of the concept of dementia in Kraepelin's term dementia praecox inferred at that time 'not only an end state but also a developing state, a process' (Gross, 1904). However, Kraepelin revised his early idea that dementia praecox was defined, in the absence of obvious brain pathology, by its poor outcome. In his later writing he indicated that he had observed 'permanent cure' in 15% of patients. (Gross, 1904). He differentiated dementia praecox from manic depressive insanity partly on the basis of the more favourable outcome of the latter (Kraepelin, 1921). Whilst the diagnostic classification systems of the present do not specify outcome as a diagnostic criterion for any of the psychotic disorders, clinicians understand the importance of considering long-term outcome and functioning in making a diagnosis.

There have been changes over time in how outcome is defined. In earlier times the persistence of symptoms, frequency of relapse and use of services were used as principal outcome measures in research which examined the prognosis of psychotic illness. Over time there has been an increase in awareness of the importance of functioning as a measure of outcome for a number of reasons, both client-centred, service provider related, and economically driven. First, as patterns of mental health care delivery have changed, measures such as hospital bed days have become obsolete in the context of many modern community-based services. Second, economic analyses of burden of care have revealed that it is baseline functioning between episodes of illness rather than frequency of relapse that determines how costly different diagnoses are to health care providers. Third, from the subjective point of view, positive symptoms are often not the aspect of psychotic illness that are most distressing to patients but, rather, variables that are more difficult to quantify. A recent qualitative article gives an interesting account of the impact of a diagnosis of SZ on peoples' lives, based on the narrative of four men: lost dreams, disruptions, losses and the

struggle to rebuild lives in spite of persistent perceived barriers emerge as the dominant and most distressing themes (Gould et al., 2005).

Functioning, therefore, emerges as an important new area of study in psychosis. It is of interest not only from the point of view of better understanding differences between psychotic disorders but also in terms of establishing whether additional variables that could be measured at baseline, other than diagnosis, might predict functioning at follow-up. This would help identify cases where more intensive input might be necessary in an attempt to mitigate long-term functional decline. Functioning is a concept that encompasses a number of domains. Here, we are particularly interested in occupational and social functioning. Each of these domains has numerous aspects. Occupational functioning, for example, needs to take into account education, employment, use of free time and the difference between predicted and actual function. Social functioning includes such aspects as sexual relationships, relationships with family and friends and level of dependency on carers.

A variety of different study designs have been employed in research on functioning. Surveys and mail studies are two examples. These are useful in that they are a relatively low cost way of looking at functioning in large groups of people; also, they may reach individuals that other study methodologies can miss. Retrospective studies use existing records to see if early variables have an effect on current functioning. The prospective type of study design reduces the many sources of bias inherent in retrospective studies. Here, cases are collected based on inclusion and exclusion criteria at baseline and an attempt is made to follow up all these cases into the future. This is a robust way of looking at how long-term functioning may be predicted. A particular type of prospective approach is the FEP study, where all cases of psychosis presenting to a given service are assessed at presentation and followed forwards. Another excellent methodology is that of the birth cohort study, whereby all individuals born in a circumscribed area over a certain time-frame are followed forwards. This reduces the possibility, present even in FEP or other prospective studies, that certain cases will be missed and introduce bias. However, they are costly and time consuming, particularly in a disorder such as psychosis which has a comparatively low incidence. All of the designs described above have been utilised in the studies described here.

Schizophrenia

Occupational functioning

Since its inception, schizophrenia has generally been thought of as having the most malignant prognosis among the psychotic disorders. However, it is only relatively recently that this has been quantified in terms of outcomes such as occupational functioning. Before discussing such studies, it is worth mentioning two studies that have looked at the sorts of choices that people with SZ make about their lives and activities. A retrospective study showed that, in general, individuals with SZ chose to work in low complexity environments in their last place of employment before becoming unwell (Muntaner et al., 1993). A qualitative study indicated that individuals with SZ choose their activities for two main reasons: the first is the reward/positive effect on their mental health [e.g. homemaking, work] and the second is stress modulation [e.g. watching television] (Minato & Zemke, 2004). Although this could indicate that people with SZ might choose employment that is less stressful and carries less responsibility, a national mail survey carried out in the USA identified some individuals with SZ who functioned at middle and upper career levels (Ellison et al., 2005)

The next group of studies looked at what percentages of people with SZ are in employment. One study revealed that a third of those with a diagnosis of SZ were working and that the strongest predictor of this was educational attainment (Mechanic, 2002). One third in employment was also the figure yielded by a German study, which followed up patients who received two years of standard aftercare subsequent to an index admission (Muller et al., 1998). Another German study followed up patients 11 years after diagnosis and showed that 34% were in employment in the general or sheltered market (Elbelt et al., 1998). A five year follow-up study carried out in Sweden on 71 patients treated for FEP revealed that 73% of patients with SZ vs. 47% of the non-SZ group were receiving a disability pension or were on long-term sick leave (Svedberg et al., 2001). A study carried out in New Zealand looking at over 5000 outpatients with SZ, BD or MDDP found that of those with SZ, 69% had no regular occupational activity, 49% had no formal qualifications and 24% were living in group

homes; all results indicated that those with SZ were the most impaired, MDDP the least, with the BD group in between (Wheeler, 2007). A cross-sectional study of over 1000 individuals with SZ found that despite 45% being in clinical remission, only 10% were functioning adequately in the social and occupational domains (San et al., 2007). Two studies indicated that rate of employment among those with SZ depends on the nature of the employment market. The first of these looked at changes in rates of employment in pre- and post-reunification Germany. Following reunification, unemployment rates in SZ rose from 7% to 50%. This study also revealed that following reunification, those with SZ who were unemployed felt financially stable and were not keen to give up their disability benefits but were socially less integrated than previously (Riedel et al., 1998). The difference between rates of employment in SZ between markets where employment is formalised to greater or lesser extents is evident on comparing the findings of approximately one third in employment in studies in America and Germany vis-à-vis two thirds in employment in India, with the majority in 'mainstream' employment (Srinivasan & Tirupati, 2005). In a 20-year follow-up study carried out on a FEP cohort in Madras, it was shown that while Global Assessment of Functioning (GAF) scores and overall social functioning were similar to levels in developed countries, more individuals in Madras were married and more were in employment (Thara, 2004). A review of outcome studies in SZ from around the world suggests that amongst other measures of outcome, occupational and social functioning are better in SZ in developing than developed countries (Isaac et al., 2007).

Employment is not the only measure of occupational functioning. Two studies focus on the concepts of disability and recovery. The first was a 14 year follow-up study of an FEP cohort (Bland et al., 1978). This showed that, at follow-up, 50% of those with SZ had little or no disability, 30% had moderate or marked disability and 20% had severe disability. In a 35 year follow-up study of the 1966 birth cohort in Finland, it was found that only 2% of those with SZ and 25% of those with SZ spectrum disorders had fully recovered, while 2% of those with SZ and 17% of those with SZ spectrum disorders had partially recovered (Lauronen et al., 2005). A useful general measure of function is the GAF; this gives information in a single score about different domains of function, including occupational, social, psychiatric and emotional. A five year follow-up study carried out in Germany

showed that less than 50% of individuals with SZ had poor global outcome (Moller et al., 1982). A study in Nigeria which followed patients up to 13 years showed that 'a substantial proportion' showed moderate to severe impairment (Gureje & Bamidele, 1999). A study carried out in the UK showed that deterioration in occupational functioning, as generally found in psychosis, is worst in SZ (Johnstone et al., 1992)

Because of the dual effects of age at onset of the disorder and presence of a prodrome in many patients, it is not surprising that SZ has negative effects on educational attainment. Among the 1966 Finland birth cohort with early onset SZ, it was found that only a minimum number of individuals completed tertiary education (Isohanni et al., 2001).

An interesting study compared those with SZ to those who were unemployed but otherwise well. It indicated that individuals with SZ had less social activity, slept more and gained less enjoyment from 'pleasant events' (Hayes & Halford, 1996).

Social functioning

The second core domain of functioning to be considered is social functioning. Much of the research on social functioning in SZ to date has focussed on whether or not patients are married. Some studies have taken a more general perspective on social functioning, such as the five year follow-up of individuals in the International Pilot Study of Schizophrenia (IPSS) study in London which calculated that 42% of those with SZ had a good social outcome (Prudo & Blum, 1987). A more recent study carried out in New York found that of 118 patients with a first episode of SZ or SA who were followed up at five years, only 26% were deemed to have shown adequate social functioning for two or more of those years (Robinson et al., 2004). A Tasmanian study comparing function in individuals with SZ to function in non-SZ psychiatric controls revealed that family and social relationships are the areas of greatest difficulty for those with SZ, more so than accommodation and employment (Holding et al., 1983). A study in Nigeria looked at people with SZ 13 years after diagnosis. They found that women with SZ had less social contact than their well counterparts and that fewer men with SZ were married those without SZ (Gureje et al., 1999). An FEP study in India

which followed patients to 10 years found that 70% of individuals were married (Thara & Srinivasan, 1997). It was also found that whilst rates of marriage were higher than those found in developed countries (Thara, 2004), males with SZ were still less likely to be married than their non-SZ counterparts and that females with SZ were more likely to have broken marriages than females without SZ (Thara & Srinivasan, 1997). A German study found that 60% of individuals with SZ were unmarried, with half living alone or with their parents and a third living very solitary lives (Muller et al., 1998). A similar figure of 67% was found in a large NZ sample of outpatients with SZ (Wheeler, 2007). One interesting finding is that poorer social functioning in SZ appears to lessen in old age (Jeste et al., 2003).

Predictors of occupational functioning

An area of study in which there has been much interest in recent years is the search for robust predictors of long-term occupational function in SZ. Whilst some of these variables are not amenable to intervention, they are still of value to improve the accurate identification of individuals who are likely to do poorly and for whom more intensive intervention may be of benefit. Variables which have been investigated and will be mentioned below are sex, age, pre-morbid functioning, cognitive function, physiological variables, neurological soft signs, duration of untreated psychosis (DUP), family history, symptoms, compliance with medication, co-morbidity, personality and social support.

Sex

Sex has been the subject of considerable study. The majority of studies have shown poorer outcome in males, with only a minority indicating the reverse. A study carried out in Germany showed that occupationally, females did worse than males (Hofer et al., 2005). Similar results were evidence in a Turkish one year follow-up study of 382 individuals with SZ (Alptekin et al., 2005a). A study in Madras showed that men and women had similar levels of occupational functioning (Thara, 2004). An FEP study showed that, along with two other variables to be discussed below, female sex best predicted work performance at 18 months (Beiser et al., 1994). The study carried out in Madras indicated that females do better

globally than males, who experience more financial hardship (Thara & Rajkumar, 1992). A study carried out in Australia on 1090 people with psychosis looked at the differences between men and women in their experience of psychosis. They found that women had better pre-morbid functioning, less severe course of illness and disability and better integration into the community across all diagnostic groupings. However, women with SZ appeared particularly impaired in comparison with women having other psychoses (Morgan et al., 2008).

Education

Education has also been shown to have an impact on occupational functioning in SZ. Ruesch et al (2002) report a positive impact of better educational attainment, while a cross-sectional study shows that level of education predicts whether individuals with SZ are in work or not (McGurk & Meltzer, 2000).

Duration of untreated psychosis

There has been much interest in the effect of duration of untreated psychosis (DUP; Marshall et al, 2005; Perkins et al, 2006) on longer-term functioning, given that it is one of few potentially modifiable variables. Studies have indicated in individuals with FEP a relationship between DUP and social, occupational and quality of life outcomes at eight years (Harris et al., 2005). Some have argued against the idea that shortening DUP should become a major focus of attention in the attempt to improve functioning in SZ; their argument is that DUP does not have a causal relationship with functioning but, rather, is a marker of poor prognosis that clusters with negative symptoms and poor pre-morbid adjustment. One study emerging from the EPPIC trial looked at the predictive effects of DUP and other variables on functioning at 12 month follow-up and found that it remained a predictor of poor outcome even after adjusting for the effect of other variables (Harrigan et al., 2003). Another study carried out in Norway looked at pre-morbid functioning and DUP among 43 FEP patients during their first admission in relation to functioning at one year follow-up. Again, it was found that whilst there is some interaction between pre-morbid functioning and DUP, DUP

remains a strong predictor of outcome after controlling for this factor (Larsen et al., 2000). DUP was also found to predict poor occupational outcome in a 10-year FEP follow-up study (White et al., 2009).

Psychopathology

Psychopathology has been subject to considerable attention in the search for robust predictors of occupational functioning at outcome. A good psychopathological predictor of outcome would be clinically very useful, as detection of symptoms and signs is part of routine assessment. The areas that have been looked at are overall symptoms, positive symptoms, negative symptoms and depression.

Overall symptoms

Overall symptoms during FEP have not been shown conclusively to be good predictors of functional outcome at follow-up. One study followed individuals with FEP for 14 years and found that severity of symptoms at the end of the first episode was the best predictor of occupational functioning (Vetter & Koller, 1996). A 10-year FEP follow-up study found baseline symptoms to predict outcome (White et al., 2009). However, another study which followed individuals to seven years did not find symptoms to predict functional outcome (Geddes et al., 1994).

Positive symptoms

One study has reported that the presence of positive symptoms was associated with occupational decline (Johnstone et al., 1995). Similar results were evident in a Turkish one year follow-up study of 382 individuals with SZ (Alptekin et al., 2004a). Another study showed that delusions in general were associated with poor occupational functioning (Harrow et al., 2004). One cross-sectional study showed that hostility was the only symptom that related to poor work performance (Lancaster, 2005). While thought disorder has been the

subject of few studies, it may predict poor occupational functioning at follow-up (Racenstein et al., 1999).

Negative symptoms

Research on the extent to which negative symptoms predict functioning at follow-up has been more consistent. Their presence at baseline has been shown to predict reduced chance of living independently at follow-up (Hofer et al., 2005). A 'deficit' syndrome at baseline has been shown to predict poor occupational outcome at five years in individuals who were chronically unwell; however, in this study the 'deficit' syndrome was also found to be associated with less distress (Tek et al., 2001). Similarly, negative symptoms at baseline predict poor occupational functioning as well as financial dependence and low GAF score at two year follow-up (Ho et al., 1998). In a cross-sectional study negative symptoms were found to be associated with unemployment (McGurk & Meltzer, 2000). A study of perceived employability ratings showed that individuals with lower levels of negative symptoms received higher employability ratings (Charisiou et al., 1989). One of the more recent studies looking at people at high risk for psychosis found that they have poorer occupational functioning which, after controlling for background factors, is associated with higher levels of negative symptoms (Svirskis et al., 2007).

Depressive symptoms

There has been considerable interest of late in the importance of depression in SZ as a predictor of poor occupational functioning. However, results have been variable. A study by Eklund et al (2003) indicated the presence of depression to predict poor occupational outcome, whereas other studies (Jin et al., 2001; Suarez, 2002) found the reverse to be the case. The study of Blanchard et al (1998) showed that social anxiety and negative affect were associated with poor outcome, whereas positive affect was associated with better outcome.

Other predictors of good occupational functioning which have been identified include good pre-morbid functioning (Glick, 1990; Beiser et al, 1994; Mueser et al., 2001; Ruesch et al.,

2002;Haim et al., 2006), overall intelligence quotient (Solinski et al., 1992; Velligan et al., 2000; Sponheim et al., 2003), executive function (McGurk & Meltzer, 2000; Addington et al., 2000; Velligan et al., 2002; Wilder-Willis et al., 2002; Reed et al., 2002), memory (Hofer et al., 2005; Schretlen et al., 2000; McGurk & Meltzer, 2000; Addington et al., 2000; Velligan et al., 2000; Fennig et al., 2002), verbal ability (Velligan et al., 2000; Schretlen et al, 2000), vigilance (Penn et al., 1997; McGurk & Meltzer, 2000; Velligan et al., 2000), processing speed (Dickinson & Coursey, 2002), eye tracking performance (Katsanis et al., 1996), low skin conductance (Schell et al., 2005), absence of disorganisation symptoms (Alptekin et al., 2005a), compliance with treatment (Rzewuska, 2002), presence of physical comorbidity (Sim et al., 2006) and good family and social support networks (Erickson et al., 1998; Evert et al., 2003; Giron & Gomez-Beneyto, 2004).

Overview

It may be concluded that whilst most signs and symptoms have been found to be relevant to functioning, negative symptoms have been shown most consistently to predict poor outcome. The general conclusion of research in the area concords with the clinical impression that overall severity of illness relates to occupational functioning.

Predictors of social functioning

Our capacity for social functioning is at the core of what it means to be human and is at least as important as occupational functioning. Deficits in this area are devastating, not only to the individual but also to those who care for that individual. Unfortunately, SZ does appear to be characterised by such deficits, as indicated above. Similar to prediction of occupational functioning, prediction of social functioning should assist in efforts to implement appropriate remediation strategies at the earliest opportunity.

Early social functioning

Social functioning, before onset of illness, has been considered a predictor of social functioning after illness onset. Unsurprisingly, it has been shown to have a relatively robust predictive relationship. One study indicated that social adjustment at baseline is the best predictor of social adjustment at follow-up (Moller et al., 1982). Similar outcomes were observed in a subsequent study showing that social outcome was principally determined by acquired social status during the prodromal phase of illness; the conclusion here is that earlier age at onset leads to more severe social consequences, this being particularly evident in men whose illness has, in general, an earlier onset (Hafner & Nowotny, 1995). Research with a slightly different focus looked at survival in community treatment as an outcome and found this to be predicted by extent of antisocial behaviour displayed while receiving community case management for early psychosis (Preston, 2000). A one year FEP follow-up study showed that good social functioning at onset predicted better social functioning at follow-up (Simonsen et al., 2007).

Early occupational functioning

A number of studies have looked at how early occupational functioning predicts social functioning later in illness course. One study looked at whether educational qualifications or best-ever occupational functioning better predicted social (and clinical) outcomes and found the latter to be the better predictor (Samele et al., 2001). Another study looked at a wide range of potential predictors of good short-term social outcome and identified the following; satisfactory work record, compulsory admission to hospital, illness having been precipitated by stressful events, longer period of hospitalisation and older age at onset (Mantonakis et al., 1982).

Psychopathology

Symptoms have also been examined as predictors of social functioning. Some studies have looked at overall symptoms and some at specific symptoms. A study of the former type

followed up an FEP cohort at 14 years and found that severity of symptoms at the end of the first episode was the best predictor of social functioning and also of illness course and occupational functioning (Vetter & Koller, 1996). As elsewhere, negative symptoms have been shown to be an indicator for poor outcome in SZ. One study looked at the power of negative symptoms at baseline to predict poor social (and occupational) functioning at follow-up and found a robust relationship (Anashkina, 1992-1993). Another study followed up individuals for two years and showed that negative symptoms at baseline predicted impaired friendship and recreation, financial dependence, lower GAF and poor occupational functioning at outcome (Ho et al., 1998). One study found that negative symptoms at onset and negative self-statements, but not social anxiety, predicted poor social functioning at follow-up (Voges & Addington, 2005). In a prospective study, thought disorder impacted on occupational functioning but had little impact on social functioning (Racenstein et al., 1999).

Other predictors of good social functioning which have been identified to date include good pre-morbid adjustment (Anashkina, 1992-3; Addington & Addington, 2005), compliance with treatment (Mantonakis et al, 1982; Rigbi et al., 2003), good personality functioning (Fassino et al., 2003), good family support (Bocker, 1984; Inoue et al., 1997), female sex (Simonsen et al., 2007), shorter DUP (Simonsen et al., 2007) and religious participation (Huguelet et al., 1997). Overall, it may be concluded that a malignant form of SZ involves poor pre-morbid adjustment in childhood and adolescence, prominent negative symptoms and poor social functioning at follow-up.

Conclusions

Functioning, both social and occupational, is markedly impaired in SZ and this contributes significantly to the burden of the condition upon the individual, their families and the exchequer. Much research has sought to improve our understanding of how to identify those most at risk for poor functioning. Most findings have made clinical sense, namely that pre-morbid functioning and aspects of severity of disease are, in general, good predictors of outcome. Carter (2006) talks in his review of the 'glass ceiling' of function in SZ and that, while positive symptoms may be treated relatively satisfactorily by antipsychotics, it is

negative symptoms and cognitive dysfunction that make the principle contribution to functional deficits. Until better treatments are available for these symptoms of SZ, this 'glass ceiling' will continue to prevent optimal occupational and social functioning. As things stand, we have little idea of how best to intervene but the shift in research to include the more subtle, but ultimately devastating, aspects of the condition is a good start.

Bipolar disorder

Occupational and social functioning

Whilst Kraepelin (1921) highlighted a difference in outcome between SZ and BD, believing that inter-episode recovery in BD was to be expected, it did not take long for dissenting voices to make themselves heard by observing that functional outcome in BD appeared not to be as good as previously thought (Rennie, 1942). More recently, studies confirming these assertions began to emerge (MacQueen, 2001). BD is now understood to be an illness that carries significant costs, both for the patient and in terms of the financial burden on society (Kleinman et al., 2003). Whilst Kraepelin might have underestimated the impact of BD regarding functional impairment, he was correct in so far as the degree of functional impairment in BD does appear to be less than that seen in SZ and SA, although greater than that seen in MDDP (Grossman et al., 1991; Morgan et al., 2005; Depp et al., 2006).

Defining functional impairment in a reliable manner has proved as much of a challenge in research in BD as in SZ. The outcome measure that makes comparison easiest is the GAF. A study by Hajek et al (2005) indicated an average GAF score of 67, with a bimodal distribution and no difference between BD I and BD II. A cross-sectional study indicated that 62% of patients with BD report functional impairment (Suppes et al., 2001). Tohen et al (2003) found that at two to four years after a first manic episode, only 43% of patients have achieved functional recovery. Another study followed up at 10 years individuals who had their onset of illness in adolescence and found a much higher rate of good outcome; outcome was intermediate or good in 74% and poor in 26% (Jarbin et al., 2003). A prospective study in China looked at patients one year after an episode of illness. It was found that 46% were

employed (70% of FEPs but only 40% of those who had had multiple previous episodes) but that only 12% were employed at a level that would have been expected; 42% were rated as incapacitated, 40% were self-sufficient, and 74% were living independently (Jiang, 1999). This article is particularly useful in that it shows rates of 'good' outcome to vary substantially depending on whether 'good' is defined as achieving pre-morbid potential or, more restrictively, as living independently. One study matched patients with BD to unaffected relatives and followed them up over five years. It was found that occupational, education, sexual and interpersonal function were all significantly worse in patients than in relatives (Coryell et al., 1993). A three year follow-up study of a FEP population, including BD, found that 73% of those with affective psychosis had good functional outcome (Singh et al., 2000). This study may have yielded a better outcome due to the inclusion of MDDP in this category. However, another study which followed up patients with BD and MDD/MDDP over 30 – 40 years found that there were no significant differences in residential, occupational, marital or psychiatric outcomes over that period (Tsuang et al., 1979). In summary, there are a wide range of estimates of the ratio of good vs. poor functional outcome in BD, confounded by problems with definition as well as diagnostic considerations. It is appears, however, that whilst functional impairment is somewhat less evident in BD than in SZ, it remains a significant problem in BD.

Predictors of functioning in bipolar disorder

Sex

Studies which have looked at sex have shown variable results. A one month census of all people in contact with mental health services in Australia yielded 115 individuals with BD; social and occupational dysfunction levels were similar in both sexes but women performed better on measures of social integration than men (Morgan et al., 2005). A cross-sectional study carried out by Hajek et al (2005) measured GAF in men and women with BD and found no significant difference. However, Tohen et al (1990) indicated male sex to have an unfavourable impact on outcome in BD.

Psychopathology and illness-related factors

The impact of symptoms and other illness-related factors on functional outcome has been studied, with particular emphasis on the presence or absence of psychotic symptoms. Tohen et al (1990) found that the presence of either depressive or psychotic symptoms has an adverse impact on outcome at four years after a first manic episode. Similar findings are reported relating to psychotic symptoms in a number of studies (Shobe & Brian, 1971; Dion et al., 1989; Coryell et al., 1993). However, more recent studies have shown no relationship between psychotic symptoms and poor functional outcome in BD (Goldberg et al., 1995; Harrow et al., 1990; Keck et al., 1998). Other illness-related factors include younger age at onset of illness, which Tohen et al (1990) found to correlate with poor functional outcome. A number of studies have looked for relationships between number of admissions or episodes and functional outcome. Again, findings have been contradictory, with some finding that increased number of episodes correlate with poor outcome (Dion et al, 1989; Tohen et al., 1990; O'Connell et al., 1991) but others failing to find evidence for such a relationship (Goldberg et al., 1995; Staner et al., 1997).

Other predictors of poor functioning in BD identified in the literature to date include: poor planning and problem-solving skills (Laes & Sponheim, 2006), impaired verbal memory (Dickerson et al., 2004; Martinez-Aran et al., 2004; Atre-Vaidya et al., 1998) and negative labeling by others (Beiser et al., 1994).

Major depressive disorder with psychotic features

Occupational and social functioning

In this section, the literature reviewed includes only studies where depressive illness is severe and/or psychotic symptoms are present. A study by Haglund et al (1998) compared patients with MDDP to patients with SZ and BD in terms of their occupational functioning and found that MDDP patients were less impaired than either of the other two groups. There has also been interest in whether extent of psychotic symptoms impacts on functioning in MDDP. A

study by Coryell & Tsuang (1982) followed up MDD/MDDP patients at 40 years and found no difference in terms of marital, residential or occupational functioning, nor any difference in rates of conversion to BD between the two groups over follow-up. Another study by Kettering et al (1987) compared individuals with MDDP to MDD and also to SZ in terms of outcome and found that functional outcomes did not differ. There has also been interest in differences in occupational functioning between MDD/MDDP and BD at follow-up. A 30-40 year follow-up study comparing the two diagnoses showed no difference between marital, residential and occupational outcome (Tsuang et al, 1979). Overall, it may be concluded that there appears not to be such a difference as might have been expected between MDDP and BD in terms of disability. Also, psychotic symptoms may have less functional prognostic impact than might have been thought.

Schizoaffective disorder

Occupational and social functioning

Compared to SZ and BD, there has been comparatively little research into functioning in SA and predictors thereof. One study estimated rates of educational and occupational impairment as being 72% in cases of SA where onset was in adolescence (Lay et al., 1997). Rather more studies have compared outcomes in SA to those in SZ and BD. In Schneider's writings (1959), he describes cases which he refers to as *zwischen-falle* or mid-cases, i.e. cases that lie between SZ and BD in terms of their psychopathology and prognosis. Research on outcome in SA reflects this idea, with varying findings. Tsuang & Dempsey (1979) found that residential, marital and occupational outcomes in SA lie between those of patients with SZ and affective disorders. A study by Nardi et al (2005) found that in terms of education, occupational status and marital status, SA was more similar to BD than to SZ. Marneros et al (1990) also found that whilst outcomes in SA lay between those found in SZ and affective disorders, they were closer to the latter. However, Lay et al (1997) found that his estimate of poor educational and occupational attainment, at 72%, was closer to that of SZ (79%) than of affective disorders (40%). Diversity in results is not inconsistent with the general finding that functional outcome in SA lays between SZ and BD.

Conclusions

It has become clear that some diagnoses within the psychotic spectrum carry a very significant level of long-term functional impairment. The most severe level of dysfunction, both occupational and social, appears to occur in SZ. However, BD also results in significant functional impairment, despite initial beliefs to the contrary. SA appears to lie somewhere between these two disorders. MDDP appears to involve more long-term functional impairment than is often thought. However, these latter diagnoses have been the subject of little systematic investigation and even less evidence is available regarding functional outcomes in other disorders within the psychotic spectrum, such as BrPsy, DD and PNOS. Unless we have a clear idea of prognostic implications with respect to functioning for all of these diagnoses, we are limited in terms of our understanding of these conditions and in our implementation of strategies to minimize long-term deficit.

Quality of Life

Introduction

Growing awareness of the impact that psychosis has on sufferers' lives is apparent in the increasing amount of research that looks at quality of life (QOL) as an outcome measure. Whilst at one level it could be argued that functioning, after measures of illness and symptoms, may be something of which doctors and relatives have a high level of awareness, QOL is perhaps the most meaningful measure from the point of view of the person who is experiencing the illness. Those around the individual having a history of psychosis may be very invested in that person returning to the best possible level of functioning but for the person themselves, this may or may not be what is most important to them. In order to better understand these illnesses, measuring QOL is one way of trying to access the subjective experience of the person who is or has been unwell and understanding their priorities. If the goals of those treating the patient and the patient themselves are not shared, aspirations to a collaborative approach to treatment are destined to be disappointed.

Before discussing QOL in the different disorders, it is worthwhile considering the meaning of the concept. QOL has been broken down into dimensions in a number of different ways. Eklund et al (2003) describe it as having two dimensions: the internal and external sphere; the internal sphere relates to the person's inner life, while the external sphere relates to that which is visible to others in terms of the person's conditions of living. Laliberte-Rudman (2000) breaks QOL down into seven dimensions in SZ: activity, social interaction, time, disclosure, being normal, finances and management of illness; in addition, these map onto three higher order factors, namely time management, connecting and belonging, and making choices and maintaining control. A study by Hansson et al (2007) arrived at an interesting perspective on QOL. A variety of patient-rated outcomes (QOL, needs, symptoms and treatment satisfaction) were explored over a follow-up period of six years. It was found that all of these outcomes mapped onto a single factor (55-65% of the cross-sectional and

longitudinal variance), namely a general appraisal tendency of the individual, which has implications for the interpretation of studies using subjective outcome measures.

As alluded to above, the relationship between QOL and functioning is an interesting one. Whilst it might be expected that objective evaluations of QOL would correlate rather highly with evaluations of functioning, it has also been found that subjective QOL is correlated with functioning (Norman et al., 2000). Other research comparing subjective and objective measures of QOL indicates a robust correlation between the two parameters, particularly in relation to psychological symptoms (Whitty et al., 2004).

First episode psychosis

QOL has been studied in FEP as well as for individual psychotic diagnoses. This may be partly driven by increasing awareness of the high risk for suicide after FEP (Altamura et al., 2003; Clarke et al., 2005; Melle et al., 2006), leading to a desire to better understand the impact of such an episode on the individual.

Indeed, some studies have indicated that QOL is particularly low following FEP (Priebe et al., 2000). Others have found that overall QOL is rated as being fair to good, with a moderate association between subjective and objective measures of QOL (Melle et al., 2005b). One study compared QOL among three groups: healthy controls, individuals with a putative early initial prodrome of FEP and those with an established first episode of SZ. It was found that healthy controls had the highest subjective QOL, followed by prodromal individuals, with individuals having an established first episode of SZ reporting the lowest QOL (Bechdolf et al., 2005). A study of 133 individuals at high risk for psychosis found them to have poor QOL compared to non-clinical controls (Svirskis et al., 2007).

A number of predictors of poor QOL have been identified in FEP studies. These include not being in a relationship, drug use, depression, presence of an affective component to the illness, poor premorbid adjustment and DUP of more than ten weeks (Melle et al., 2005b). Research by Malla et al (2002a) corroborated the importance of pre-morbid adjustment.

They also found that outlook on symptoms correlated with presence of depression. The presence of negative symptoms at baseline in FEP was found in one study to predict poor QOL at two years (Ho et al., 1998). In another cross sectional study, looking at people vulnerable to psychosis, negative symptoms were also found to be associated with poor QOL (Svirskis et al., 2007). Similarly, the presence of depressive symptoms at baseline predicted poor QOL at follow-up (Sim et al., 2004). A study looking at the relative contributions of symptomatology and cognition to QOL found that symptoms, in particular depression, are more strongly related to poor QOL than are any measures of cognitive function (Wegener et al., 2005). Among individuals in the prodromal phase of illness, it was found that QOL was reduced and that high depression score best explained variance in QOL (Ruhrmann et al., 2008). Another study found that any DSM IV Axis 1 co-morbidity had an adverse effect on QOL (Sim et al., 2004). An Irish study carried out in Dublin found that FEP patients evidenced poorer QOL with increasing DUP (Browne et al., 2000). In another study, change in QOL over a five year period in 74 FEP patients was explored; it was found that objective QOL improved generally over this period, whereas subjective QOL was stable. Predictors of poorer QOL at follow-up were high psychopathology scores and higher DUP (Gorna et al., 2008). The Scandinavian Early Treatment Intervention in Psychosis Study (TIPS) compared QOL in individuals with first episode non-affective psychosis who were detected early in the course of their illness to those who were detected later; no difference was found between QOL in the two groups (Melle et al., 2005a)

Schizophrenia

Quality of life

As might be expected, QOL is impaired in individuals with SZ compared to controls (Bechdolf et al., 2005). As mentioned in the introduction to this section, subjective and objective measures of QOL can differ. Eklund & Hansson (2001) found that subjective estimates of QOL were higher than objective measures. Subjective and objective measures of QOL were found to be in agreement for items relating to symptoms and function, to show less agreement on items relating to physical health and little agreement on social and

occupational items (Sainfort et al., 1996). In research looking at subjective and objective measures of QOL in SZ, they were found to be only moderately correlated, with subjective measures being more sensitive to the presence of depressive symptoms (Gorna et al., 2007) and objective measures being more sensitive to the presence of negative symptoms (Kusel et al., 2007; Tomotake et al., 2006). A study by Narvaez et al (2008) showed that good neuropsychological functioning was associated with poor subjective QOL. Such findings may lead to a better understanding of the discrepancies that exist between the subjective experience of someone with SZ and the objective evaluation of that experience.

Predictors of quality of life

Demographic and situational factors

A number of demographic and situational factors appear to be correlated with QOL. The findings relating to sex have been mixed. Females were found to have better QOL in some studies (Katschnig, 2000; Salokangas et al., 2006; Caron et al., 2005a) but at least one study reported the opposite finding (Hofer et al., 2005). Marriage has been found to enhance QOL, as has living at home and in the community compared to institutional living (Pinikahana et al., 2002). Some studies considered below find that psychopathological variables such as depression are stronger predictors of QOL compared to socio-demographic variables (Xiang et al., 2007, 2008). However, a multicentre study of 219 individuals with SZ across three European countries which followed up participants at one year found that marital status and income were better predictors of QOL than psychopathological variables (Kovess-Masfety et al., 2006).

A study carried out in Dublin revealed that individuals with SZ who were living in a hostel or group home had poorer QOL than those who were living independently or with their family (Browne et al., 1996). A large multi-centre study of over 1000 people with SZ living in France, Germany and the UK found that demographic factors were important, with those living in Germany experiencing the best QOL. It was also found that many of the associations with QOL were similar to those found in non-clinical populations, namely

depressive symptoms, living conditions and employment (Marwaha et al., 2008). A study of recently discharged individuals with SZ found that black participants reported higher QOL than their white counterparts after controlling for other demographic and psychopathological variables (Prince, 2006). Furthermore, the impact of education on QOL was found to differ between whites and blacks in recently discharged patients with SZ in New York, with whites but not blacks showing poorer subjective QOL with increased educational attainment (Prince, 2007). It should be noted that many of the findings relating to QOL in SZ mirror findings in non-clinical populations, for example the report of Bankole et al (2007) that fewer acute life stressors, less financial strain and better self-rated health have a positive effect on QOL.

One interesting finding (Katschnig, 2000) was that QOL was higher in individuals with lower levels of educational attainment, suggesting that a greater degree of discrepancy between expected and actual life outcome may be important in determining QOL. Findings relating to employment have been relatively consistent. Having employment (Hofer et al., 2004; Caron et al., 2005a), a satisfying daily occupation (Eklund et al., 2001) or good psychosocial functioning overall (Salokangas et al., 2006) have been found to have a positive effect on QOL. Subjective QOL was found in another study to be higher where individuals were employed and this appeared to be mediated by measures of social support (Ruesch et al., 2004). Employment rehabilitation was found to improve QOL (Holzner et al., 1998) and a supported work environment was found to be better than occupational therapy for enhancing QOL (Browne, 1999).

Psychopathology

Psychopathology has also been found to have a significant relationship to QOL. High measures of overall symptoms have been shown in a number of studies to be related to reduced QOL (Voruganti et al., 1998; Huppert et al., 2001; Ritsner et al., 2002; Savilla et al., 2008; Perlick et al., 2008). Two studies investigated if the correlation between total measures of symptoms and QOL differed for subjective vs. objective measures; only subjective QOL is affected adversely by overall increases in symptomatology (Hofer et al., 2005; Packer et al., 1997). High levels of positive symptoms on their own correlated with

poor QOL (Norman et al., 2000) and improvement in psychotic symptoms during the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness Study) trial was associated with improvements in QOL (Mohamed et al., 2008). Paranoia, when considered separately, also correlates inversely with QOL (Ritsner, 2003). A similar pattern is seen for negative symptoms (Rudnick, 2001; Norman et al., 2000; Fitzgerald et al., 2001, 2003; Katschnig, 2000: Browne et al., 1996; Aki et al., 2008). Indeed, negative symptoms were found in one study to be the best single predictor of QOL (Kennedy, 2003). One study found that this inverse relationship between negative symptoms and QOL is stronger in females than in males (Jarema & Konieczynska, 2001).

However, it is not only the symptoms of psychosis that have a negative impact on QOL in SZ. Depression also demonstrates such a relationship (Huppert et al., 2001; Hofer et al., 2004; Bankole et al., 2007; Mittal et al., 2006; Cardoso et al., 2007; Xiang et al., 2007,2008; Aki et al., 2008). When subjective and objective QOL are considered separately, no difference emerges, with both being affected negatively by the presence of depressive symptomatology (Fitzgerald et al., 2001, 2003; Jarema & Konieczynska, 2001). General measures of emotional distress have also been shown to reduce measures of QOL (Ritsner, 2003; Bengtsson-Tops & Hansson, 1999). Good quality sleep was shown in one study to have a positive impact on QOL in SZ (Ritsner et al., 2004).

Co-morbidity might be expected to have a negative impact on QOL and indeed a diagnosis of post traumatic stress disorder (PTSD) was found to be associated with poorer QOL in individuals with SZ, as well as with poorer attention, working memory and executive functioning (Fan et al., 2008).

Social functioning and supports

The relationship between social support, interpersonal functioning and QOL has been explored. Increased capacity to form attachments has a positive impact on QOL (Caron et al., 2005b). Rudnick & Kravetz (2001) investigated whether the capacity of an individual with SZ to seek social support had an effect on QOL but found no relationship. Extent of

emotional attachment on the part of the caregiver has been found to increase QOL of the person with SZ who is being cared for (Mubarak & Barber, 2003). One study found that company and sexual expression lead to improved QOL (Bengtsson-Tops & Hansson, 1999). However, another study found no significant relationship between sexual functioning and QOL in 124 people with SZ/SA (Fan et al., 2007). Good social support, in a general sense, has been found to improve QOL (Ritsner, 2003). Research carried out in Singapore indicated the importance of good family relations on health-related QOL (Tan et al., 2004). Good sibling relationships were found to have a positive impact on subjective QOL measures in a study of 93 adult SZ patients and their siblings (Smith & Greenberg, 2007). However, Erickson et al (1998) found that non-family social support, rather than support from the family, has the stronger relationship with QOL at five years after the first episode of illness. In a study by Caron et al (2005b), QOL is likely to be higher where an individual with SZ receives reassurance of their worth. Findings by Greenberg et al (2006) indicated that good relationships between adults with SZ and their parents, characterized by warmth and praise as perceived by the patient and a close relationship as perceived by the parent, had a positive association with QOL in SZ.

Other predictors of QOL which have been identified in the literature include: improved overall cognition (Mohamed et al., 2008), good executive functioning (Brekke et al., 2001; Alptekin et al., 2005b; Ritsner, 2007), social cognition and memory (Matsui et al., 2008), good personality functioning, including good self-efficacy and self-directedness (Eklund et al., 2003), absence of physical comorbidity (Sim et al., 2006) and low perceived stigma (Katschnig, 2000).

Bipolar disorder

Quality of life

Less research is available on QOL in BD than in SZ, with very little research into QOL in other psychotic disorders. Compared to the normal population, several researchers have found that QOL is significantly impaired in BD (Sierra et al., 2005; Hakkaart-van Roijen et al., 2004; Depp et al., 2006). Interestingly, health-related QOL was found to be poorer in BD II than BD I in a study comparing these two groups with healthy controls (Maina et al., 2007).

Most of the research on QOL in BD to date has focused on the effect of mood state. One study looked to see if there were differences in QOL of patients with BD depending on their mood state at the time of the interview. It was found that subjective QOL was worst when individuals were in a depressive phase of illness and best when they were euthymic. Interestingly, QOL in mania/hypomania was intermediate between depression and euthymia (Vojta et al., 2001). The same difference between effects of manic and depressive symptoms was shown in a study of QOL in people with residual symptoms in full and early remission (Piccinni et al., 2007). Other research has corroborated the findings regarding depressive symptoms (Goldberg & Harrow, 2005; Zhang et al., 2006) and adds that functional impairment also has a negative association with QOL (Goldberg & Harrow, 2005). Gazalle et al (2007a) studied mood symptoms in BD and found that there was no difference in ratings of QOL between those in euthymic and manic mood states; depressed BD patients rated their QOL lower than the other two groups. More specifically, they also found that manic symptoms of irritability and poor sleep were associated with poor QOL (Gazalle et al., 2007b). A study comparing people with BD to controls found that daily hassles and their opposite 'uplifts' were appraised differently, with those currently depressed or with more previous depressive episode perceiving daily hassles as more stressful (Havermans et al., 2007).

Predictors of quality of life

Research carried out by SanMighuel et al (2005) examined whether various demographic variables such as age, sex, occupation and marital status predicted QOL in BD; no robust associations were found.

Social and family support appears to be important in BD. In a qualitative analysis of the impact of disease on QOL, social support was described as the most important factor, followed by mental health (Michalak et al., 2006). As with SZ, co-morbidity appears to have a negative impact on QOL in BD. Co-morbid anxiety disorder was found to impact

negatively on heath related QOL in BD I but not BD II in a cross-sectional Italian study of 105 patients (Albert et al., 2008).

Conclusions

As can be seen from the above review, there has been a substantial amount of research carried out on QOL in SZ, with lesser amounts in FEP and BD and almost none in other psychotic disorders. What is clear is that QOL is impaired in psychotic disorders compared to the normal population. It appears to be more impaired in those patients who have poor pre-morbid functioning, more severe levels of symptomatology, particularly negative symptoms, fewer psychological resources and reduced social supports. Many questions remain about QOL. The use of proxy measures of QOL in many studies has not helped to clarify our understanding of these issues. As yet, there has been little attempt to compare QOL between different psychotic disorders and, whilst we know something about the correlates of QOL, we know less about its predictors. The better our understanding of what is likely to enhance a patient's QOL, the more effective we are likely to be in engaging them in effective treatment. Similarly, the earlier we can identify patients who are at long-term risk of impaired QOL, the better we may aspire to modifying their environment in a way that is likely to benefit them.

Service engagement

Introduction

Disagreement between patients and clinicians about treatment of psychosis is a significant problem. It has been estimated that if patients were entirely in agreement with their doctors on the best course of action for them, relapse rates would fall from 50% to 15% per year in the case of SZ (Kissling, 1994). This makes poor adherence to medication an expensive problem, with one study estimating that it increases external service costs by a factor of three (Knapp et al., 2004). The effect of differing levels of engagement was put to the test in a recent study looking at the effect of engagement with treatment on outcome in FEP. It was found that good adherence to treatment recommendations improved both the speed and the degree of remission (Malla et al., 2006).

Language relating to this concept has evolved over the years. The old idea of compliance, indicating a unilateral process whereby the patient passively accepts the clinician's counsel, was replaced by that of collaboration and concordance, suggestive of a bilateral process (Corrigan et al., 1990). Here, the clinician and patient seek to reach agreement by communicating about the best treatment plan, with responsibilities implicit on both sides (Gray et al., 2002). Service engagement (SE) is another relatively new concept which reflects the understanding that whether or not a client takes their medication is part of a complex interaction between the service, the service provider and the client. It refers to the extent to which a patient's behaviour indicates whether they find the services provided useful. A scale has been developed by Tait et al (2002) which covers four domains – availability of the client, collaboration, help seeking behaviour and treatment adherence.

First, the literature relating specifically to SE and appointment keeping in each of the disorders will be examined, followed by that concerning adherence to treatment, which in the main refers to concordance with medication. Finally, research pertaining to help-seeking and therapeutic alliance in each of the disorders will be considered.

Service engagement

First episode psychosis

There has been considerable interest in SE in FEP over the early period of illness, in view of emerging evidence for the value of early initiation of treatment and the development of early intervention services. One study carried out in the Northumberland catchment area, which delivered a traditional service to FEP patients, showed that at one year follow-up, only 50% of patients were still in contact with the service (Proctor et al., 2004). The EPPIC study in Australia showed that at 18 month follow-up, the Kaplan-Meier 18-month risk of service disengagement was 0.28. Factors which best predicted disengagement included the patient being less ill at baseline, their family not being involved and persistent (i.e. not only baseline) substance abuse (Schimmelmann et al., 2006). A smaller cohort of FEP patients was followed up over two years in France, again in a generic adult psychiatry setting; at follow-up, a third had no contact with a psychiatrist (Cougnard et al., 2006).

Schizophrenia

SE is important in SZ in terms of improving outcome. The worst of outcomes is suicide, which in a homeless population with SZ was predicted by disengagement from services (Bickley et al., 2006). Self-perpetuating cycles of poor engagement, poor access to treatment and poor outcome have also been identified. Overall, rates of engagement of patients with SZ have been shown to be higher than might be expected in a population which is thought of as frequently lacking in insight. One study carried out in the US looked at an old age mental health population across a range of diagnoses and found that out of 174 patients, one of the strongest predictors of engagement with services was a diagnosis of SZ, as well as younger age, receipt of Medicaid and shorter duration of illness (Cohen & Teresi, 1996). A study carried out in the context of a prevalence study of SZ in the Hampstead area of London showed that levels of contact with services improved between the years 1986 and 1991 (Jeffreys et al., 1997). A study which followed up a consecutive sample of 323 new referrals to a mental health service found that after four months, continuity of care was higher in SZ than in other disorders (Bergofer et al., 2002). Another study carried out an inner London sample showed that 25% of patients with SZ were not in contact with services (Harvey,

1996). A study carried out in the Cavan/Monaghan region showed that when a prevalent sample of people with SZ was followed up over the course of 7.5 years, 94% of them were still in contact with services (Morgan et al., 2003).

A number of studies have looked for predictors of good engagement in SZ and have identified the following variables: integrative rather than sealing-over style of recovery (Tait et al., 2003), absence of substance abuse, in particular alcohol abuse (Marshall et al., 1994; Coodin et al., 2004), female sex (Miner et al., 1997), presence of negative symptoms (Miner, 1997) and older age (Coodin et al., 2004)

Bipolar disorder

Compared to research carried out in FEP and SZ, there have been few studies of SE or appointment keeping in BD, despite a considerable body of research into adherence in this disorder. One study looked at correlates of attendance at a lithium clinic and found that perception of continuity of care was associated with improved attendance (Connelly et al., 1982).

Major depressive disorder with psychotic features

As in BD, there has been little specific research into SE in MDDP, despite considerable research into adherence in this disorder. One study looked at general attendance at a mental health outpatient clinic. Of a total of 1620 appointments, 142 were missed by a total of 130 patients. It was noted that patients with MDD were the least likely to be non-attenders compared to other diagnoses (Sparr et al., 1993). Another study looked at attendance patterns in primary care and found that the presence of depression increased the likelihood of being a frequent attender by a factor of five in the elderly and of three in younger patients (Menchetti et al., 2006). These two studies indicate that patients with depressive symptoms may be more likely to attend appointments, whether at primary or secondary service level, than are those with other diagnoses.

Adherence

First episode psychosis

Evidence for the importance of adherence to treatment in early psychosis is found in the work of researchers such as Malla et al (2002a, 2006), who have shown that adherence improves the degree and speed of remission and correlates with functioning at one year, independent of the contributions of other variables. A number of studies have focused on rates of adherence over FEP. Good adherence has been estimated at 41% (Coldham et al., 2002); estimates of partial adherence range from 20-63% (Coldham et al., 2002; Mojtabai et al., 2002); poor adherence has been estimated as ranging from 33-63% (Svedberg et al., 2001; Coldham et al., 2002; Novak-Grubic, 1999). A body of research has emerged regarding correlates and predictors of good adherence in FEP. These include higher level of functioning (Malla et al., 2002a), lower levels of symptoms (Kamali et al., 2006; Perkins et al., 2008), absence of substance abuse (Verdoux et al., 2000; Kamali et al., 2006; Perkins et al., 2008), positive attitude to medication and good insight (Mutsatsa et al., 2003; Kamali et al., 2006), shorter DUP (Chow et al., 2005) and minority ethnicity (Perkins et al., 2008).

Schizophrenia

As suggested above, rates of SE in SZ are perhaps higher than might have been expected. The general impression of clinicians is that adherence to medication is poor and several studies have investigated whether or not this is the case. To summarise, studies examining rates of adherence generate estimates ranging from 41 – 64% for those with a diagnosis of SZ (Valenstein et al., 2006; Gilmer et al., 2004; Olfson et al., 2000); estimates of non-adherence range from 2 – 20% (Leslie & Rosenheck, 2004; Gilmer et al., 2004; Dolder et al., 2003), with estimates of partial adherence ranging between 16 and 60% (Kim et al., 2006a). From the above, it would appear that variation between studies, in particular between estimates of adherence, are less than might be expected given the various methodologies used. Indeed, adherence and non-adherence in SZ appears to occur at similar rates to those observed in other chronic illnesses (McPhillips & Sensky, 1998).

Good adherence has been shown to be associated with good functioning (Rittmannsberger et al., 2004; Weiss et al., 2002; Linden et al., 2001), treatment with atypical vs. typical antipsychotics (Weiss et al., 2002; Valenstein et al., 2004; Glick, 2006), positive attitude to medication (Lin et al., 1979; Donohoe et al., 2001; Mutsatsa et al., 2003; Lambert et al., 2004; Hudson et al., 2004; Hofer et al., 2007), absence of side-effects of medication (Cooper et al., 2007; Lambert et al., 2004; Karow et al., 2007; Mutsatsa et al., 2003; Robinson et al., 2002;), older age (Maeda et al., 2006; Valenstein et al., 2004, 2006; Linden et al., 2001), non-minority ethnicity (Valenstein, 2004, 2006; Opolka et al., 2003; Ahn, 2008), higher educational attainment (Hudson et al., 2004), stable living conditions (Elbogen et al., 2005), longer duration of illness (Linden et al., 2001), paranoid rather than disorganised symptoms of psychosis (Castro et al., 2004; Mutsatsa et al., 2003), absence of substance abuse (Elbogen et al., 2005; Hudson et al., 2004; Olfson et al., 2000; Valenstein et al., 2006; Tunis et al., 2007; Ascher-Svanum et al., 2006), better cognitive functioning (Cuffel et al., 1996; Jeste et al., 2003; Heinrichs et al., 2008; Donohoe et al., 2001; Robinson et al., 2002; Kim et al., 2006b), insight (Day et al., 2005; Lin et al., 1979; Lysaker et al., 1994) and good therapeutic alliance (Olfson et al., 2000; Chadwick, 2001; Day et al., 2005; Tunis et al., 2007; Weiss et al., 2002)

Bipolar disorder

Like SZ, BD is considered by physicians to be another chronic condition characterised by poor adherence to medication with associated high rates of relapse. Estimates of good adherence in BD range from 34% (Coletti et al., 2005) to 52% (Sajatovic et al., 2006a); rates of partial adherence have been estimated as 30-32% (Scott & Pope, 2002a; 2002b), with rates of poor adherence in BD estimated as 48-64% (Keck et al., 1997; Fleck et al., 2005; Sajatovic et al., 2006a).

Studies have also looked for clues as to what might be causal factors in adherence vs. non-adherence, using either correlational or predictive study designs. Factors found to be associated with good adherence in BD include: older age (Sajatovic et al., 2007), non-minority ethnicity (Johnson et al., 2007; Gonzalez et al., 2007; Copeland et al., 2008; Zeber

et al., 2008), better educational attainment (Johnson et al., 2007), absence of substance abuse (Comtois et al., 1994; Sajatovic et al., 2006a, 2006b, 2007; Copeland et al., 2008), absence of manic or psychotic symptoms (Jamison et al., 1979; Miklowitz, 1992; Copeland et al., 2008), longer duration of treatment (Scott & Pope, 2002b), absence of side-effects (Weiss et al., 1998) and both insight into and acceptance of illness (Schumann et al., 1999; Greenhouse et al., 2000; Scott & Pope, 2002b; Yen et al., 2005).

Major depressive disorder with psychotic features

Little specific research exists with regard to adherence in MDDP. However, two studies have examined discontinuation of antidepressants by individuals with MDD within one month of starting treatment and found rates of 28% (Lin et al., 1995) and 68% (Johnson, 1973). Being given choice and education about medication appears to be associated with good adherence (Myers & Branthwaite, 1992; Lin et al., 1995), as is good therapeutic alliance (Fawcett, 1995; Paykel, 1995).

Help-seeking behaviour and therapeutic alliance

Schizophrenia

It is likely that significant difficulties with help-seeking exist in the initial phases of SZ. However, there is little research describing what patterns emerge in relation to help-seeking as illness progresses. There is more research into factors associated with delayed help-seeking behaviour in FEP. These include perceived stigma (Jorm et al., 2007), a biomedical rather than spiritual or mystical understanding of illness (Saravanan et al., 2007), subacute onset of illness (Asai, 1987), poor quality of available services (Asai, 1987), younger age at onset and poor adolescent pre-morbid adjustment (Bechard-Evans et al., 2007), avoidant coping style and poor family insight into illness (Boydell et al., 2006) and lack of family involvement (Morgan et al., 2006). Similarly, whilst problems undoubtedly exist with regard to therapeutic alliance in SZ, these are not well-described in the literature to date. Factors associated with enhanced help-seeking behaviour include higher educational attainment and

socio-economic status (Yang, 1992). Therapeutic alliance is of key importance in SZ, as it has been shown to relate to adherence and outcome (Holzinger et al., 2002; Smerud & Rosenfarb, 2008).

Bipolar disorder

There is a paucity of research on help-seeking behaviour and therapeutic alliance in BD but that which exists points to the possibility that rates of help-seeking in BD are very low. The Netherlands Mental Health Survey and Incidence Study (NEMESIS), a population-based epidemiological study, found that of the 2% of the prevalent population with BD, 25% of these had never sought help (ten Have et al., 2002). Another study carried out in Canada looked at people with BD and MDD/MDDP and found the rate of conventional mental health service use by both groups, but particularly those with BD, to be very low (49% of those with BD; 53% of those with MDD/MDDP; Wang et al., 2005). Some research has looked at associations between therapeutic alliance and individual factors. Factors associated with good therapeutic alliance include: good treatment adherence (Zeber et al., 2008), absence of depressive symptoms and good baseline alliance (Strauss & Johnson, 2006).

Major depressive disorder with psychotic features

Rates of help-seeking in depression have been found to be variable, which is likely to be the result of different studies having different thresholds for severity of the depressive disorder examined. These studies do not relate specifically to MDDP. However, they have been included as they may highlight some issues likely also to operate in this group. The term 'MDD' will be used here, rather than MDDP.

Estimates of help-seeking in individuals found in community samples to have MDD range from 13-47% (Roness et al., 2005; Henderson et al., 1992; Bland et al., 1997). Research seeking to identify variables associated with enhanced help-seeking behaviour has not yielded consistent results. However, perfectionism (Derosa, 2000) and neuroticism (Gormley & O'Leary, 1998) both appear to impact negatively on help-seeking behaviour, as

does endorsing a psychological rather than a medical model of illness (Ying, 1990; Jorm et al., 2006; Halter, 2003).

Conclusions

Poor SE has been shown to have a negative effect on outcome in terms of an individual's course of illness, as well as for society in terms of the financial burden of serious illness and lost productivity. SE is not as poor in SZ as might have been thought, with better engagement in MDD/MDDP, but very little information on BD. Predictors of poor engagement tend to be predictors of poor outcome in general, including factors such as substance abuse and poor family support.

Rates of non-adherence in psychotic illness are high, with estimates of partial or complete non-adherence in excess of 50%. As mentioned, these findings are not that different to those observed in many chronic illnesses (McPhillips & Sensky, 1998) and this may be explained as follows: demographic variables, clinical variables and side-effects of medication have, in the main, been shown to have less of an effect on adherence than might have been expected; exceptions to this include co-morbid alcohol and substance abuse, poor insight and the effect of poor cognitive function in SZ. Far more important factors include attitudes toward medication and illness. These are less likely to be diagnosis-specific characteristics and probably reflect attitudes toward illness and medication that are present in the general population, resulting in similar levels of non-adherence in all chronic illnesses.

There is some evidence to suggest that help-seeking behaviour is particularly impaired in BD compared to other psychotic illnesses. In general, factors such as low socio-economic status, poor pre-morbid adjustment and lower levels of educational attainment have a negative effect on help-seeking behaviour; health attitudes seem to be particularly important in determining behaviour in this area.

Aims

This thesis describes a follow-up study which seeks to assess all cases of psychosis identified over the initial eight years of the Cavan/Monaghan First Episode Psychosis Study (Baldwin, 2005), that is between 1995 and 2003, at an average of 6.4 (SD 2.3, range 2.6 – 11.7) years after onset of illness.

Two important factors were taken into account in the design of this first episode study, in order to make it as representative and informative as possible, and have contributed to the design of the follow-up study: the size of the population studied and the completeness of the data on this population. Thus, the study was designed to cover a geographical area large enough to ensure a representative population base that would provide an accurate estimate of the incidence of psychosis. Once the population to be studied was identified, it was important to ensure that case-finding protocols were such as to ensure the highest capture of FEP in the area, giving as complete a patient population as possible. The catchment area served by Cavan/Monaghan Mental Health Service is well-suited to such a study. First, it is large enough to yield an adequate number of new cases of psychosis every year for the purposes of the study. It is also sufficiently geographically stable over time to facilitate follow-up. The nature of the community-based service, with its home based treatment teams and excellent links with primary care, results in both relative ease of detection of new cases of psychosis as well as relative ease in tracing all participants, including those no longer in contact with the service.

Specific aims of this follow-up study are diagnostic stability, functioning, quality of life and SE in the long term. The size of the inception population means that a sufficient number of cases had accrued from 1995 – 2003 to be able to draw meaningful conclusions about the long-term outcome of FEP. The completeness of the inception population results in a database that can be held to be representative of FEP and not subject to the biases inherent in studies of outcome which are based on 'samples of convenience'. This follow-up study also aspired to assess, either personally or via a key informant, the highest possible number of the

inception population identified, again in order to minimise biases that are likely to occur in studies with less complete levels of follow up.

Incidence data

Incidence rates for FEP from the Cavan/Monaghan FEP study and incidence rates for diagnostic subcategories over eight years have been reported previously (Baldwin et al, 2005).

Diagnostic stability

One of the principle aims of this study is to examine diagnostic stability over a relatively long follow-up period in as large and as representative a population as possible, to include the full spectrum of psychotic diagnoses, so as to maximise understanding of notional boundaries between the different psychotic diagnoses within this spectrum. An FEP population is ideal for studying stability of psychotic diagnoses for a number of reasons. First, an FEP study which is designed to detect 'all' cases of psychosis in a defined geographical area should result in identification of a representative population which will not be susceptible to selection or sampling biases which might affect study outcome. Second, an FEP study such as this, which includes all psychotic diagnoses and minimises exclusion criteria, allows for longitudinal examination of the boundaries between the various psychotic diagnoses. Psychosis is a much more diagnostically heterogenous phenomenon than is often considered, with the focus usually being on a subset of diagnoses. By including all categories within this spectrum, valuable information is retained which may contribute to the understanding of psychosis. Given the aspiration to include the full spectrum of disorders, it was even more important that a sufficiently large population be followed up, as numbers in some of the less populous diagnostic categories might otherwise have been too small to be able to draw meaningful conclusions. Also important was to ensure the follow-up period was sufficiently long to allow more complete evolution of disease processes. Many longitudinal FEP studies have been limited by their relatively short periods of follow-up. Another important feature of the design of the study was to maximise the degree of completeness of follow-up so as to minimise bias.

Functioning

The second focus of interest for this study is functioning. In the past, follow up studies were likely to focus on measures such as days spent in hospital, frequency of relapse or measures of symptomatology as proxies for outcome. Whilst these are all important, it is now recognised that more meaningful measures can be used. The measures above reflect burden of care on the health system but give only a limited sense of the impact of the illness on the individual and little indication of the burden of disease on society as a whole. Measures which take into account social, occupational and interpersonal functioning not only give a better indication of consequences of these illnesses for society but also for the individual bearing a diagnosis of psychosis. Subjective and objective measures of functioning were included in the study. Information from many sources, including health care professionals and relatives, was integrated into the latter, to give the most valid estimate of the construct. Because the period of follow-up is longer than is often the case, the study allows for emergence of more lifelong patterns, consequent to the settling of the aftermath of what is often a traumatic life event. Were characteristic patterns of functioning to be found within each of the diagnoses in the psychotic spectrum, it would give weight to that diagnostic category, with the reverse also being true. Because the assessment performed at the outset of illness is wide ranging, it provides a number of measures aside from diagnosis that might have the potential to predict this important aspect of outcome, allowing for identification of individuals who are more vulnerable to poor long term functioning and the early implementation of relevant therapeutic interventions.

Quality of life

The third outcome of interest in the study is QOL. Over recent years, this concept has increasingly become a focus for health care research. It emerged in the context of therapeutic interventions that had the potential to lengthen life and the resultant concern about the quality of life experienced. It is a useful measure to use in conjunction with functional measures. Whilst functioning takes into account the practical aspects of life and also gives an indication of the extent to which a person is likely to be reliant on others and require input from the

relevant services, quality of life describes something else: it aims to give an estimate of how a person evaluates their life and how it measures up to their aspirations.

In psychosis, it is recognised that quality of life is affected but neither the extent to which this differs between the various diagnoses, nor what other predictors of quality of life might be, are well understood. Subjective and objective measures of quality of life were used, as the research described in detail in the preceding literature review indicates that subjective and objective ratings of QOL can differ in psychosis. Given the inclusion of the full spectrum of psychotic diagnoses in this study, it is possible to compare quality of life between them. The other strength of the study is that the population is selected on the basis of presence of psychotic illness and followed up in its entirety, eliminating the many sources of bias that result from other study designs commonly used in the investigation of quality of life.

Service engagement

The last of the principal outcome measures used in this study is SE. It has been postulated that the extent to which a person with psychosis is engaged or not engaged with services is a significant determinant of outcome. Research in this area, with the exception of the study of compliance with medication, is in its early stages. As yet, there is only a partial understanding of the effects of the different aspects of SE on outcome and indeed what determines level of SE. The concept has been developed, as described by Tait et al (2002), to include four dimensions: adherence, appointment keeping, help-seeking behaviour and therapeutic alliance. The aim of the study is first to establish the extent of SE in the follow up population, so that this can then be compared to that found in other FEP populations in different services. The home-based treatment model of service delivery applied by Cavan/Monaghan Mental Health Service has characteristics that could potentially increase or decrease SE at follow-up and there has been no research to date which has explored this issue. Second, it has not been established whether specific psychotic diagnosis has an impact on SE, another question which this study explores. Third, whilst it is not possible to establish whether there is a predictive relationship between SE at baseline and functional outcome, as it was not part of the initial assessment battery, it is possible in this study to see whether there

is a cross-sectional relationship between SE and functioning. Last, the study aims to investigate, using data collected at initial assessment, whether there are any reliable predictors of future SE that might service as indicators of those patients less likely to engage with treatment and therefore requiring more assertive methods of follow-up.

Geography, population and mental health service characteristics

Geography

Cavan/Monaghan Mental Health Service is the psychiatric catchment area service for the counties of Cavan and Monaghan. These two counties are located in the province of Ulster but are part of the Republic of Ireland; they are inland counties which share borders with the Northern Ireland counties of Armagh and Fermanagh (Figure 1). The counties combined have an area of 3225 square kilometers. The landscape is predominantly rural and is comprised in the main of small farms. It is characterised by the presence of small hills called drumlins, typically 10 – 30 meters in height. The intervening ground is characterized by multiple small lakes and by boggy soil due to the poor drainage qualities of boulder clay. There are larger areas of bogland in the north of Co. Monaghan, but there are few areas of the two counties that are uninhabited. The largest towns are Monaghan, Co. Monaghan, with a population of 6 221, and Cavan, Co. Cavan, with a population of 3 934 (Central Statistics Office, 2006).

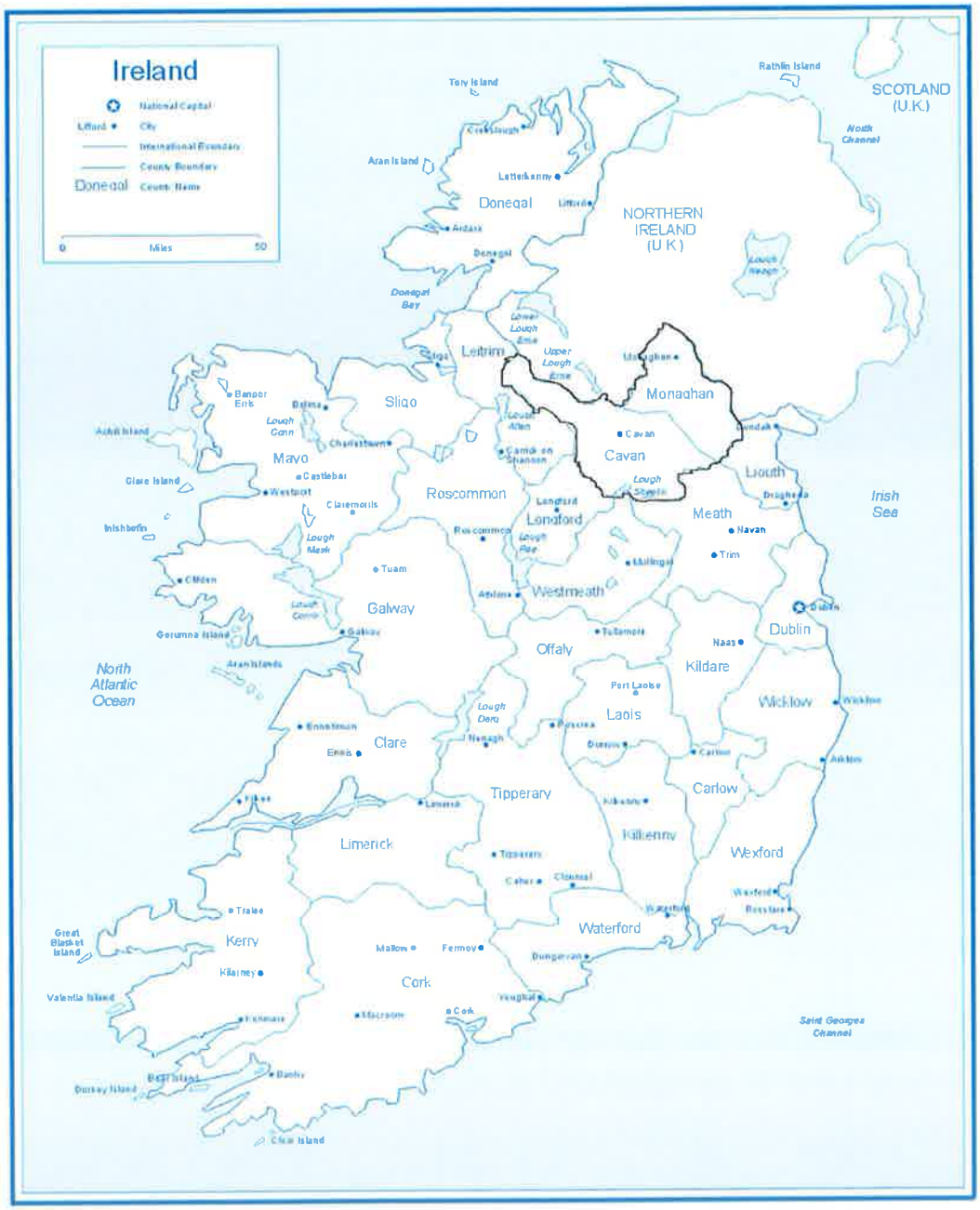
Population at 2006 census

The total population of the two counties at the 2006 census was 120 000, with 64 003 in Co. Cavan and 55 997 in Co. Monaghan. The total population of the Republic of Ireland was 4 239 848. The increase in population since the last census in 2002 was 6.5% in Co. Monaghan and 13.5% in Co. Cavan, compared to 8.2% in the country as a whole. Population growth in recent years can therefore be taken to be generally similar in the region as a whole to that seen country-wide. Sex breakdown in the two counties differs slightly from the country as a whole, with males slightly outweighing females in both counties. These data are summarised in Table 7.

Table 7: Total population in Ireland/Cavan/Monaghan in 2006, by sex

Area	Total population	% change since 2002	% male	% female
Ireland	4 239 848	+8.2	50.0	50.0
Cavan	64 003	+13.2	51.0	49.0
Monaghan	55 997	+6.2	51.4	48.6

Figure 1: Map of Ireland, with counties Cavan and Monaghan outlined.



Some other characteristics of the population differ slightly from those of the country as a whole. Table A1 (Tables A1 – A11 to be found in Appendix) enumerates the breakdown of the population by decades of age for Cavan, Monaghan and the state. There is a greater preponderance of individuals in the age range 0 – 19 and relatively fewer for 20 – 39.

Between the ages of 40 – 69 frequencies are similar. However, there are more individuals in the 70 – 80+ age range in Cavan and Monaghan. The area is also somewhat more stable geographically over time (Table A2), with a slightly higher percentage being resident at the same address for the year preceding the census. A higher percentage of the population is Irish by nationality, thus increasing the ethnic homogeneity in the two counties compared to the rest of the country (Table A3). Table A4, however, clearly shows that there has been considerable change since 1996 in this regard, not only in Ireland as a whole but also in the Cavan/Monaghan region, with a rise in immigration over this period.

The 2006 census also revealed that there is more socioeconomic homogeneity in these two counties compared to the rest of the country, with lower percentages populating the professional/employer/non-manual classes, and a greater percentage in the manual/farming group of classes (Table A5). Table A6 demonstrates that there are some differences in marital status in the border counties as compared to the country as a whole. Data for the border counties (Cavan, Monaghan, Leitrim, Donegal, Louth and Sligo) are quoted, as figures are given on the basis of larger regions with regard to marital status. The other four counties share general sociodemographic and geographic characteristics with the counties of Cavan and Monaghan. Between the ages of 15 and 24, there is little difference between this region and the rest of the country. Between the ages of 25 and 44, more people in the region define their marital status as other than single (married, divorced, separated, widowed) relative to Ireland as a whole. Between the ages of 45 and 74, a greater number of men but fewer women are single in this region compared to the country as a whole. Above this age, in general there are more single women than men; however, smaller numbers and differing patterns of longevity make it difficult to infer social trends. Regarding unemployment statistics, the figures available again refer to the border counties, where unemployment figures are somewhat higher compared to Ireland as a whole. These figures relate to the first quarter of 2007 and to the percentage of the population available for employment that are unemployed (Table A7). Table A8 shows the age at which those who have completed full-time education finished their education in Ireland, Cavan and Monaghan. In the two counties, age at which education is completed is markedly lower than in the rest of the country. Size of family units in the Cavan/Monaghan region also differs from the rest of the country, with

these differences being particularly evident when compared to the number of people in family units in Dublin City (Table A9). Households containing one individual are considerably less common in Cavan/Monaghan, with the difference narrowing for households of 2, 3 or 4 individuals. Households of 5 or 6+ individuals are considerably more frequent in Cavan/Monaghan compared to the rest of the country. No specific figures on rates of alcohol and substance misuse are available for Cavan/Monaghan. The best figures available are those published in 2005 (National Advisory Committee on Drugs) based on a sample of 8 434 individuals who were interviewed in 2002/3 about their drug and alcohol use. Specific figures for Cavan/Monaghan are not available; figures are presented by Health Board area. Cavan and Monaghan are included in the figures for the North Eastern Health Board (NEHB). However, much of the population in this region resides in large urban centres having considerable problems with substance abuse, such as Dundalk and Drogheda, which are located in other counties. Yet, prevalence of alcohol and illicit substance use is still lower in each instance in the NEHB compared to the rest of the country (Table 8).

Table 8: Percentage of adults age 15-64 years using drugs and alcohol in Ireland and the North Eastern Health Board area in past month (2007)

Substance	Ireland	North Eastern Health Board
Any illegal drugs	3.0	2.4
Cannabis	2.6	1.9
Heroin	0.1	-
Methadone	0.1	-
Cocaine	0.3	-
Amphetamines	0.2	0.2
Ecstasy	0.3	-
LSD/magic mushrooms	0.1	-
Alcohol	74.0	71.2

The sociodemographic profile of the population of Cavan/Monaghan therefore has a number of characteristics which are relevant to both the FEP and follow-up studies, both in general

terms and when compared to the population of Ireland as a whole. First, the slight overall preponderance of males should be taken into account when considering numbers in each diagnostic category, for some of which sex is a risk factor. Second, incidence of some of the conditions, in particular SZ and BD, peaks in late adolescence/early adulthood. The age structure of the population of Cavan and Monaghan is unlikely to have a significant effect on numbers in these diagnostic categories compared to the country as a whole, as although there are more 0 – 19 year olds this is balanced by the fact that there are fewer individuals between the ages of 20 – 29. MDDP will be seen to have an older age at onset and it might therefore be hypothesised that this may interact with the population's age structure in the Cavan/Monaghan region to give a relatively high incidence of the disorder. The age groups 40 – 69 have similar numbers to those found in the country as a whole, while the age groups 70 - 80+ are relatively populous in the two counties. It might thus be expected that the rate of MDDP could be higher than elsewhere. The relative geographical stability over a period of one year for the two counties should impact positively on obtaining a high rate of follow-up in the study. This is particularly evident when geographical stability in the area is compared to urban areas such as Dublin, where the population is more transient.

There is a considerable degree of ethnic homogeneity in the Cavan/Monaghan area. This minimises any effect of immigrant status on the incidence of psychotic disorder in this study. However, whilst ethnic homogeneity rates remain high, there has been some increase in immigration in Cavan/Monaghan over the past decade, as recorded to a greater extent over the rest of the country. Employment categories in the region may impact on the follow-up study. The categories E (skilled manual), F (semi-skilled manual), G (unskilled manual), H (own account worker), L (farmer) and J (agricultural worker) are more common, with categories A (employer/manager), B (higher professional), C (lower professional), D (non-manual) and Z (unknown) being less common. The more frequent categories in the area are, in the main, types of work that would be more accessible to individuals who experienced the onset of an illness that involved functional decline during the period of their lives when they would otherwise have been receiving formal occupational training; farming, agricultural work, semi-skilled and unskilled manual labour require less formal training in comparison to other employment categories and are probably more flexible in the context of individuals

with serious mental illness who may have their employment history interrupted by periodic relapses. Many households are located on small farms that are no longer financially viable in today's agricultural market, though frequently these continue to be farmed on a part-time basis.

In summary, the population of the region is, relatively speaking, typical of rural populations in that it is characterised by a considerable degree of sociodemographic and geographic stability. Thus, data on incidence may be inferred to be representative of other rural populations in other parts of the country and indeed elsewhere in the world. With regard to the impact of the social characteristics of the region at follow-up, the lower frequency of single marital status, the higher rate of unemployment in the region, the fact that deficiencies in functioning may be obscured by the greater availability of less challenging occupations and the greater likelihood of living in larger family units all have the potential to impact on follow-up findings.

Mental health service characteristics

Cavan/Monaghan Mental Health Service is provided on a strict catchment area basis and serves a total population of 120 000. The service is subdivided into Child Psychiatry (up to age 16 years), Community Mental Health (ages 16 – 65 years) and Psychiatry for the Elderly (age 65+ years). There is also a Community Rehabilitation team who provide an assertive outreach service to those with chronic, severe mental health problems. There are four consultants in General Adult Psychiatry, one Consultant in Psychiatry for the Elderly, one Consultant in Community Rehabilitation Psychiatry and two Consultants in Child & Adolescent Psychiatry. There is also one Consultant in Intellectual Disability who is based in Co. Louth but provides a service to the Cavan/Monaghan region.

The mental health service operates from two principal locations: St Davnet's Hospital in Monaghan town, and Cavan General Hospital in Cavan town. In each of these locations a small number of inpatient beds are provided. However, the service uses the home-based treatment model of care, whereby most patients in need of a higher level of care than that

provided by outpatient services and Community Psychiatric Nurse input are managed in their homes by a multidisciplinary home-based treatment team, thus avoiding inpatient admission. This mode of service delivery was implemented in 1998 in Monaghan and in 1999 in Cavan, with the establishment of Psychiatry for the Elderly and Community Rehabilitation teams in 1999. The FEP study thus spans the introduction of the new service model (McCauley, 2003). Some of the results of the introduction of the model have been a reduction in admission rates and bed days in the two units, as well as lower rates of involuntary admission under the Mental Health Act 2001; over this period, the trend over the rest of the country was for higher rates of involuntary admission. However, it has been observed that this model of care is more easily delivered in areas with demographic characteristics such as those of Cavan/Monaghan, namely where good family support is the norm and substance abuse and homelessness are not substantial problems. From the point of view of this study, one of the impacts of this model of care delivery on achieving a high level of follow-up is that there are generally good links between patients and mental health professionals in terms of awareness of patients' circumstances and location. In addition to the two principal service locations, there are outpatient centres and day care centres at four additional locations (Carrickmacross and Ballybay in Co. Monaghan and Virginia and Bailieborough in Co. Cavan). As these two counties cover a large but relatively sparsely populated area, with poor transport links, it is important from a service delivery perspective that the distances people need to travel to the nearest clinic are minimised. Similarly, the presence in these centres of nursing staff with good local knowledge facilitates the process of making contact with patients for follow-up. One of the emphases of the service is on having excellent links with primary care, with consultant psychiatrists providing some liaison sessions in GP surgeries (Russell et al, 2003). These links were also of considerable advantage when looking to follow up patients who had participated in the FEP study but were no longer in contact with mental health services. The characteristics of the service therefore made the Cavan/Monaghan region an ideal place in which to carry out this study, where poor rates of follow-up are the greatest challenge to obtaining meaningful results.

Methods

Ethics approval

Approval for the initial FEP study was obtained from the Research Ethics Committee of the North Eastern Health board (now Health Service Executive North East) in 1995 and is renewed approximately every five years, with the most recent renewal having been granted in December 2005. Approval for the FEP study was also granted by the Research Ethics Committees of St. Patrick's Hospital and St. John of God Hospital, the two main private psychiatric hospitals in Dublin, to seek and assess patients from Cavan and Monaghan who choose to access psychiatric services through the private health care system; approval was granted by both institutions to extend the study to include the FEP follow-up study. In 2006, approval was also applied for and granted by the Research Ethics Committee of the Central Mental Hospital, the national forensic psychiatry facility, to seek, assess, and follow up cases that presented for the first time with psychosis to the forensic services; approval was granted to search the records of the Central Mental Hospital retrospectively, to cover the period from the inception of the FEP study in 1995 onwards. A patient information sheet was provided to all prospective cases prior to assessment detailing the purposes of the study, why the patient had been selected, the nature of the study, confidentiality issues and the fact that treatment would not be affected by declination to participate. Consent was obtained in writing on a consent form, in accordance with the approval granted by each institution. Approval to record demographics and clinical histories to allow case-note diagnoses for those declining assessment was granted by each of the above institutions.

Ascertainment of incident cases

Inclusion and exclusion criteria

Inclusion criteria for eligibility for the FEP study are presence of a first episode of psychotic illness, to include a first manic episode, and residency in the Cavan/Monaghan Mental Health Service catchment area, i.e., the counties of Cavan and Monaghan.

The only exclusion criteria are:

- Age less than 16 years, as stipulated by the Research Ethics Committee
- Psychosis in the context of a pre-existing primary diagnosis of gross neurodegenerative disease, such as Alzheimer's disease, Huntington's disease or Parkinson's disease
- Individual not resident in the catchment area for a period of three months or longer
- Previously treated psychotic illness, either inside or outside the catchment area

Individuals who were studying or in employment outside the two counties but who resided during the weekends in Cavan/Monaghan, for example students or people working outside the counties, were eligible for the study. Also included were those who were resident in the county but who received their care outside the counties in one of the two main private psychiatric hospitals or the national forensic services, each based in Dublin. Similarly, those found to have a previously treated episode of psychotic illness that was not detected at initial presentation but occurred over the timeframe of the FEP study were included in the study, with retrospective assessment from case-notes in relation to their first presentation.

Cavan/Monaghan Mental Health Service

Incident FEP cases were ascertained via a process of close liaison with the psychiatric teams within the catchment area. This process involved: attendance at the weekly acute team meetings where new referrals were discussed; a hand search of the records of new referrals; weekly contact with the inpatient units; weekly personal contact with members of each consultant team (with the exception of the Psychiatry for the Elderly team, who were contacted on a fortnightly basis, and the Intellectual Disability team, who were contacted on a six monthly basis); and approximately twice weekly contact with the home-based treatment teams.

Private psychiatric hospitals

In Ireland, 98% of private psychiatric admissions for psychosis and affective disorder are to St. John of God Hospital in South Dublin and St. Patrick's Hospital in the centre of Dublin (Daly & Walsh, 2000). As described above, approval has been granted by both hospitals to search for and assess cases of psychosis admitted from Cavan or Monaghan which meet inclusion criteria for the FEP study. When cases were identified, specific consultant permission was sought to initiate contact with each patient in question, via his/her consultant.

Central Mental Hospital

Since 2006, approval has been in place to permit the search for and the assessment of patients who met inclusion criteria for the FEP study and had a forensic presentation of their illness. The Central Mental Hospital is the only forensic psychiatric facility in the country and provides outreach psychiatric clinics to the national prison service. A search of the admission register of the hospital revealed two patients who were retrospectively included in the FEP study and in long-term follow-up.

Identification and tracing of follow-up cases

The 202 individuals to be followed up were identified from the FEP dataset. These individuals experienced the onset of psychotic illness in the Cavan/Monaghan Mental Health Service catchment area between June 1995 and May 2003 and met inclusion and exclusion criteria for the FEP study as described above at the time of onset of illness. The number to be followed up increased from 200 during the two year period of the study, due to retrospective inclusion of the two cases identified from examination of the Central Mental Hospital admissions records.

Principals governing patient tracing

One of the key tenets determining the mode of contact with patients for participation in the follow-up study was that initial contact should be made by an individual with whom they had

previous clinical contact. Given the fact that in some cases 12 years had elapsed since what might have been a first and only episode, it was felt that it needed to be handled with sensitivity, so that potential participants did not feel that their confidentiality had been violated. The intention was to minimise risk that they be taken by surprise from unforeseen contact from an individual unknown to them, who was unfamiliar with aspects of their personality and belief system, such as degree of receptivity to contact from health care professional, their attitude towards their previous episode of illness and their feelings about the service they had received at a vulnerable time of their lives. This resulted in a process of tracing potential participants that had (a) the disadvantage of being time consuming and reliant on the cooperation of a large number of other healthcare professionals but (b) the considerable advantage of greater acceptibility to those being contacted and the resultant benefit of being more likely to result in their cooperation. In cases where a person declined to participate, approval had been granted by the Research Ethic Committee to perform an objective assessment of diagnosis, functioning, quality of life and SE on the basis of information gathered from their current keyworker, whether a mental health professional or GP, and their clinical casenotes.

Electronic and medical records

Once name and date of birth had been identified for each individual, a search of the hospital electronic record of contact was performed in order to identify those individuals still in contact with the service and their point of contact. For those who were no longer in contact with the service, a search of the medical notes was performed in order to gather information on address, GP and past keyworkers. A notice was placed on the front of each candidate's medical chart identifying them as a potential candidate for the study and requesting the mental health care professional (i) to ask them if they would be willing to participate, and (ii) then contact the clinical research fellow with the outcome of the request. For the small number of charts that were missing, as many details as possible regarding possible whereabouts were gleaned from the dataset to facilitate tracing.

Mental health teams

The next step was to make contact with the individual clinical teams to establish, for those patients still in contact with the service, when their next appointment was and with whom. The strategy used was to attend a team meeting with as many members of that team as possible and, at the start of the meeting, to run through all the individuals thought to be in contact with the team in order to gain the above information. The relevant health care professional could then be prompted before the next appointment so that the subject's degree of willingness to accept further contact from the clinical research fellow could be assessed. Community psychiatric nurses (CPNs) were extremely important in this process. They maintain occasional contact with a very large proportion of individuals with a history of psychosis, including those who still have a high degree of service need but also those who are relatively well but are likely to benefit from some level of ongoing contact in order to maintain links with the service in case of future need of assistance. The quality of the relationships established by the CPNs with candidates made the process of tracing potential participants and gaining their cooperation much easier than might otherwise have been the case. As described in *Principals governing patient tracing* above, for those who declined to participate, objective information on the patient's current status was obtained on the basis of an interview with the mental health care professional and this process pertained to any other keyworker (GP, psychiatrist from another service) identified, as long as they had regular contact with the patient within the past year.

Primary care

For those individuals who were no longer under the care of the mental health services (approximately 50% of participants), the next point of contact in the process of tracing was their GP. A record of the person's GP was noted from the contact details contained in their medical notes or from correspondence with GPs contained in their medical notes or on the service computerised system. Telephone contact was made with the GP in the first instance to establish whether or not the person still attended them and, if not, who their new GP was. The relevant GP was then requested to inform the patient about the study and ask them if

they would be willing to participate, either when the patient next attended a GP appointment or by telephone if the GP felt comfortable doing this. If the candidate was willing to participate, they were informed that the clinical research fellow would make contact with them to arrange an assessment appointment.

Private psychiatric hospitals and national forensic service

A small number of FEP cases (n=5) had been identified in accordance with approval granted by St. John of God Hospital, St. Patrick's Hospital and the Central Mental Hospital. Approval had also been granted to follow up these individuals. This was achieved through contact with their treating psychiatrist who was requested to ask the patient if they were willing to participate and be contacted by the clinical research fellow.

Mental health services other than Cavan/Monaghan

In a small number of cases (n = 3) the participant had moved out of the catchment area and was now being treated by another Mental Health Service. In these instances, similar procedures were followed as for primary care, substituting treating psychiatrist for GP.

Other statutory community agencies

In cases where there was difficulty identifying a current address for a subject, other community agencies were utilised, such as the Garda Síochána (police), Medical Card Offices and Community Welfare Officers. Once an address was identified, all GPs in the area were contacted to establish the GP currently providing care.

Births, Marriages & Deaths

The Births, Marriages & Deaths Offices for Cavan and Monaghan were contacted with a list of all names of individuals who were thought to be deceased by health care professionals or who had not been traced successfully through the above means. The Officer provided death

certificates for all individuals who were deceased and from these date and cause of death were noted and included in the dataset.

Assessment of incident cases

Assessment of incident cases, where the individual consented to participate, was usually arranged through their keyworker for the earliest possible time after detection of the case, balancing the importance of the person being assessed whilst still symptomatic with the need of the treating team to maintain a good therapeutic relationship with the patient. The assessment took place either on the ward, in an outpatient clinic or in the patient's home. The assessment instruments include the following:

Structured Clinical Interview for DSM IV (SCID IV)
Positive and Negative Syndrome Scale (PANSS)
Mini-Mental State Examination (MMSE)
Executive Interview (EXIT)
Edinburgh Handedness Inventory (EHI)
Neurological Evaluation Scale (NES)
Condensed Neurological Evaluation (CNE)
Abnormal Involuntary Movement Scale (AIMS)
Simpson Angus Scale (SAS)
National Adult Reading Test (NART)
Scale of Unawareness of Mental Disorder (SUMD)
Beiser Scale for duration of untreated illness and duration of untreated psychosis
Premorbid Adjustment Scale
Family history interview
Obstetric history interview

Additional demographic and clinical data was recorded, including date of birth, sex, marital status, living status, smoker/non-smoker, father's occupation, district electoral division of

birth and at onset, co-morbid DSM IV diagnoses in addition to the primary psychotic diagnosis and medications used and dates on which these were first prescribed.

A clinical research fellow has been employed since 1995 to carry out these assessments. During this time, six successive fellows have occupied the post. To enhance inter-rater reliability, each outgoing research fellow is involved in instructing the incoming research fellow in their use; each incoming fellow and the incumbent also attends training sessions in the administration of assessment instruments in the St. John of God Psychiatric Service FEP Programme in Dublin (Browne et al, 2000), which has close academic ties with, and employs methodology similar to that of, the Cavan/Monaghan First Episode Study.

Six month follow-up

At six months after initial presentation, the individual's chart is reviewed and the case discussed with their keyworker. On the basis of all available information, a second DSM IV diagnosis is determined without reference to inception diagnosis.

Assessment of follow-up cases

Assessment of individuals identified as subjects for the study was arranged via phone contact with the participant or through their keyworker, at a time and place convenient to the subject; location for the assessment was either in the participant's home or in one of the mental health service facilities. In one case, face-to-face assessment was not possible and the assessment was carried out over the telephone. In all cases, information from a number of different sources was used to inform ratings, including the participant themselves, keyworkers, medical and nursing notes and family members. Where an individual declined to be assessed, assessment was carried out on the basis of keyworker history following interview with that keyworker in one of the mental health service facilities or in the primary care setting when the person was now being treated by their GP. Additional sources of information were used when available. In a number of cases, the interview with a GP or keyworker was carried out

over the telephone when it was not possible to carry out a face-to-face interview. The assessment instruments included the following:

Structured Clinical Interview for DSM IV (SCID IV)
Positive and Negative Syndrome Scale (PANSS)
Health of the Nation Outcomes Scale (HoNOS)
Global Assessment of Functioning (GAF)
Strauss-Carpenter Levels of Functioning Scale
Specific Levels of Functioning (SLOF)
Quality of Life Scale (QLS)
World Health Organisation Quality of Life – short version (WHOQOL-Bref)
Service Engagement Scale (SES)

Additional demographic and clinical information was also recorded, including age at follow-up, number of months to follow-up, alive/dead/suicide, marital status, living status, medication, location of treatment, co-morbidity at follow-up and place of assessment.

A single investigator was responsible for the assessment of all follow-up cases, thus ensuring uniformity of use of the above instruments and eliminating the need for inter-rater reliability. The investigator could not be formally blind to initial diagnosis and other data obtained at FEP assessment but an ideal of strict objectivity was maintained and, in the majority of cases, the investigator was not aware of diagnosis at presentation when assessing this at follow-up. Because diagnoses at initial presentation were made by five different individuals, the possibility of systematic error resulting from an idiosyncratic difference in diagnostic practice between two individuals was reduced. In no instance was the follow-up investigator aware of scores on other instruments, either at inception or follow-up.

Assessment instruments – first episode psychosis study

Diagnosis: Structured Clinical Interview for DSM Axis 1 Disorders

The research version of the Structured Clinical Interview for DSM (Diagnostic and Statistical Manual, American Psychiatric Association 1994) Axis 1 Disorders (SCID) (First et al., 2002) is a semi-structured interview schedule for making DSM IV-based Axis 1 psychiatric diagnoses. It is widely used for research and clinical purposes and, via a suggested order of questions relating to psychopathological as well as personal and socio-economic details, guides the interviewer through a diagnostic algorithm. There are a number of sections, respectively relating to affective symptoms, psychotic symptoms, psychotic diagnosis, affective diagnosis, substance abuse disorders, anxiety disorders, somatoform disorders, eating disorders and adjustment disorder. Information from other sources, including casenotes and collateral from relatives and keyworkers, was used in addition to information resulting from patient interview in order to make the most accurate diagnosis possible. Semi-structured interviews such as this have been designed to improve on the limitations and inaccuracies of routine clinical diagnosis. The LEAD diagnosis developed by Spitzer (1983) is a longitudinal assessment (L) performed by expert diagnosticians (E) using all data (AD) sources available, including medical records, keyworkers and relatives. This diagnosis, despite difficulties in its implementation, is the closest available approximation to a 'gold standard' available. Comparison of the SCID to the LEAD shows that validity of the SCID is superior to that of standard clinical interview at initial presentation for most diagnoses, including psychotic disorders (Fennig et al., 1994b) and substance abuse disorders (Kranzler et al., 1995).

The use of the SCID involves a specific training procedure. This was carried out as recommended by the guidelines (SCID Training Sequence of Steps, 2008). First, the SCID User's Guide and accompanying videos were studied. Next, the researcher sat in on interviews where clinical researchers already trained in using the assessment instrument were performing the SCID. These clinical researchers were post-membership psychiatrists who

were engaged in FEP research in St. John of God Psychiatric Service in Dublin. The researcher performed supervised SCID assessments and then the researcher performed the assessment alone. At each of the last three stages, the assessments were followed by a detailed discussion with the more expert clinical researcher on difficulties and diagnostic issues that might have arisen during the assessment.

A diagnosis not included in the primary SCID algorithm but which appears as an appendix in DSM IV (see DSM-IV: ''Criteria Sets and Axes Provided for Further Study'') is Simple Deteriorative Disorder (SDD). The present finding elaborates to the first-episode setting an evolving contemporary literature on a rare, 'rediscovered' entity that is best encapsulated as a form of schizophrenia (Kendler et al, 1994; Galderisi et al, 1991; Serra-Mestres et al, 2000). One case was identified at onset, with this diagnosis evolving to one of SZ at follow-up.

Psychopathology: Positive and Negative Syndrome Scale

The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1986) is a 30-item scale that was designed to measure symptoms in schizophrenia patients but is also used more generally in any patient with psychosis. The wide range of symptoms rated in the PANSS, including general and affective as well as positive psychotic and negative symptoms, makes it suitable in a study such as this which seeks to quantify and examine the differences between all of the diagnoses in the psychosis spectrum. Each item is rated on the basis of general clinical assessment, supplemented by information from casenotes, keyworkers and relatives where possible. There are three sections: positive symptoms, negative symptoms and general psychopathology, each of which is scored on a seven point Likert scale ranging from 1 (normal) to 7 (extremely severe). Accompanying guidelines give specific instructions relating to how each item should be rated on that scale. As well as generating a subscale for each of the sections, a further five subscales are generated from selections of the items, namely anergia, thought disturbance, activation, paranoid belligerence and depression. Training in the use of the scale was undertaken at the same time as training in the SCID under the tutelage of experienced researchers. It has been shown to be reliable both in SZ

and in psychotic mood disorders (Purine et al., 2000; Bell et al., 1992). The five-factor structure has also been shown to have good internal consistency (Lancon et al., 2000). An article reviewing five studies of the PANSS indicates its good criterion and predictive validity (Kay et al., 1987).

Global cognitive function: Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) is a very widely used rating scale developed by Folstein et al (1975) and used to detect the presence of general cognitive impairment. It has been shown to have satisfactory reliability and construct and criterion validity (Tombaugh & McIntyre, 1992).

Executive function: Executive Interview

The Executive Interview (EXIT) was developed in 1992 (Royall et al., 1992) and is used to measure executive functioning. It has both general applicability, including patients unable to complete more incisive instruments such as the Wisconsin Card Sort Test, and ecological validity (Royall et al., 1993) in SZ.

Handedness: Edinburgh Handedness Inventory

The Edinburgh Handedness Inventory is an assessment instrument investigating individuals' preference for right/left hand/foot/eye (Oldfield, 1971). It shows good test-retest reliability and is widely used as a measure of handedness (Ransil & Schachter, 1994).

Neurological soft signs I: Neurological Evaluation Scale

The Neurological Evaluation Scale (NES) is an assessment instrument which was designed for use in SZ to examine for the presence of neurological soft signs (Buchanan & Heinrichs, 1989). Its subscales show good construct validity (Sanders et al., 2000).

Neurological soft signs II: Condensed Neurological Examination

The Condensed Neurological Examination (CNE) was also developed specifically for use in patients with SZ (Rossi et al., 1990).

Insight: Scale to Assess Unawareness of Mental Disorder

The Scale to Assess Unawareness of Mental Disorder (SUMD) is an objective rating of a subject's degree of insight into each of a given list of symptoms that they may have now or have had in the past (Amador et al., 1993). This scale has been shown to have good reliability and validity (Amador et al., 1994)

Quality of life: Quality of Life Scale

The Quality of Life Scale (QLS) was designed specifically for use in SZ (Heinrichs & Carpenter, 1984). It provides a clinician rating of QOL based on patients' self-report and the interviewer's assessment of their current life circumstances. It consists of 21 items, each rated on a scale of 0 – 6. There are three subscales, namely Interpersonal Relations & Social Network, Instrumental Role Functioning & Intrapsychic Foundations and Common Objects & Activities. It has been shown to have acceptable levels of validity (Lehman, 1996) and reliability (Heinrichs & Carpenter, 1984).

Antipsychotic-induced movement disorder I: Simpson-Angus Scale

The Simpson-Angus Scale (Simpson & Angus, 1970) is a commonly used 10-item instrument used to evaluate the presence and severity of parkinsonian side-effects of antipsychotic medication. It has been shown to have good reliability and validity (Janno et al., 2005).

Antipsychotic-induced movement disorder II: Abnormal Involuntary Movement Scale

This scale was designed to identify and quantify the presence of involuntary movements, most typically tardive dyskinesia (TD), in patients with psychotic illness who may or may not be taking antipsychotic medication (Guy 1976). The scale has been shown to have good reliability (Schooler & Kane, 1982) and validity (Smith et al., 1979)

Pre-morbid intelligence: National Adult Reading Test

The National Adult Reading Test (NART) developed by Nelson (1982) measures reading ability and is used as a measure of pre-morbid intelligence, given that reading ability is highly correlated with general intellectual ability in the general population and is relatively well-preserved even in groups where intellectual ability has declined (Bright et al., 2002). It has excellent internal consistency (Crawford et al., 1988), test-retest and inter-rater reliability (Crawford et al., 1989) and validity when compared to other tests of verbal IQ but less so when compared to other tests of performance and general IQ (Spreen & Strauss, 1998).

Duration of untreated psychosis: Beiser Scale

This instrument (Beiser et al., 1993) measures the duration between the emergence of first noticeable behavioural abnormality, first noticeable psychotic symptoms and receipt of treatment, to allow determination of duration of untreated illness (DUI) and DUP. The instrument has been shown to have good inter-rater reliability (Beiser et al., 1993).

Premorbid functioning: Premorbid Adjustment Scale

The Premorbid Adjustment Scale (PAS, Cannon-Spoor et al., 1982) measures functioning prior to the onset of psychosis. The scale has been shown to have good reliability and validity (Krauss et al., 1998).

Family history

Family history is recorded on the basis of information from both the subject and relatives where available. A family tree of psychiatric illness is recorded, including all convincing histories of psychotic and non-psychotic psychiatric illness.

Obstetric complications

Obstetric complications are recorded on the basis of a semi-structured interview with the patient's mother (Lewis & Murray, 1987). This records the presence or absence of a wide range of pre-, peri- and post-natal complications.

Assessment instruments – first episode psychosis follow-up study

Diagnosis: Structured Clinical Interview for DSM Axis 1 Disorders

This instrument has been described in the FEP study section above.

Psychopathology: Positive and Negative Syndrome Scale

This instrument has been described in the FEP study section above.

Functioning I: Global Assessment of Functioning

This measure of functioning used in the FEP follow-up (FUFEP) study is widely used and forms part V of the DSM-IV assessment and axial classification of mental disorder. It was developed by Spitzer et al (1996), based on an earlier version (Global Assessment Scale), and is used to evaluate psychological, social and occupational functioning along a continuum of mental health-illness. The most severe disorder of functioning on any of the three dimensions (psychological, social and occupational) is considered in the overall score, which consists of a single rating between 0-100, with 100 reflecting optimal functioning in all domains. The scale is divided into domains of ten points, with an 'anchor' description being given of the psychological, social and occupational profile included within each ten-point domain. Interrater reliability of this instrument in a clinical setting for which it was designed has been extensively studied and is summarised as being variable (Vatnaland et al., 2007). However, the same study indicates that inter-rater reliability is very high when it is used in a research setting.

Functioning II: Health of the Nation Outcome Scale

The Health of the Nation Outcome Scale (HoNOS) was developed by Wing et al (1996, 1998) to measure the social functioning and health of people with severe mental illness. It was commissioned by the Royal College of Psychiatrists' Research Unit in order to follow progress of the health service target of improving the social functioning of people with mental illness. The scale consists of 12 items which examine behaviour, impairment, symptoms and social functioning; they are completed on the basis of clinician impression following assessment. The scale has been assessed for acceptability, usability, sensitivity, reliability and validity and has been found to be adequate in each of these domains (Amin et al, 1999b).

Functioning III: Strauss-Carpenter Levels of Functioning Scale

This assessment instrument was designed for use in individuals with a diagnosis of schizophrenia (Strauss & Carpenter, 1972) on the basis of clinician impression following enquiry during assessment of each of the domains included (symptoms/illness, social functioning, occupational functioning, activities of daily life and general functioning). It is comprised of nine items, each of which is marked on a scale of 0-4, with higher values reflecting higher functioning. This scale has been shown to have good sensitivity to change and moderate-high validity (Cramer et al., 2000).

Functioning IV: Specific Level of Functioning Assessment

This scale is a multidimensional behavioural rating instrument developed to help clinical staff working in a mental health setting to plan treatment for clients. It aims to rate directly observable behaviour and life skills (Schneider & Struening, 1983). It consists of 43 items, each of which is rated on a scale of 1-5, with 5 representing best functioning on any given item. Six subscales are yielded by completion of the scale: physical functioning, personal care skills, interpersonal relationships, social acceptability, activities and work skills. The

reliability and validity of the instrument are reported as being good (Schneider & Struening, 1983).

Quality of life I: Quality of Life Scale

This instrument has been described in the FEP study section above.

Quality of life II: World Health Organisation Quality of Life-Bref

This scale to assess quality of life was developed from another instrument, the World Health Organisation Quality of Life-100 (WHOQOL-100) as a shorter version for use when the burden of assessment on the subject must be reduced (The WHOQOL Group, 1998). The 26 items were selected from the WHOQOL-100 on the basis of explaining a considerable proportion of the variance in the numerous domains contained in the longer version of the scale. The WHO Quality of Life-Bref (WHOQOL-Bref) contains four domains: physical health, psychological health, social relationships and environment. It has been shown to have good to excellent internal consistency, test-retest reliability and discriminant and construct validity (Skevington et al., 2004).

Service engagement: Service Engagement Scale

This is a relatively new scale developed by Tait et al (2002), following identification of the absence of an instrument measuring engagement with community mental health services. The scale consists of 14 clinician-rated items, each of which is rated on a scale of 0-3, with a score of 0 indicating good engagement with respect to each of the items. It consists of four subscales: availability, collaboration, help-seeking and treatment adherence. It has been shown to have good to excellent test-retest reliability, good internal consistency and good criterion validity. The factor structure of the instrument has not, however, been examined (Tait et al., 2002).

Data analysis and statistics

Descriptive statistics included determination of means, standard deviations and ranges for continuous variables and cross-tabulation of frequencies for categorical variables.

Comparisons across diagnostic groups were carried out using: (a) analysis of variance for main effects of diagnosis and sex and for diagnosis x sex interactions, and Student's t-tests (2-tailed), for continuous variables; (b) χ^2 tests for categorical variables.

Principal component analysis was applied across measures of function and of QOL to derive principal components, with determination of the proportions of total variance accounted for (Meagher et al., 2001, 2004). Relationships between these measures were determined using Pearson correlations.

Variable s predicting the principal component factors for function and for QOL were explored using multiple linear regression modeling (Meagher et al., 2001, 2004); each of forced entry, forward and stepwise models were applied and compared.

SPSS version 12 was used throughout these analyses, with the assistance of a statistician, Mr Anthony Kinsella, MSc, FIS.

Results

Demographic profile of participants

A total of 202 participants (mean age 36.0 years, SD 18.1; 121 males, mean age 32.4 years, SD 15.7; 81 females, mean age 41.5 years, SD 20.2; older age at onset among females, $p<0.05$) were identified as being eligible for follow-up, namely all those individuals identified in the Cavan/Monaghan catchment area with onset of psychotic illness over a period of eight years between the onset of the study in June 1995 and the end of May 2003. Of these, three presented to private hospitals in Dublin and two participants were identified through the forensic services. Of the 202 eligible cases, follow-up data was obtained on 196 (mean age 42.6 years, SD 18.6; 115 males, mean age 38.9 years, SD 16.3; 81 females, mean age 48.0 years, SD 20.3) during the period between January 2006 and May 2007, giving a follow-up rate of 97%. The reasons for which it was not possible to follow up the remaining six participants were as follows:

- Moved out of the country and untraceable (2)
- No chart or record of the patient identifiable (2)
- Records in private hospital and unable to access tracing details due to process of renewal of Research Ethics Committee approval so to do; this process was not completed within the timeframe of the study (2)

These six individuals represented the spread of diagnoses included in the study with one case having each of the following diagnoses at onset: SZ, BD, MDDP, SA, DD and PNOS. The mean age at onset for this group was 29.3 years (SD 9.2), which is somewhat younger than mean age at onset for the population as a whole.

Table 9: Number of FEP cases by diagnostic category and sex at onset

Diagnosis	Sex		Total
	Male	Female	
	n (%)	n (%)	n
SZ	25 (78%)	6 (22%)	31
SF	14 (64%)	8 (36%)	22
BrPsy	2 (15%)	11 (85%)	13
SA	1 (17%)	5 (83%)	6
BD	17 (53%)	15 (47%)	32
MDDP	18 (45%)	22 (55%)	40
DD	9 (69%)	4 (31%)	13
PGMC	2 (50%)	2 (50%)	4
SIP	12 (100%)	-	12
PNOS	10 (67%)	5 (33%)	15
SIM	4 (67%)	2 (33%)	6
SDD	1 (100%)	-	1
MGMC	-	1 (100%)	1
	115 (59%)	81 (41%)	196

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
BD Bipolar I disorder
MDDP Major depressive disorder with psychotic features
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
SDD Simple deteriorative disorder
MGMC Mania due to a general medical condition

Table 10: Number of FEP cases by diagnostic category and sex at six months

Diagnosis	Sex		Total
	Male	Female	
	n (%)	n (%)	n
SZ	34 (81%)	8 (19%)	42
SF	5 (45%)	6 (55%)	11
BrPsy	2 (20%)	8 (80)%	10
SA	6 (55%)	5 (45%)	11
BD	17 (50%)	17 (50%)	34
MDDP	17 (43%)	23 (57%)	40
DD	6 (60%)	4 (40%)	10
PGMC	2 (50%)	2 (50%)	4
SIP	11 (100%)	-	11
PNOS	8 (62%)	5 (38%)	13
SIM	4 (67%)	2 (33%)	6
SDD	1 (100%)	-	1
MGMC	-	1 (100%)	1
Suicide	2 (100%)	-	2
	115 (59%)	81 (41%)	196

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
BD Bipolar I disorder
MDDP Major depressive disorder with psychotic features
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
SDD Simple deteriorative disorder
MGMC Mania due to a general medical condition

Table 11: Number of FEP cases by diagnostic category and sex at six year follow-up

Diagnosis	Sex		Total
	Male	Female	
	n (%)	n (%)	n
SZ	42 (70%)	18 (30%)	60
SF	1 (33%)	2 (67%)	3
BrPsy	2 (50%)	2 (50%)	4
SA	16 (59%)	11 (412%)	27
BD	18 (51%)	17 (49%)	35
BDII	-	1 (100%)	1
MDDP	13 (48%)	14 (52%)	27
DD	2 (67%)	1 (33%)	3
PGMC	1 (33%)	2 (67%)	3
SIP	8 (100%)	-	8
PNOS	2 (50%)	2 (50%)	4
SIM	3 (50%)	3 (50%)	6
MGMC	-	1 (100%)	1
ALZ	-	1 (100%)	1
RIP	3 (33%)	6 (67%)	9
Suicide	4 (100%)	-	4
	115 (59%)	81 (41%)	196

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
BD Bipolar I disorder
BD II Bipolar II disorder
SDD Simple deteriorative disorder
DD Delusional disorder
RIP deceased natural causes/accident
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MDDP Major depressive disorder with psychotic features
MGMC Mania due to a general medical condition
Alz Alzheimer's disease

As can be seen in Tables 9, 10 and 11, 115 individuals were male and 81 were female. The diagnostic categories in order of populousness at onset are MDDP (n=40), BD (n=32), SZ (n=31), SF (n=22), PNOS (n=15), DD (n=13), BrPsy (n=13), SIP (n=12), SA (n=6), SIM (n=6), PGMC (n=4), MGMC (n=1) and SDD (n=1).

When diagnoses were re-examined at six months, a rise in cases of SZ is observed, which then becomes the most populous diagnostic category (n=42); no change in MDDP is seen (n=40), with a small increase in BD (n=34); SF has declined markedly (n=11), whereas there has been a marked increase in SA (n=11); other categories which have lost a small number of cases to other diagnoses include PNOS (n=13), DD (n=10) and SIP (n=11). PGMC (n=4), SIM (n=6), SDD (n=1) and MGMC (n=1) have all remained the same in terms of caseness over the first six months following inception into the study. There were two suicides over the first six months.

By follow-up [mean duration since onset 6.4 (SD 2.3) years] SZ has shown a further rise in caseness (n=60); the next most common diagnosis is SA (n=27) which has shown a marked increase over the follow-up period; the only other diagnostic category to have seen an increase is BD (n=35), with decreases in MDDP (n=27), SF (n=3), BrPsy (n=4), PNOS (n=4), DD (n=3) and SIP (n=8); smaller decreases were seen in PGMC (n=3); for SIM (n=6) and MGMC (n=1), caseness remained the same; one case of MDDP had evolved into BDII by follow-up. One individual had gone on to develop Alzheimer's disease after their six month diagnosis; in retrospect, the cause of their initial psychotic symptoms may have been influenced by this disorder. By time of follow-up there had been nine deaths from natural or accidental causes and four cases of suicide, as described further below.

Changes in caseness by sex within each of these diagnostic categories over the period of the study are also observable (Tables 9-11). For SZ, the sex balance is stable over the first six months with a male:female (M:F) ratio of 4.2:1 at onset and 4.3:1 at six months. However, by follow-up proportionally more females than males have moved into this diagnostic category, with a final M:F ratio of 2.3:1. For SF, at onset males outnumber females (1.8:1)

but by six months females marginally outnumber males, with the same being the case for the few remaining cases at follow-up. In BrPsy, the reverse is seen, with an M:F ratio of 1:5.5 changing to 1:4 at 6 months and declining to 1:1 at follow-up. SA at inception occurs more frequently in females (1:5); the M:F ratio is 1.2:1 at 6 months and 1.5:1 by follow-up. In BD, M:F ratio remains essentially constant: 1.1:1 at onset, 1:1 at six months and 1.1:1 at follow-up. The pattern is similar for MDDP (1:1.2, 1:1.4 and 1:1.1) Despite being a diagnosis that declines markedly in occurrence over time, DD also does not show much variation in M:F ratio over time (2.3:1, 1.5:1, 2:1, respectively). SIP is notable in that at each point in time it is an exclusively male diagnosis. PNOS exhibits male preponderance at onset (2:1) but over time this becomes a less common diagnosis and M:F ratio attains unity (1.6:1 at 6 months, 1:1 at follow-up). The other diagnostic categories are not sufficiently populous at any time point to draw any meaningful conclusions about sex ratios (PGMC, SIM, MGMC, SDD).

Table 12: Age at onset and sex by diagnostic category at onset

Sex	Diagnosis	n	Mean	SD	Sex	Diagnosis	n	Mean	SD
Male	SZ	25	29.8	13.7	Female	SZ	6	38.7	12.0
	SF	14	28.0	11.3		SF	8	45.3	29.7
	BrPsy	2	41.5	-		BrPsy	11	34.1	8.7
	SA	1	21.0	-		SA	5	22.8	4.6
	BD	17	32.8	15.8		BD	15	35.3	17.7
	MDDP	18	40.9	23.0		MDDP	22	48.9	21.2
	DD	9	34.8	8.9		DD	4	43.0	21.5
	PGMC	2	44.0	-		PGMC	2	57.5	-
	SIP	12	29.8	14.8		SIP	-	-	-
	PNOS	10	27.9	17.6		PNOS	5	45.6	28.4
	SIM	4	36.0	18.9		SIM	2	46.5	-
	SDD	1	23.0	-		SDD	-	-	-
	MGMC	-	-	-		MGMC	1	69.0	-
	Total	115	32.3	15.7		Total	81	41.6	20.2

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
BD Bipolar I disorder
MDDP Major depressive disorder
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
SDD Simple deteriorative disorder
MGMC Mania due to a general medical condition

Table 13: Age at onset and sex by diagnostic category at six months

Sex	Diagnosis	n	Mean	SD	Sex	Diagnosis	N	Mean	SD
Male	SZ	34	28.1	14.2	Female	SZ	8	33.6	13.9
	SF	5	35.6	12.1		SF	6	54.2	29.1
	BrPsy	2	41.5	-		BrPsy	8	35.3	9.3
	SA	6	27.3	7.9		SA	5	22.8	4.6
	BD	17	32.0	15.6		BD	17	34.6	16.9
	MDDP	17	42.9	22.9		MDDP	23	48.3	20.9
	DD	6	38.8	8.0		DD	4	43.0	21.5
	PGMC	2	44.0	-		PGMC	2	57.5	-
	SIP	11	29.6	15.2		SIP	-	-	-
	PNOS	8	22.1	3.7		PNOS	5	45.6	28.4
	SIM	4	36.0	18.9		SIM	2	46.5	-
	SDD	1	23.0	-		SDD	-	-	-
	MGMC	-	-	-		MGMC	1	69.0	-
	Suicide	2	47.5	-		Suicide	-	-	-
	Total	115	32.5	16.0		Total	81	41.5	20.2

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
BD Bipolar I disorder
MDDP Major depressive disorder
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
SDD Simple deteriorative disorder
MGMC Mania due to a general medical condition

Table 14: Age at onset and sex by diagnostic category at six year follow-up

Sex	Diagnosis	n	Mean	SD	Sex	Diagnosis	n	Mean	SD
Male	SZ	42	30.1	14.1	Female	SZ	18	35.6	17.4
	SF	1	25.0	-		SF	2	81.5	-
	BrPsy	2	17.0	1.4		BrPsy	2	40.5	-
	SA	16	28.9	11.1		SA	11	28.9	13.2
	BD	18	33.2	15.9		BD	17	36.6	15.8
	BDII	-	-	-		BD II	1	57.0	-
	MDDP	13	40.4	19.5		MDDP	14	45.7	18.6
	DD	2	31.0	-		DD	1	31.0	-
	PGMC	1	44.0	1		PGMC	2	69.0	-
	SIP	8	27.0	10.7		SIP	-	-	-
	PNOS	2	18.5	-		PNOS	2	27.5	-
	SIM	3	21.7	4.0		SIM	3	38.0	19.3
	MGMC	-	-	-		MGMC	1	69.0	-
	ALZ	-	-	-		ALZ	1	80.0	-
	RIP	3	63.0	15.1		RIP	6	64.2	25.3
	Suicide	4	55.0	19.2		Suicide	-	-	-
	Total	115	32.5	16.0		Total	81	41.5	20.2

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
MDDP Major depressive disorder with psychotic features
BD Bipolar disorder
BDII Bipolar disorder II
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MGMC Mania due to a general medical condition
Alz Alzheimer's disease
RIP deceased natural causes/accident

Age at onset is older for MDDP than for any of the other main follow-up diagnostic groupings ($p<0.05$ for MDDP vs. SZ, MDDP vs. SA, MDDP vs. BD; no sex x diagnosis interactions). Overall mean age at onset for males [32.5 years (n=115, SD 16.0)], is younger ($p<0.05$) than for females [at 41.5 years (n=81, SD 20.2)]. This pattern held for each of the major diagnostic groupings.

Table 15: Age at death, by sex, diagnosis at inception and cause of death for participants deceased by six year follow-up

Participant	Age at death	Sex	Diagnosis at inception	Cause of death
1	79	Male	MDDP	Myocardial infarction
2	51	Male	MDDP	Suicide
3	27	Female	MDDP	Head injury in road traffic accident
4	81	Male	MDDP	Suicide
5	47	Male	BD	Congestive cardiac failure
6	71	Female	MDDP	Cerebrovascular accident (CVA)
7	66	Male	SZ	Suicide
8	36	Male	SZ	Suicide
9	82	Female	MDDP	Bronchopneumonia
10	83	Female	MDDP	Pneumonia
11	68	Male	SIP	Myocardial infarction
12	81	Female	BD	Pneumonia
13	81	Female	SF	Acute cardiac failure

BD Bipolar disorder MDDP Major depressive disorder with psychotic features
SZ Schizophrenia
SIP Substance induced psychosis
SF Schizophreniform disorder

Of the 196 individuals on whom follow-up data was obtained, 13 were deceased at follow-up (Table 15). Mean age at onset for this group was 62.3 years (SD 19.7). Four of these deaths were by suicide (mean age at onset 56.5 years, SD 19.5); all of these individuals were male. One death was the result of a road traffic accident. The other eight deaths were the result of a variety of typical natural causes.

Table 16: Marital status at follow-up by sex and diagnosis at follow-up

Sex	Diagnosis	Single	Married/living as if married	Widowed	Separated/ divorced	Total
		n (%)	n (%)	n (%)	n (%)	n (%)
Male	SZ	36 (85%)	4 (10%)	-	2 (5%)	42
	SF	-	1 (100%)	-	-	1
	BrPsy	2 (100%)	-	-	-	2
	SA	11 (69%)	3 (19%)	-	2 (12%)	16
	BD I	8 (44%)	8 (44%)	1 (6%)	1 (6%)	18
	MDDP	11 (85%)	2 (15%)	-	-	13
	DD	2 (100%)	-	-	-	2
	PGMC	1 (100%)	-	-	-	1
	SIP	7 (88%)	1 (12%)	-	-	8
	PNOS	2 (100%)	-	-	-	2
	SIM	2 (67%)	1 (33%)	-	-	3
	RIP	2 (67%)	1 (33%)	-	-	3
	Suicide	2 (50%)	2 (50%)	-	-	4
	Total	86 (75%)	23 (20%)	1 (1%)	5 (4%)	115
Female	SZ	13 (72%)	3 (16%)	1 (6%)	1 (6%)	18
	SF	1(50%)	-	1(50%)	-	2
	BrPsy	-	2 (100%)	-	-	2
	SA	8 (73%)	3 (27%)	-	-	11
	BD I	6 (35%)	8 (47%)	2 (12%)	1 (6%)	17
	BDII	-	1 (100%)	-	-	1
	MDDP	3 (21%)	10 (72%)	-	1 (8%)	14
	DD	-	1 (100%)	-	-	1
	PGMC	-	-	2 (100%)	-	2
	PNOS	-	2 (100%)	-	-	2
	SIM	2 (67%)	-	-	1 (33%)	3
	MGMC	-	-	1 (100%)	-	1
	ALZ	-	-	1 (100%)	-	1
	RIP	3 (50%)	1 (17%)	2 (33%)	-	6
	Total	36 (45%)	31 (38%)	10 (12%)	4 (5%)	81

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified

MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BD II Bipolar disorder II
DD Delusional disorder
SIM Substance induced mania
MGMC Mania due to a general medical condition
ALZ Alzheimer's disease
RIP deceased natural causes/accident

As can be seen in Table A10, males and females differed in marital status at onset of illness, with 83% of males and 48% of females being single. This may be compared to the proportion of unmarried males and females in the 2006 Census (Central Statistics Office, 2006), which indicates that both males and females with psychotic illness are less likely to be married than the age and sex-matched population from which they are drawn: in the general population, 53% of males aged 32 years are single and 19% of females aged 41 years are single. When the diagnostic categories at onset are examined individually, it may be seen that among the primary diagnoses (SZ, BD, MDDP), males with SZ are least likely to be married (4%) and those with BD (35%) most likely to be married, with MDDP (22%) occupying an intermediate position. This is despite those with MDDP having an older mean age at onset than BD and thus having had a longer opportunity to marry. Among women, those with BD are least likely to be married (27%), followed by SZ (32%), with MDDP being most likely to marry (64%). Notably, among the other diagnostic categories women with BrPsy are most likely to have married (82%). Similar findings are evident six months later (Table A11).

The marital patterns noted above in relation to diagnoses at onset and six months are little altered over the course of an additional six years of illness and diagnostic evolution (Table 16).

Demographic comparison of those completing different measures

As described above, follow-up data were obtained on 196 of the potential 202 participants. All of these 196 individuals completed diagnostic assessment at onset of illness and at six months, and were assessed at follow-up (mean 6.4years). A basic dataset was available for all of these 196 individuals, consisting of demographic data and diagnostic evolution from

onset, through six months to follow-up. As extent of detail and demands of participation for each instrument increased, numbers completing assessment decreased. Table 17 indicates the numbers of participants on whom data was successfully completed for each assessment instrument.

Table 17: Number of participants completing each assessment instrument at follow-up

Assessment instrument	Number of participants
DSM IV diagnosis	196
PANSS	179
GAF	184
HoNOS	179
Strauss-Carpenter	178
SLOF	178
QLS	178
WHOQOL-Bref	120
SES	180

DSM IV Diagnostic and Statistical Manual IV
PANSS Positive and Negative Syndrome Scale
GAF Global Assessment of Functioning
HoNOS Health of the Nation Outcome Scale
SLOF Specific Levels of Functioning Scale
QLS Quality of Life Scale
WHOQOL-Bref World Health Organisation Quality of Life Bref Scale
SES Service Engagement Scale

As can be seen, a DSM IV diagnosis was obtained for all 196 individuals followed up, with a cluster of assessment instruments (PANSS, GAF, HoNOS, Strauss-Carpenter, SLOF, QLS, SES) completed on between 178 and 184 participants. A less complete dataset was obtained for the WHOQOL-Bref, with 120 participants. Comparisons of demographics [age and sex] between participants completing vs not completing DSM IV diagnosis, PANSS [used as a

proxy for GAF, HoNOS, Strauss-Carpenter, SLOF, QLS and SES, as individuals completing any one of these six measures almost always completed the other five] and WHOQOL-Bref were carried out (Table 18). The only significant difference encountered was that participants not completing the PANSS were slightly older ($p<0.05$) than those completing this assessment.

Table 18: Age at onset and sex for those completing and not completing diagnostic evaluation, PANSS and WHOQOL-Bref

	Diagnosis	PANSS	WHOQOL-Bref
Age			
Completing	36.5 (18.5)	34.7 (16.8)	34.5 (16.5)
Not completing	-	41.2 (21.1)*	39.0 (20.7)
Males			
Completing	115	106	70
Not completing	-	9	45
Females			
Completing	81	73	50
Not completing	-	8	31
Totals	196	196	196

*$p<0.05$ vs. those completing PANSS

Diagnostic stability

Table 19: Diagnostic status at six months in comparison with onset

Diagnosis at onset	Diagnosis at six months														
	SZ	SF	BrPsy	SA	BD	MDDP	DD	PGMC	SIP	PNOS	SIM	SDD	MGMC	RIP suicide	Total at onset
SZ	30	0	0	0	0	0	0	0	0	0	0	0	0	1	31
SF	8	11	0	1	1	1	0	0	0	0	0	0	0	0	22
BrPsy	0	0	10	0	2	1	0	0	0	0	0	0	0	0	13
SA	0	0	0	6	0	0	0	0	0	0	0	0	0	0	6
BD	0	0	0	1	31	0	0	0	0	0	0	0	0	0	32
MDDP	1	0	0	1	0	38	0	0	0	0	0	0	0	0	40
DD	2	0	0	1	0	0	10	0	0	0	0	0	0	0	13
PGMC	0	0	0	0	0	0	0	4	0	0	0	0	0	0	4
SIP	0	0	0	1	0	0	0	0	10	0	0	0	0	1	12
PNOS	1	0	0	0	0	0	0	0	1	13	0	0	0	0	15
SIM	0	0	0	0	0	0	0	0	0	0	6	0	0	0	6
SDD	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
MGMC	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Total at 6 mths	42	11	10	11	34	40	10	4	11	13	6	1	1	2	196

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
MDDP Major depressive disorder with psychosis
BD Bipolar disorder
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder

Table 20: Diagnostic stability at six year follow-up in comparison with six months

Diagnosis at 6 months	Diagnosis at follow-up																
	SZ	SF	BrPsy	SA	BD	BD2	MDDP	DD	PGMC	SIP	PNOS	SIM	MGMC	Alz	RIP	Suicide	Total at 6 months
SZ	37	0	0	3	1	0	0	0	0	1	0	0	0	0	0	0	42
SF	5	3	0	0	0	0	0	0	0	2	0	0	0	0	1	0	11
BrPsy	2	0	2	1	2	0	2	1	0	0	0	0	0	0	0	0	10
SA	1	0	0	9	0	0	1	0	0	0	0	0	0	0	0	0	11
BD	2	0	0	3	26	0	0	0	0	0	0	1	0	0	2	0	34
MDDP	2	0	0	3	4	0	22	0	0	1	0	0	0	0	5	2	40
DD	5	0	0	1	0	0	1	2	1	0	0	0	0	0	0	0	10
PGMC	1	0	0	1	0	0	0	0	2	0	0	0	0	0	0	0	4
SIP	1	0	1	2	1	0	0	0	0	4	0	1	0	0	1	0	11
PNOS	3	0	0	3	0	0	1	0	0	0	4	1	0	1	0	0	13
SIM	0	0	1	1	1	0	0	0	0	0	0	3	0	0	0	0	6
MGMC	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
SDD	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Suicide	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2
Total at follow-up	60	3	4	27	35	1	27	3	3	8	4	6	1	1	9	4	196

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BD II Bipolar disorder II
DD Delusional disorder
RIP deceased due to natural/accidental causes
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder
Alz Alzheimer's disease

Diagnostic stability at six months

The initial period over which diagnostic stability (percentage of cases retaining an initial diagnosis at follow-up) was evaluated extended from inception into the FEP study through to six months, at which time the individual's diagnosis was reassessed. The three primary diagnoses were noted to be extremely stable over this time period (SZ=97%, BD=97%, MDDP=95%). However, some differences in patterns start to emerge at this time; MDDP and BD have similar numbers at both time points, whereas SZ has increased from 31 to 42 individuals. Less stable is SF (50%). This is the only category other than SZ which shows a marked change in populousness over this period; expected diagnostic transitions from SF to SZ are the primary reason for loss of cases from SF and gain in cases for SZ. Other generally stable categories over the initial six month period include SA (100%), SIP (84%), PNOS (88%), DD (78%), SIM (100%) and BrPsy (77%). Of the minor diagnoses with four or fewer members at onset (PGMC, SDD and MGMC), all are 100% stable over the six month period following inception into the study.

Diagnostic stability at six year follow-up

At six year follow-up, some of the trends observed between onset and six month follow-up are elaborated, while some new findings emerge. By this point, the most stable diagnostic categories continue to be SZ (88%) and BD (76%), together with SA (82%). However, MDDP has reduced in stability to 55%. In considering these categories, which are by far the most populous at follow-up and account for 77% of all participants by this time, it is necessary to comment on changes in their occurrence over time. Cases of SZ have continued to increase, with 60 members by follow-up compared to 31 at onset and 42 by six months. Much of this increase is accounted for by movement from the diagnostic categories SF, DD and PNOS, with smaller numbers from BrPsy, BD and MDDP. BD has remained largely unchanged, with 32 members at onset, 34 at six months and 35 at follow-up. MDDP has decreased from 40 at onset and at six months to 27 at follow-up; several individuals with MDDP at onset developed BD or were deceased by 6 year follow-up. SA, however, has increased from 5 at onset to 11 at six months and 27 at follow up; this influx is mainly from

SZ, BD, MDDP and PNOS. SF has decreased from 22 at onset and 11 at 6 months to 3 at follow-up, the majority of this change being accounted for by change from an early diagnosis of SF to a later diagnosis of SZ. Of the intermediate diagnostic categories, SIP has the highest diagnostic stability at 36%, having lost relatively few members over time: 12, 11 and 8 cases at onset, six months and six year follow-up, respectively. This pattern indicates that whilst SIP has lost several members over time to a variety of other diagnoses, it has also gained several members who initially received other diagnoses. PNOS has a diagnostic stability of 30% and decreased markedly in frequency over time, from 15 to 13 to 4 members at onset, six months and six year follow-up, respectively, with many individuals being re-classified to SZ or SA over the follow-up period. BrPsy has also shown a similar pattern (13, 10 and 4 members at onset, six months and six year follow-up, respectively) with a diagnostic stability of 20% over the period from six months to follow-up; BrPsy evolves to SZ, BD and MDDP over the follow-up period. DD is another diagnosis showing a very similar pattern, with a diagnostic stability of 20% and considerable loss of members over time (13, 10 and 3 members at onset, six months and six year follow-up, respectively), largely to SZ. Of the two smallest categories, the single participant with SDD evolved into SZ over time and the single participant with MGMC retained that diagnosis throughout the study. One participant who was initially diagnosed with PNOS was considered to have possibly had psychotic symptoms at onset due to incipient Alzheimer's disease that became evident at follow-up.

Of the total 13 deaths, four were by suicide, two of whom had an onset diagnosis of MDDP. Of the nine deaths other than by suicide, five of these cases had an onset diagnosis of MDDP. MDDP is thus substantially over-represented in deaths of whatever cause.

Follow-up variables

Scores on each of the assessment instruments applied at six year follow-up are given in the following tables. The first table for each instrument shows the scores for each of the full range of diagnoses. These are tabulated by diagnosis at onset, six months, six year follow-up and 'core' diagnosis [i.e. those in receipt of that diagnosis at all three time points] for all

individuals and by sex. The second table for each instrument shows only the scores for the main diagnoses (SZ, SA, BD and MDDP), as numbers in other diagnostic categories are too small for meaningful statistical analysis and interpretation. Comparisons are made across the sexes within and between each diagnostic category. In addition, the tables show any significant differences ($p<0.05$) in scores between SZ and each of the main diagnoses (SA, BD and MDDP); SZ is used as the reference diagnosis as it is the largest diagnostic category at follow-up, would be expected to show the poorest outcome at follow-up and historically constitutes the prototypical psychosis spectrum diagnosis.

Psychopathology

PANSS total score

Table 21a: PANSS total scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all three occasions

Diagnosis	All PANSS total (SD) (n)	Male PANSS total (SD) (n)	Female PANSS total (SD) (n)
SZ inception	63.0 (22.7) (30)	63.9 (23.8) (24)	59.7 (18.8) (6)
6 months	64.8 (23.3) (42)	65.4 (23.6) (34)	62.3 (23.4) (8)
Follow-up	65.2 (20.7) (60)	67.9 (21.0) (42)	58.9 (19.0) (18)
Core	65.8 (22.8) (26)	67.2 (23.5) (21)	59.8 (21.0 (5)
SF Inception	54.3 (23.1) (21)	50.8 (23.8) (14)	61.3 (21.5) (7)
6 months	49.8 (14.5) (10)	41.8 (12.2) (5)	57.8 (12.7) (5)
Follow-up	53.7 (19.4) (3)	41.0 (-) (1)	60.0 (-) (2)
Core	53.7 (19.4) (3)	41.0 (-) (1)	60.0 (-) (2)
BrPsy Inception	47.9 (17.7) (13)	74.0 (-) (2)	43.2 (14.2) (11)
6 months	47.2 (17.9) (10)	74.0 (-) (2)	40.5 (11.7) (8)
Follow-up	44.8 (7.2) (4)	44.0 (-) (2)	45.5 (-) (2)
Core	45.5 (-) (2)	-	45.5 (-) (2)
SA Inception	55.2 (12.6) (6)	63.0 (-) (1)	53.6 (13.5) (5)
6 months	62.2 (23.7) (11)	69.3 (29.1) (6)	53.6 (13.5) (5)
Follow-up	56.8 (20.7) (27)	60.44 (24.8) (16)	51.5 (12.1) (11)
Core	55.2 (12.6) (6)	63.0 (-) (1)	53.6 (13.5) (5)
BD I Inception	48.4 (19.1) (29)	55.4 (21.9) (16)	39.7 (9.9) (13)

6 months	46.7 (16.0) (31)	50.8 (18.0) (16)	42.3 (12.6) (15)
Follow-up	44.6 (11.8) (33)	48.2 (11.8) (17)	40.7 (10.9) (16)
Core	42.9 (10.7) (24)	47.8 (10.9) (12)	38.1 (8.3) (12)
BD II Follow-up	30.0 (-) (1)	-	30.0 (-) (1)
MDDP Inception	48.3 (19.) (31)	51.9 (19.7) (13)	45.7 (18.5) (18)
6 months	44.7 (15.3) (31)	44.3 (9.7) (12)	45.0 (18.2) (19)
Follow-up	43.6 (15.1) (26)	44.5 (9.5) (12)	42.9 (18.9) (14)
Core	44.7 (16.3) (21)	45.2 (10.3) (9)	44.3 (20.1) (12)
DD Inception	60.1 (20.4) (13)	64.7 (21.9) (9)	49.8 (13.1) (4)
6 months	58.3 (19.9) (10)	64.0 (22.6) (6)	49.8 (13.1) (4)
Follow-up	40.7 (9.1) (3)	45.5 (-) (2)	31.0 (-) (1)
Core	45.5 (-) (2)	45.5 (-) (2)	-
PGMC Inception	56.8 (8.0) (4)	57.5 (-) (2)	56.0 (-) (2)
6 months	56.8 (8.0) (4)	57.5 (-) (2)	56.0 (-) (2)
Follow-up	50.3 (2.1) (3)	52.0 (-) (1)	49.5 (-) (2)
Core	50.0 (-) (2)	52.0 (-) (1)	48.0 (-) (1)
SIP Inception	47.6 (11.3) (10)	47.6 (11.3) (10)	-
6 months	45.8 (11.8) (10)	5.8 (11.8) (10)	-
Follow-up	38.1 (4.4) (8)	38.1 (4.4) (8)	-
Core	40.0 (3.3) (4)	40.0 (3.3) (4)	-
PNOS Inception	51.1 (14.1) (14)	51.7 (14.5) (10)	49.5 (15.0) (4)
6 months	50.7 (13.1) (12)	51.3 (13.1) (8)	49.5 (15.0) (4)
Follow-up	38.0 (9.5) (3)	35.5 (-) (2)	43.0 (-) (1)
Core	38.0 (9.5) (3)	35.5 (-) (2)	43.0 (-) (1)
SIM Inception	46.2 (11.9) (6)	49.0 (14.1) (4)	40.5 (-) (2)
6 months	46.2 (11.9) (6)	49.0 (14.1) (4)	40.5 (-) (2)
Follow-up	41.2 (8.2) (6)	43.7 (11.6) (3)	38.7 (4.0) (3)
Core	39.7 (2.9) (3)	38.0 (-) (1)	40.5 (-) (2)
MGMC Inception	49.0 (-) (1)	-	49.0 (-) (1)
6 months	49.0 (-) (1)	-	49.0 (-) (1)
Follow-up	49.0 (-) (1)	-	49.0 (-) (1)
Core	49.0 (-) (1)	-	49.0 (-) (1)
SDD Inception	46.0 (-) (1)	46.0 (-) (1)	-
6 months	46.0 (-) (1)	46.0 (-) (1)	-
Alz Follow-up	50.0 (-) (1)	-	50.0 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BD II Bipolar disorder II
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder
Alz Alzheimer's disease
PANSS Positive and Negative Syndrome Scale

Table 21b: PANSS total scores at six year follow-up for SZ, SZ, BD and MDDP at follow-up

Diagnosis	All PANSS total (SD) (n)	Male PANSS total (SD) (n)	Female PANSS total (SD) (n)
SZ	65.2 (20.7 (60)	67.9 (21.0) (42)	58.9 (19.0) (18)
SA	56.8 (20.7) (27)	60.4 (24.8) (16)	51.5 (12.1) (11)
BD	44.6[c] (11.8) (33)	48.2 (11.8 (17)	40.7 (10.9) (16)
MDDP	43.6[c] (15.1) (26)	44.5 (9.5) (12)	42.9 (18.9) (14)

[c] $p<0.001$ vs. SZ

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
PANSS total Positive and Negative Syndrome Scale total score

As indicated in Tables 21a/b, PANSS total scores for SZ are high, indicating enduring psychopathology; BD and MDDP evidence lower scores, while SA lies between SZ and the two affective psychoses. All the major diagnoses show a similar pattern of lower scores among females at follow-up (effect of sex, $p<0.001$; no diagnosis x sex interaction.) SF has scores between SZ and BD/MDDP. DD scores are high for the diagnosis made at onset or 6 months but lower for the few remaining individuals with this diagnosis at follow-up. Among

the moderately populated diagnostic groupings, BrPsy and SIP have the lowest PANSS total scores, indicating low levels of psychopathology. Both SIP and PNOS show a similar pattern, perhaps reflecting the evolution of some higher scoring individuals at onset towards follow-up diagnoses characterized by more severe levels of psychopathology.

PANSS positive score

Table 22a: PANSS positive scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all three occasions

Diagnosis	All PANSS pos (SD) (n)	Male PANSS pos (SD) (n)	Female PANSS pos (SD) (n)
SZ Inception	12.3 (5.6) (30)	12.8 (6.0) (24)	10.3 (3.3) (6)
6 months	13.1 (6.0) (42)	13.3 (6.1) (34)	11.9 (5.7) (8)
Follow-up	13.0 (5.5) (60)	13.6 (5.8) (42)	11.4 (4.6) (18)
Core	12.9 (5.8) (26)	13.3 (6.2 (21)	11.0 (3.2) (5)
SF Inception	11.5 (6.2) (21)	10.8 (6.1) (14)	12.9 (6.5) (7)
6 months	9.8 (4.0) (10)	8.2 (1.8) (5)	11.4 (5.1) (5)
Follow-up	12.3 (6.1) (3)	11.0 (-) (1)	13.0 (-) (2)
Core	12.3 (6.1) (3)	11.0 (-) (1)	13.0 (-) (2)
BrPsy Inception	10.1 (4.6) (13)	13.5 (-) (2)	9.6 (4.1) (11)
6 months	9.2 (3.9) (10)	13.5 (-) (2)	8.1 (2.1) (8)
Follow-up	8.5 (1.9) (4)	9.0 (-) (2)	8.0 (-) (2)
Core	8.0 (-) (2)	-	8.0 (-) (2)
SA Inception	10.3 (3.0) (6)	13.0 (-) (1)	9.8 (3.0) (5)
6 months	11.1 (4.5) (11)	12.2 (5.5) (6)	9.8 (3.0) (5)
Follow-up	11.5 (5.5) (27)	12.7 (6.6) (16)	9.8 (2.9) (11)
Core	10.3 (3.0 (6)	13.0 (-) (1)	9.8 (3.0) (5)
BD I Inception	9.5 (3.9) (29)	10.5 (4.7) (16)	8.2 (2.0) (13)
6 months	9.6 (4.0) (31)	9.9 (4.5) (16)	9.3 (3.6) (15)
Follow-up	8.8 (3.2) (33)	9.1 (3.3) (17)	8.5 (3.2) (16)
Core	8.4 (2.2) (24)	8.8 (2.4) (12)	8.0 (1.9) (12)
BD II Follow-up	7.0 (-) (1)	-	7.0 (-) (1)

MDDP Inception	8.9 (3.5) (31)	9.2 (3.6) (13)	8.8 (3.5) (18)
6 months	8.3 (2.7) (31)	7.8 (0.9) (12)	8.7 (3.4) (19)
Follow-up	7.8 (1.8) (26)	7.5 (0.8) (12)	8.0 (2.3) (14)
Core	8.0 (1.9) (21)	7.7 (0.9) (9)	8.2 (2.5) (12)
DD Inception	11.5 (6.5) (13)	13.0 (7.3) (9)	8.0 (1.2) (4)
6 months	11.4 (6.9) (10)	13.7 (8.3) (6)	8.0 (1.2) (4)
Follow-up	9.3 (1.2) (3)	10.0 (-) (2)	8.0 (-) (1)
Core	10.0 (-) (2)	10.0 (-) (2)	-
PGMC Inception	11.3 (3.5) (4)	12.5 (-) (2)	10.0 (-) (2)
6 months	11.3 (3.5) (4)	12.5 (-) (2)	10.0 (-) (2)
Follow-up	8.0 (1.7) (3)	10.0 (-) (1)	7.0 (-) (2)
Core	8.5 (-) (2)	10.0 (-) (1)	7.0 (-) (1)
SIP Inception	9.2 (2.7) (10)	9.2 (2.7) (10)	-
6 months	9.2 (2.7) (10)	9.2 (2.7) (10)	-
Follow-up	8.3 (0.9) (8)	8.3 (0.9) (8)	-
Core	8.0 (0.8) (4)	8.0 (0.8) (4)	-
PNOS Inception	10.4 (4.2) (14)	11.3 (4.6) (10)	8.3 (1.9) (4)
6 months	10.2 (4.0) (12)	11.1 (4.5) (8)	8.3 (1.9) (4)
Follow-up	7.3 (0.6) (3)	7.0 (-) (2)	8.0 (-) (1)
Core	7.3 (0.6) (3)	7.0 (-) (2)	8.0 (-) (1)
SIM Inception	10.5 (4.6) (6)	12.0 (5.1) (4)	7.5 (-) (2)
6 months	10.5 (4.6) (6)	12.0 (5.1) (4)	7.5 (-) (2)
Follow-up	9.2 (3.1) (6)	11.0 (3.6) (3)	7.3 (0.6) (3)
Core	8.3 (1.5) (3)	10.0 (-) (1)	7.5 (-) (2)
MGMC inception	14.0 (-) (1)	-	14.0 (-) (1)
6 months	14.0 (-) (1)	-	14.0 (-) (1)
follow-up	14.0 (-) (1)	-	14.0 (-) (1)
core	14.0 (-) (1)	-	14.0 (-) (1)
SDD inception	11.0 (-) (1)	11.0 (-) (1)	-
6 months	11.0 (-) (1)	11.0 (-) (1)	-
Alz follow-up	7.0 (-) (1)	-	7.0 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania

MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BD II Bipolar disorder II
DD Delusional disorder
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder
Alz Alzheimer's disease
PANSS pos Positive and Negative Syndrome Scale positive subscale

Table 22b: PANSS positive scores at six year follow-up for SZ, SZ, BD and MDDP at follow-up

Diagnosis	All PANSS pos scores (SD) (n)	Male PANSS pos scores (SD) (n)	Female PANSS pos scores (SD) (n)
SZ	13.0 (5.5) (60)	13.6 (5.8) (42)	11.4 (4.6) (18)
SA	11.5 (5.5) (27)	12.7 (6.6) (16)	9.8 (2.9) (11)
BD	8.8[c] (3.2) (33)	9.1 (3.3) (17)	8.5 (3.2) (16)
MDDP	7.8[c] (1.8) (26)	7.5 (0.8) (12)	8.0 (2.3) (14)

[c] <0.001 vs. SZ

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
PANSS pos Positive and Negative Syndrome Scale positive subscale

As indicated in Table 22a/b, PANSS positive scores, though generally low, are highest for SZ; BD and MDDP evidence lower scores while SA lies between SZ and the two affective psychoses.

While PANSS positive scores are generally higher in males than in females for all major diagnoses, no significant differences were apparent at follow-up (no effect of sex, no diagnosis x sex interaction). PANSS positive scores are generally lower for SF, DD, SIP, BrPsy and PNOS.

PANSS negative score

Table 23a: PANSS negative scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all three occasions

Diagnosis	All PANSS neg (SD) (n)	Male PANSS neg (SD) (n)	Female PANSS neg (SD) (n)
SZ Inception	18.9 (10.0) (30)	18.4 (9.6) (24)	20.7 (12.4) (6)
6 months	19.1 (10.2) (42)	18.9 (9.8) (34)	20.3 (12.3) (8)
Follow-up	20.3 (8.8) (60)	20.9 (8.6) (42)	18.9 (9.5) (18)
Core	20.4 (9.8) (26)	20.1 (9.1) (21)	22.0 (13.3) (5)
SF Inception	15.7 (9.1) (21)	15.4 (10.0) (14)	16.1 (7.6) (7)
6 months	14.6 (6.7) (10)	14.2 (9.5) (5)	15.0 (3.1) (5)
Follow-up	13.3 (3.2) (3)	12.0 (-) (1)	14.0 (-) (2)
Core	13.3 (3.2) (3)	12.0 (-) (1)	14.0 (-) (2)
BrPsy Inception	10.9 (4.9) (13)	14.5 (-) (2)	10.2 (4.5) (11)
6 months	10.6 (5.2) (10)	14.5 (-) (2)	9.6 (4.5) (8)
Follow-up	10.8 (3.3) (4)	11.0 (-) (2)	10.5 (-) (2)
Core	10.5 (-) (2)	-	10.5 (-) (2)
SA Inception	14.0 (6.3) (6)	12.0 (-) (1)	14.4 (7.0) (5)
6 months	18.6 (10.7) (11)	22.0 (12.6) (6)	14.4 (7.0) (5)
Follow-up	15.8 (9.3) (27)	17.3 (11.2) (16)	13.6 (5.3) (11)
Core	14.0 (6.3) (6)	12.0 (-) (1)	14.4 (7.0) (5)
BD I Inception	12.9 (9.1) (21)	15.9 (11.1) (16)	9.2 (3.4) (15)
6 months	11.8 (7.1) (31)	13.7 (8.9) (16)	9.8 (3.8) (15)
Follow-up	10.1 (4.3) (33)	11.3 (5.0) (17)	8.8 (2.7) (16)
Core	10.3 (4.7) (24)	12.1 (5.7) (12)	8.6 (2.8) (12)
BD II Follow-up	7.0 (-) (1)	-	7.0 (-) (1)
MDDP Inception	13.1 (7.8) (31)	14.0 (7.0) (13)	12.5 (8.6) (18)
6 months	12.3 (7.2) (31)	12.4 (5.0) (12)	12.2 (8.5) (19)
Follow-up	11.4 (7.3) (26)	10.9 (5.0) (12)	11.9 (9.1) (14)
Core	12.4 (7.9) (21)	12.0 (5.3) (9)	12.7 (9.6) (12)
DD inception	18.8 (10.0) (13)	19.8 (11.1) (9)	16.5 (7.8) (4)
6 months	17.5 (9.2) (10)	18.2 (10.7) (6)	16.5 (7.8) (4)
follow-up	8.3 (2.3) (3)	9.0 (-) (2)	7.0 (-) (1)
Core	9.0 (-) (2)	9.0 (-) (2)	-

PGMC Inception	16.5 (7.6) (4)	19.5 (-) (2)	13.5 (-) (2)
6 months	16.5 (7.6) (4)	19.5 (-) (2)	13.5 (-) (2)
Follow-up	12.7 (3.1) (3)	12.0 (-) (1)	13.0 (-) (2)
Core	11.0 (-) (2)	12.0 (-) (1)	10.0 (-) (1)
SIP Inception	10.5 (4.8) (10)	10.5 (4.8) (10)	-
6 months	9.3 (3.9) (10)	9.3 (3.9) (10)	-
Follow-up	7.6 (1.4) (8)	7.6 (1.4) (8)	-
Core	7.3 (0.5) (4)	7.3 (0.5) (4)	-
PNOS Inception	13.0 (6.4) (14)	12.2 (4.7) (10)	15.0 (10.1) (4)
6 months	13.1 (6.5) (12)	12.1 (4.5) (8)	15.0 (10.1) (4)
Follow-up	7.7 (1.2) (3)	8.0 (-) (2)	7.0 (-) (1)
Core	7.7 (1.2) (3)	8.0 (-) (2)	7.0 (-) (1)
SIM Inception	11.0 (4.0) (6)	11.0 (4.9) (4)	11.0 (-) (2)
6 months	11.0 (4.0) (6)	11.0 (4.9) (4)	11.0 (-) (2)
Follow-up	8.5 (2.3) (6)	7.3 (0.6) (3)	9.7 (3.1) (3)
Core	9.6 (3.1) (3)	7.0 (-) (1)	11.0 (-) (2)
MGMC Inception	7.0 (-) (1)	-	7.0 (-) (1)
6 months	7.0 (-) (1)	-	7.0 (-) (1)
Follow-up	7.0 (-) (1)	-	7.0 (-) (1)
Core	7.0 (-) (1)	-	7.0 (-) (1)
SDD inception	16.0 (-) (1)	16.0 (-) (1)	-
6 months	16.0 (-) (1)	16.0 (-) (1)	-
Alz follow-up	18.0 (-) (1)	-	18.0 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BD II Bipolar disorder II
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder
Alz Alzheimer's disease
PANSS neg Positive and Negative Syndrome Scale negative subscale

Table 23b: PANSS negative scores at six year follow-up for SZ, SZ, BD and MDDP at follow-up

Diagnosis	All PANSS neg scores (SD) (n)	Male PANSS neg Scores (SD) (n)	Female PANSS neg scores (SD) (n)
SZ	20.3 (8.8) (60)	20.9 (8.6) (42)	18.9 (9.5) (18)
SA	15.8[a] (9.3) (27)	17.3 (11.2) (16)	13.6 (5.3) (11)
BD	10.1[c] (4.3) (33)	11.3 (5.0) (17)	8.8 (2.7) (16)
MDDP	11.4[c] (7.3) (26)	10.9 (5.0) (12)	11.9 (9.1) (14)

[a] $p<0.05$, [c] $p<0.001$ vs. SZ

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
PANSS neg Positive and Negative Syndrome Scale negative subscale

As indicated in Tables 23a/b, PANSS negative scores are highest for SZ, lower for SA and lower still for BD and MDDP. While PANSS negative scores are generally higher in males than in females for SZ, SA and BD, no significant differences were evident at follow-up (no effect of sex, no diagnosis x sex interaction). PANSS negative scores are generally modest for SF. For DD scores are lower at follow-up than at onset and six months, perhaps reflecting the evolution of some higher scoring individuals at onset towards follow-up diagnoses characterized by more severe negative symptoms. BrPsy and SIP have low scores.

PANSS general score

Table 24a: PANSS general scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all three occasions

Diagnosis	All PANSS gen (SD) (n)	Male PANSS gen (SD) (n)	Female PANSS gen (SD) (n)

SZ Inception	32.9 (12.0) (30)	33.7 (12.5) (24)	29.7 (9.9) (6)
6 months	33.6 (11.5) (42)	34.2 (11.8) (34)	30.9 (10.6) (8)
Follow-up	32.9 (10.4) (60)	34.6 (11.0) (42)	29.1 (8.0) (18)
Core	33.8 (12.4) (26)	35.1 (12.7) (21)	28.0 (10.1) (5)
SF Inception	27.8 (10.1) (21)	25.4 (10.4) (14)	32.4 (8.4) (7)
6 months	26.2 (7.6) (10)	20.8 (4.6) (5)	31.6 (6.1) (5)
Follow-up	29.7 (10.0) (3)	22.0 (-) (1)	33.5 (-) (2)
Core	29.7 (10.0) (3)	22.0 (-) (1)	33.5 (-) (2)
BrPsy Inception	27.2 (10.3) (13)	46.0 (-) (2)	23.8 (6.6) (11)
6 months	27.7 (11.1) (10)	46.0 (-) (2)	23.1 (6.0) (8)
Follow-up	25.5 (6.8) (4)	24.0 (-) (2)	27.0 (-) (2)
Core	27.0 (-) (2)	-	27.0 (-) (2)
SA Inception	30.2 (6.4) (6)	38.0 (-) (1)	28.6 (5.7) (5)
6 months	32.2 (10.7) (11)	35.2 (13.4) (6)	28.6 (5.7) (5)
Follow-up	30.0 (9.2) (27)	31.5 (11.0) (16)	27.7 (5.6) (11)
Core	30.2 (6.4) (6)	38.0 (-) (1)	28.6 (5.7) (5)
BD I Inception	27.0 (9.4) (29)	29.8 (10.6) (16)	23.5 (6.4) (13)
6 months	26.2 (8.7) (31)	28.0 (10.0) (16)	24.2 (6.8) (15)
Follow-up	26.2 (8.9) (33)	28.0 (10.0) (17)	24.3 (7.3) (16)
Core	24.9 (7.8) (24)	27.1 (8.9) (12)	22.8 (6.2) (12)
BD II Follow-up	16.0 (-) (1)	-	16.0 (-) (1)
MDDP Inception	26.3 (9.9) (31)	28.8 (11.6) (13)	24.5 (8.4) (18)
6 months	24.2 (7.7) (31)	24.2 (7.0) (12)	24.2 (8.3) (19)
Follow-up	24.6 (7.7) (26)	26.3 (6.8) (12)	23.1 (8.4) (14)
Core	24.6 (8.9) (21)	25.9 (7.0) (9)	23.7 (9.0) (12)
DD Inception	30.0 (6.7) (13)	32.0 (6.4) (9)	25.3 (5.1) (4)
6 months	29.5 (6.8) (10)	32.3 (6.6) (6)	25.3 (5.1) (4)
Follow-up	23.3 (6.7) (3)	27.0 (-) (2)	16.0 (-) (1)
Core	27.0 (-) (2)	27.0 (-) (2)	-
PGMC Inception	32.3 (3.3) (4)	32.5 (-) (2)	32.0 (-) (2)
6 months	32.3 (3.3) (4)	32.5 (-) (2)	32.0 (-) (2)
Follow-up	31.3 (4.2) (3)	35.0 (-) (1)	29.0 (-) (2)
Core	33.0 (-) (2)	36.0 (-) (1)	30.0 (-) (1)
SIP Inception	28.0 (6.3) (10)	28.0 (6.3) (10)	-
6 months	27.4 (6.7) (10)	27.4 (6.7) (10)	-
Follow-up	21.8 (4.4) (8)	21.8 (4.4) (8)	-

Core	24.3 (2.5) (4)	24.3 (2.5) (4)	-
PNOS Inception	28.5 (8.0) (14)	29.4 (9.1) (10)	26.3 (4.3) (4)
6 months	28.1 (7.5) (12)	29.0 (8.8) (8)	26.3) (4.3) (4)
Follow-up	24.0 (7.0) (3)	22.0 (-) (2)	28.0 (-) (1)
Core	24.0 (6.9) (3)	22.0 (-) (2)	28.0 (-) (1)
SIM Inception	24.7 (7.3) (6)	26.0 (9.0) (4)	22.0 (-) (2)
6 months	24.7 (7.3) (6)	26.0 (9.0) (4)	22.0 (-) (2)
Follow-up	23.5 (5.7) (6)	25.3 (8.4) (3)	21.7 (0.6) (3)
Core	21.7 (0.6) (3)	21.0 (-) (1)	22.0 (-) (2)
MGMC Inception	28.0 (-) (1)	-	28.0 (-) (1)
6 months	28.0 (-) (1)	-	28.0 (-) (1)
Follow-up	28.0 (-) (1)	-	28.0 (-) (1)
Core	28.0 (-) (1)	-	28.0 (-) (1)
SDD Inception	25.0 (-) (1)	25.0 (-) (1)	-
6 months	25.0 (-) (1)	25.0 (-) (1)	-
Alz follow-up	25.0 (-) (1)	-	25.0 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BD II Bipolar disorder II
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder
Alz Alzheimer's disease
PANSS gen Positive and Negative Syndrome Scale, general subscale

Table 24b: PANSS general scores at six year follow-up for SZ, SZ, BD and MDDP at follow-up

Diagnosis	All PANSS gen scores (SD) (n)	Male PANSS gen Scores (SD) (n)	Female PANSS gen scores (SD) (n)
SZ	32.9 (10.4) (60)	34.6 (11.0) (42)	29.1 (8.0) (18)
SA	30.0 (9.2) (27)	31.5 (11.0) (16)	27.7 (5.6) (11)
BD	26.2[b] (8.9) (33)	28.0 (10.0) (17)	24.3 (7.3) (16)

MDDP	24.6[b] (7.7) (26)	26.3 (6.8) (12)	23.1 (8.4) (14)

[b] $p<0.01$ vs. SZ

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
PANSS gen Positive and Negative Syndrome Scale general subscale

As indicated in Tables 24a/b, PANSS general scores are highest for SZ, only slightly lower for SA and lower still for BD and MDDP. All four diagnoses show a similar pattern of lower scores among females at follow-up (effect of sex, $p<0.05$; no diagnosis x sex interaction). Other diagnoses show similar levels of general psychopathology.

Functioning

GAF scores

Table 25a: GAF scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all three occasions

Diagnosis	All GAF (SD) (n)	Male GAF (SD) (n)	Female GAF (SD) (n)
SZ Inception	53.4 (16.0) (30)	53.3 (16.6) (24)	54.0 (14.5) (6)
6 months	53.2 (14.7) (42)	52.8 (15.1) (34)	54.6 (13.8) (8)
Follow-up	52.5 (12.8) (60)	51.0 (13.1 (42)	56.1 (11.7) (18)
Core	51.0 (15.6) (26)	50.5 (15.8) (21)	53.2 (16.1) (5)
SF Inception	61.0 (14.6) (21)	62.4 (16.8) (14)	58.0 (9.1) (7)
6 months	63.3 (12.2) (10)	68.0 (14.8) (5)	58.6 (7.6) (5)
Follow-up	67.7 (2.5) (3)	70.0 (-) (1)	66.5 (-) (2)
Core	67.7 (2.5) (3)	70.0 (-) (1)	66.5 (-) (2)
BrPsy Inception	68.0 (11.8) (13)	52.5 (-) (2)	70.7 (9.9) (11)
6 months	67.8 (12.2) (10)	52.5 (-) (2)	71.6 (9.6) (8)
Follow-up	69.3 (3.0) (4)	70.0 (-) (2)	68.5 (-) (2)
Core	68.5 (-) (2)	-	68.5 (-) (2)

SA Inception	59.3 (8.4) (6)	58.0 (-) (1)	59.6 (9.4) (5)
6 months	53.7 (16.0) (11)	48.8 (19.5) (6)	59.6 (9.4) (5)
Follow-up	59.2 (13.3) (27)	57.1 (15.0) (16)	62.4 (10.0) (11)
Core	59.3 (8.4) (6)	58.0 (-) (1)	59.6 (9.4) (5)
BD I Inception	65.0 (15.3) (30)	60.5 (16.2) (16)	70.2 (12.9) (14)
6 months	67.2 (13.8) (32)	64.4 (14.6) (16)	70.0 (12.9) (16)
Follow-up	66.7 (12.4) (35)	63.9 (12.8) (18)	70.0 (11.7) (17)
Core	68.2 (12.5) (25)	64.7 (11.9) (12)	71.4 (12.6) (13)
BD II follow-up	85.0 (-) (1)	-	85.0 (-) (1)
MDDP Inception	65.2 (12.8) (33)	60.73 (11.2) (15)	68.6 (13.1) 18)
6 months	66.8 (10.7) (33)	64.0 (6.6) (14)	68.9 (12.8) (19)
Follow-up	68.2 (10.6) (27)	64.8 (7.7) (13)	71.4 (12.1) (14)
Core	67.4 (11.3) (22)	63.1 (7.4) (10)	70.9 (13.0) (12)
DD Inception	60.6 (9.2) (14)	59.3 (9.3) (10)	63.8 (9.5) (4)
6 months	62.4 (8.2) (11)	61.6 (8.0) (7)	63.8 (9.5) (4)
Follow-up	75.3 (11.0) (3)	69.0 (-) (2)	88.0 (-) (1)
Core	69.0 (-) (2)	69.0 (-) (2)	-
PGMC Inception	51.5 (12.2) (4)	41.5 (-) (2)	61.5 (-) (2)
6 months	51.5 (12.2) (4)	41.5 (-) (2)	61.5 (-) (2)
Follow-up	56.0 (15.6) (3)	38.0 (-) (1)	65.0 (-) (2)
Core	51.5 (-) (2)	38.0 (-) (1)	65.0 (-) (1)
SIP Inception	66.4 (12.0) (10)	66.4 (12.0) (10)	-
6 months	68.7 (9.9) (10)	68.7 (9.9) (10)	-
Follow-up	75.0 (4.9) (8)	75.0 (4.9) (8)	-
Core	74.5 (3.3) (4)	74.5 (3.3) (4)	-
PNOS Inception	60.5 (14.3) (15)	59.5 (10.9) (10)	62.6 (21.1) (5)
6 months	60.0 (15.2) (13)	58.4 (11.7) (8)	62.6 (21.1) (5)
Follow-up	71.5 (10.8) (4)	70.0 (-) (2)	73.0 (-) (2)
Core	71.5 (10.8) (4)	70.0 (-) (2)	73.0 (-) (2)
SIM Inception	67.5 (10.7) (6)	65.0 (11.4) (4)	72.5 (- (2)
6 months	67.5 (10.7) (6)	65.0 (11.4) (4)	72.5 (-) (2)
Follow-up	74.3 (7.8) (6)	72.0 (-) (2)	76.7 (10.4) (3)
Core	74.3 (8.1) (3)	78.0 (-) (1)	72.5 (-) (2)

MGMC Inception	45.0 (-) (1)	-	45.0 (-) (1)
6 months	45.0 (-) (1)	-	45.0 (-) (1)
Follow-up	45.0 (-) (1)	-	45.0 (-) (1)
Core	45.0 (-) (1)	-	45.0 (-) (1)
SDD Inception	55.0 (-) (1)	55.0 (-) (1)	-
6 months	55.0 (-) (1)	55.0 (-) (1)	-
Alz Follow-up	35.0 (-) (1)	-	35.0 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BD II Bipolar disorder II
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder
Alz Alzheimer's disease
GAF Global Assessment of Functioning

Table 25b: GAF scores at six year follow-up for SZ, SZ, BD and MDDP at follow-up

Diagnosis	All GAF scores (SD) (n)	Male GAF scores (SD) (n)	Female GAF scores (SD) (n)
SZ	52.5 (12.8) (60)	51.0 (13.1) (42)	56.1 (11.7 (18)
SA	59.2[a] (13.3) (27)	57.1 (15.0) (16)	62.4 (10.0) (11)
BD	66.7[c] (12.4) (35)	63.9 (12.8) (18)	70.0 (11.7) (17)
MDDP	68.2[c] (10.6) (27)	64.8 (7.7) (13)	71.4 (12.1) (14)

[a] $p<0.05$, [c] $p<0.001$ vs. SZ

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
GAF Global Assessment of Functioning

As indicated in Tables 25a/b, GAF scores show overall outcome to be poor for SZ, slightly better for SA and better still for BD and MDDP. All four diagnosis show a similar pattern of higher scores (better functioning) among females at follow-up (effect of sex, $p<0.01$; no diagnosis x sex interaction). Other diagnoses show GAF scores generally similar to those for BD and MDDP, with the exception of poor functioning in PGMC and MGMC.

HoNOS scores

Table 26a: HoNOS scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all three occasions

Diagnosis	All HoNOS (SD) (n)	Male HoNOS (SD) (n)	Female HoNOS (SD) (n)
SZ Inception	11.0 (7.2) (30)	11.4 (7.7) (24)	9.7 (5.1) (6)
6 months	11.7 (6.9) (42)	11.9 (7.2) (34)	11.0 (5.9) (8)
Follow-up	10.8 (6.8) (60)	11.7 (7.3) (42)	8.6 (5.2) (18)
Core	11.5 (7.3) (26)	12.3 (7.7) (21)	8.4 (4.5) (5)
SF Inception	8.6 (6.7) (21)	7.5 (6.8) (14)	10.9 (6.3) (7)
6 months	7.1 (5.0) (10)	5.0 (3.9) (5)	9.2 (5.4) (5)
Follow-up	8.7 (6.4) (3)	5.0 (-) (1)	10.5 (-) (2)
Core	8.7 (6.4) (3)	5.0 (-) (1)	10.5 (-) (2)
BrPsy Inception	4.9 (4.4) (13)	8.0 (-) (2)	4.4 (3.4) (11)
6 months	4.5 (4.6) (10)	8.0 (-) (2)	3.6 (6.1) (8)
Follow-up	6.3 (3.1) (4)	5.0 (-) (2)	7.5 (-) (2)
Core	7.5 (-) (2)	-	7.5 (-) (2)
SA Inception	7.5 (2.9) (6)	10.0 (-) (1)	7.0 (2.9) (5)
6 months	9.5 (6.0) (11)	11.5 (7.4) (6)	7.0 (2.9) (5)
Follow-up	8.1 (5.2) (27)	9.3) (6.1) (16)	6.4 (3.0) (11)
Core	7.5 (2.9) (6)	10.0 (-) (1)	7.0 (2.9) (5)
BD I Inception	5.7 (5.5) (29)	7.5 (6.0) (16)	3.5 (4.1) (13)
6 months	5.4 (5.2) (31)	6.7 (5.8) (16)	3.9 (4.2) (15)
follow-up	6.1 (5.6) (33)	7.4 (5.7) (17)	4.7 (5.3) (16)
Core	5.2 (5.2) (24)	7.1 (5.6) (12)	3.3 (4.2) (12)
BD II Follow-up	1.0 (-) (1)	-	1.0 (-) (1)

MDDP Inception	7.5 (7.1) (31)	10.2 (8.1) (13)	5.6 (5.7) (18)
6 months	6.3 (6.1) (31)	7.6 (6.9) (12)	5.5 (5.6) (19)
Follow-up	6.0 (6.1) (26)	8.4 (6.4) (12)	4.0 (5.2) (14)
Core	6.6 (6.5) (21)	9.4 (7.0) (9)	4.4 (5.5) (12)
DD Inception	7.2 (3.4) (13)	7.6 (3.1) (9)	6.5 (4.4) (4)
6 months	6.3 (2.8) (10)	6.2 (1.3) (6)	6.5 (4.4) (4)
Follow-up	4.0 (2.0) (3)	5.0 (-) (2)	2.0 (-) (1)
Core	5.0 (-) (2)	5.0 (-) (2)	-
PGMC Inception	12.3 (6.1) (4)	17.5 (-) (2)	7.0 (-) (2)
6 months	12.3 (6.1) (4)	17.5 (-) (2)	7.0 (-) (2)
Follow-up	12.3 (5.5) (3)	18.0 (-) (1)	9.5 (-) (2)
Core	12.5 (-) (2)	18.0 (-) (1)	7.0 (-) (1)
SIP Inception	8.6 (4.8) (10)	8.6 (4.8) (10)	-
6 months	9.0 (5.1) (10)	9.0 (5.1) (10)	-
Follow-up	6.3 (4.0) (8)	6.3 (4.0) (8)	-
Core	7.3 (5.2) (4)	7.3 (5.2) (4)	-
PNOS Inception	10.4 (5.8) (14)	10.9 (6.2) (10)	9.0 (5.2) (4)
6 months	9.7 (6.0) (12)	10.0 (6.7) (8)	9.0 (5.2) (4)
Follow-up	4.7 (4.7) (3)	5.5 (-) (2)	3.0 (-) (1)
Core	4.7 (4.7) (3)	5.5 (-) (2)	3.0 (-) (1)
SIM Inception	6.0 (3.7) (6)	6.3 (4.4) (4)	5.5 (-) (2)
6 months	6.0 (3.7) (6)	6.3 (4.3) (4)	5.5 (-) (2)
Follow-up	5.3 (3.5) (6)	4.7 (4.7) (3)	6.0 (2.6) (3)
Core	4.7 (2.9) (3)	3.0 (-) (1)	5.5 (-) (2)
MGMC Inception	15.0 (-) (1)	-	15.0 (-) (1)
6 months	15.0 (-) (1)	-	15.0 (-) (1)
Follow-up	15.0 (-) (1)	-	15.0 (-) (1)
Core	15.0 (-) (1)	-	15.0 (-) (1)
SDD Inception	5.0 (-) (1)	5.0 (-) (1)	-
6 months	5.0 (-) (1)	5.0 (-) (1)	-
Alz Follow-up	15.0 (-) (1)	-	15.0 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
MDDP Major depressive disorder with psychosis
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder

BD I Bipolar disorder I
BD II Bipolar disorder II
DD Delusional disorder
Alz Alzheimer's disease
HoNOS Health of the Nation Outcome Scale

Table 26b: HoNOS scores at six year follow-up for SZ, SZ, BD and MDDP at follow-up

Diagnosis	All HoNOS scores (SD) (n)	Male HoNOS scores (SD) (n)	Female HoNOS scores (SD) (n)
SZ	10.8 (6.8) (60)	11.7 (7.3) (42)	8.6 (5.2) (18)
SA	8.1 (5.2) (27)	9.3 (6.1) (16)	6.4 (3.0) (11)
BD	6.1[b] (5.6) (33)	7.4 (5.7) (17)	4.7 (5.3) (16)
MDDP	6.0[b] (6.1) (26)	8.4 96.4) (12)	4.0 (5.2) (14)

[b] $p<0.01$ vs. SZ

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
HoNOS Health of the Nation Outcome Scale

As indicated in Tables 26a/b, HoNOS scores also show outcome to be poorest for SZ, slightly better for SA and better still for BD and MDDP. All four diagnoses show a similar pattern of lower scores (better functioning) among females at follow-up (effect of sex, $p<0.01$; no diagnosis x sex interaction). Other diagnoses show HoNOS scores generally similar to those for BD and MDDP, with the exceptions of poor functioning in the small number of cases of PGMC and MGMC.

Strauss-Carpenter scores

Table 27a: Strauss-Carpenter scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all three occasions

Diagnosis	All Strauss-Carpenter (SD) (n)	Male Strauss-Carpenter (SD) (n)	Female Strauss-Carpenter (SD) (n)
SZ Inception	21.8 (8.6) (30)	22.6 (9.0) (24)	18.7 (6.6) (6)
6 months	21.8 (8.4) (42)	22.1 (8.7) (34)	20.4 (7.5) (8)
Follow-up	21.4 (7.7) (60)	21.1 (8.1) (42)	22.1 (6.9) (18)
Core	20.4 (8.2) (26)	21.1 (8.6) (21)	17.2 (6.1) (5)
SF Inception	24.4 (8.0) (20)	25.5 (9.1) (13)	22.1 (5.5) (7)
6 months	23.4 (6.6) (9)	26.8 (8.8) (4)	20.8 (3.1) (5)
Follow-up	18.0 (-) (2)	-	18.0 (-) (2)
Core	18.0 (-) (2)	-	18.0 (-) (2)
BrPsy Inception	29.6 (5.8) (13)	22.5 (-) (2)	31.0 (5.1) (11)
6 months	30.5 (5.6) (10)	22.5 (-) (2)	32.5 (3.8) (8)
Follow-up	34.3 (1.7) (4)	35.0 (-) (2)	33.5 (-) (2)
Core	33.5 (2.1) (2)	-	33.5 (-) (2)
SA Inception	28.5 (3.1) (6)	28.0 (-)(1) (1)	28.6 (3.4) (5)
6 months	25.6 (8.0) (11)	23.0 (10.1) (6)	28.6 (3.4) (5)
Follow-up	25.3 (6.1) (27)	24.2 (6.9) (16)	26.9 (4.6) (11)
Core	28.5 (3.1) (6)	28.0 (-) (1)	28.6 (3.4) (5)
BD I Inception	28.6 (8.2) (29)	26.7 (9.0) (16)	31.0 (6.5) (13)
6 months	29.0 (7.6) (31)	28.0 (8.4) (16)	30.0 (6.7) (15)
Follow-up	29.5 (6.8) (33)	28.0 (7.4) (17)	31.0 (5.8) (16)
Core	30.1 (7.3) (24)	28.7 (8.0) (12)	31.6 (6.5) (12)
BD II Follow-up	35.0 (-) (1)	-	35.0 (-) (1)
MDDP Inception	26.8 (7.8) (31)	24.0 (7.8) (13)	28.9 (7.3) (18)
6 months	27.9 (7.0) (31)	25.9 (6.5) (12)	29.1 (7.2) (19)
Follow-up	28.5 (7.0) (26)	26.1 (6.7) (12)	30.6 (6.8) (14)
Core	27.5 (7.3) (21)	24.1 (6.3) (9)	30.1 (7.2) (12)
DD Inception	25.3 (6.4) (13)	24.9 (6.9) (9)	26.3 (7.8) (4)
6 months	26.2 (5.7) (10)	26.2 (4.6) (6)	26.3 (7.8) (4)
Follow-up	31.3 (4.5) (3)	29.0 (-) (2)	36.0 (-) (1)
Core	29.0 (-) (2)	29.0 (-) (2)	-

PGMC Inception	16.5 (9.4) (4)	8.5 (-) (2)	24.5 (-) (2)
6 months	16.5 (9.4) (4)	8.5 (-) (2)	24.5 (-) (2)
Follow-up	21.7 (10.2) (3)	10.0 (-) (1)	27.5 (-) (2)
Core	18.0 (-) (2)	10.0 (-) (1)	26.0 (-) (1)
SIP Inception	30.1 (5.6) (10)	30.1 (5.6) (10)	-
6 months	29.8 (5.9) (10)	29.8 (5.9) (10)	-
Follow-up	32.3 (2.6) (8)	32.3 (2.6) (8)	-
Core	32.5 (2.6) (4)	32.5 (2.6) (4)	-
PNOS Inception	25.1 (6.7) (14)	24.9 (4.7) (10)	25.8 (11.3) (4)
6 months	25.7 (7.1) (12)	25.6 (5.0) (8)	25.8 (11.3) (4)
Follow-up	32.0 (5.3) (3)	31.0 (-) (2)	
Core	32.0 (5.3) (3)	31.0 (-) (2)	34.0 (-) (1)
SIM Inception	30.2 (6.0) (6)	30.0 (7.6) (4)	31.0 (-) (2)
6 months	30.1 (6.0) (6)	29.8 (7.6) (4)	31.0 (-) (2)
Follow-up	33.5 (2.6) (6)	34.3 (1.5) (3)	32.7 (3.5) (3)
Core	32.0 (2.6) (3)	34.0 (-) (1)	31.0 (-) (2)
MGMC Inception	14.0 (-) (1)	-	14.0 (-) (1)
6 months	14.0 (-) (1)	-	14.0 (-) (1)
Follow-up	14.0 (-) (1)	-	14.0 (-) (1)
Core	14.0 (-)	-	14.0 (-) (1)
SDD Inception	27.0 (-) (1)	27.0 (-) (1)	-
6 months	27.0 (-) (1)	27.0 (-) (1)	-
Alz Follow-up	12.0 (-) (1)	-	12.0 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BD II Bipolar disorder II
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder
Alz Alzheimer's disease
DD Delusional disorder

Table 27b: Strauss-Carpenter scores at six year follow-up for SZ, SZ, BD and MDDP at follow-up

Diagnosis	All Strauss-Carpenter scores (SD) (n)	Male Strauss-Carpenter scores (SD) (n)	Female Strauss-Carpenter scores (SD) (n)
SZ	21.4 (7.7) (60)	21.1 (8.1) (42)	22.1 (6.9) (18)
SA	25.3[a] (6.1) (27)	24.2 (6.9) (16)	26.9 (4.6) (11)
BD	29.5[c] (6.8) (33)	28.0 (7.4) (17)	31.0 (5.8) (16)
MDDP	28.5[c] (7.0) (26)	26.1 (6.7) (12)	30.6 (6.8) (14)

[a] $p<0.05$, [c] $p<0.001$ vs. SZ

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis

As indicated in Tables 27a/b, scores show outcome to be poorest for SZ, slightly better for SA and better still for BD and MDDP. All four diagnoses show a similar pattern of higher scores (better functioning) among females at follow-up (effect of sex, $p<0.05$; no diagnosis x sex interaction). Other diagnoses show Strauss-Carpenter scores generally similar to those for BD and MDDP, with the exception of poor functioning for SF and the small number of cases of PGMC and MGMC.

SLOF scores

Table 28a: SLOF scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all three occasions

Diagnosis	All SLOF (SD) (n)	Male SLOF (SD) (n)	Female SLOF (SD) (n)
SZ Inception	184.4 (23.9) (30)	185.6 (24.2) (24)	179.7 (23.9) (6)
6 months	184.7 (23.4) (42)	185.6 (23.3) (34)	180.9 (25.1) (8)
Follow-up	186.1 (22.9) (60)	183.8 (23.7) (42)	191.6 (20.6) (18)
Core	180.7 (23.4) (26)	181.7 (23.4) (21)	176.4 (25.2) (5)
SF Inception	187.2 (34.4) (20)	194.3 (27.3) (13)	173.9 (43.9) (7)
6 months	181.7 (42.1) (9)	196.8 (30.5) (4)	169.6 (49.3) (5)
Follow-up	175.0 (-) (2)	-	175.0 (-) (2)
Core	125.0 (-) (2)	-	125.0 (-) (2)
BrPsy Inception	205.9 (10.3) (13)	186.5 (-) (2)	209.4 (6.3) (11)
6 months	205.6 (11.8) (10)	186.5 (-) (2)	210.4 (7.0) (8)
follow-up	212.5 (3.0) (4)	215.0 (-) (2)	210.0 (-) (2)
Core	210.0 (-) (2)	-	210.0 (-) (2)
SA Inception	209.3 (4.3) (6)	207.0 (-) (1)	209.8 (4.7) (5)
6 months	194.9 (27.1) (11)	182.5 (32.4) (6)	209.8 (4.7) (5)
Follow-up	197.7 (19.7) (27)	191.6 (23.4) (16)	206.5 (6.5) (11)
Core	209.3 (4.3) (6)	207.0 (-) (1)	209.8 (4.7) (5)
BD I Inception	202.2 (24.8) (29)	196.1 (31.6) (16)	209.7 (8.8) (13)
6 months	204.9 (21.1) (31)	200.8 (28.1) (16)	209.3 (8.3) (15)
Follow-up	205.7 (19.8) (33)	202.8 (26.2) (17)	208.7 (8.9) (16)
Core	206.1 (22.5) (24)	201.5 (30.8) (12)	210.7 (8.4) (12)
BD II Follow-up	215.0 (-) (1)	-	215.0 (-) (1)
MDDP Inception	197.5 (26.8) (31)	195.1 (20.3) (13)	199.2 (31.2) (18)
6 months	200.6 (24.9) (31)	202.1 (13.3) (12)	199.6 (30.4) (19)
Follow-up	201.1 (27.0) (26)	202.2 (13.4) (12)	200.1 (35.3) (14)
Core	198.1 (29.3) (21)	198.3 (13.4) (9)	198.0 (37.9) (12)
DD Inception	197.9 (17.1) (13)	201.2 (9.7) (9)	190.5 (28.5) (4)
6 months	199.1 (19.2) (10)	204.8 (8.8) (6)	190.5 (28.5) (4)
Follow-up	211.0 (4.0) (3)	209.0 (-) (2)	215.0 (-) (1)
Core	209.0 (-) (2)	209.0 (-) (2)	-

PGMC Inception	175.3 (41.6) (4)	142.5 (-) (2)	208.0 (-) (2)
6 months	175.3 (41.6) (4)	142.5 (-) (2)	208.0 (-) (2)
Follow-up	175.7 (33.8) (3)	163.0 (-) (1)	182.0 (-) (2)
Core	188.5 (-) (2)	163.0 (-) (1)	214.0 (-) (1)
SIP Inception	209.7 (7.2) (10)	209.7 (7.2) (10)	-
6 months	210.8 (5.7) (10)	210.8 (5.7) (10)	-
Follow-up	213.3 (2.4) (8)	213.3 (2.4) (8)	-
Core	214.5 (0.6) (4)	214.5 (0.6) (4)	-
PNOS Inception	194.1 (23.2) (14)	197.9 (11.6) (10)	184.5 (42.1) (4)
6 months	193.3 (24.9) (12)	197.8 (12.1) (8)	184.5 (42.1) (4)
follow-up	208.3 (8.3) (3)	207.0 (-) (2)	211.0 (-) (1)
Core	208.3 (8.3) (3)	207.0 (-) (2)	211.0 (-) (1)
SIM Inception	204.8 (14.0) (6)	202.3 (17.2) (4)	210.0 (-) (2)
6 months	204.8 (14.0) (6)	202.3 (17.2) (4)	210.0 (-) (2)
Follow-up	211.3 (3.5) (6)	211.0 (3.6) (3)	211.7 (4.2) (3)
Core	210.0 (3.0) (3)	210.0 (-) (1)	210.0 (-) (2)
MGMC Inception	182.0 (-) (1)	-	182.0 (-) (1)
6 months	182.0 (-) (1)	-	182.0 (-) (1)
Follow-up	182.0 (-) (1)	-	182.0 (-) (1)
Core	182.0 (-) (1)	-	182.0 (-) (1)
SDD Inception	209.0 (-) (1)	209.0 (-) (1)	-
6 months	209.0 (-) (1)	209.0 (-) (1)	-
Alz Follow-up	124.0 (-) (1)	-	124.0 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
PNOS Psychosis not otherwise specified
MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BDII Bipolar disorder II
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
BrPsy Brief psychotic disorder
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder
Alz Alzheimer's disease
SLOF Specific Levels of Functioning Scale

Table 28b: SLOF scores at six year follow-up for SZ, SZ, BD and MDDP at follow-up

Diagnosis	All SLOF scores (SD) (n)	Male SLOF scores (SD) (n)	Female SLOF scores (SD) (n)
SZ	186.1 (22.9) (60)	183.8 (23.7) (42)	191.6 (20.6) (18)
SA	197.7[a] (19.7) (27)	191.6 (23.4) (16)	206.5 (6.5) (11)
BD	205.7[c] (19.8) (33)	202.8 (26.2) (17)	208.7 (8.9) (16)
MDDP	201.1[a] (27.0) (26)	202.2 (13.4) (12)	200.1 (35.3) (14)

[a] $p<0.05$, [c] $p<0.001$ vs. SZ

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
SLOF Specific Level of Functioning

As indicated in Tables 28a/b, SLOF scores show outcome to be poorest for SZ, slightly better for SA and MDDP and better still for BD. While SLOF scores appear somewhat higher in females, with the exception of MDDP, no significant differences were evident at follow-up (no effect of sex, no diagnosis x sex interaction). Other diagnoses show SLOF scores generally similar to or slightly better than those for BD and MDDP, with the exception of poor functioning for the small number of cases of PGMC and MGMC.

Quality of life

QLS scores

Table 29a: QLS scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all three occasions

Diagnosis	All QLS (SD) (n)	Male QLS (SD) (n)	Female QLS (SD) (n)
SZ Inception	72.2 (32.1) (30)	73.1 (32.4) (24)	68.7 (33.6) (6)
6 months	72.4 (29.8) (42)	72.2 (29.5) (34)	73.1 (33.2) (8)
Follow-up	70.2 (27.1) (60)	67.8 (27.2) (42)	75.8 (26.9) (18)
Core	66.9 (31.1) (26)	67.7 (31.0) (21)	63.6 (34.9) (5)
SF Inception	80.7 (28.0) (20)	83.0 (31.8) (13)	76.3 (20.7) (7)
6 months	78.9 (27.3) (9)	87.3 (40.0) (4)	72.2 (12.8) (5)
Follow-up	63.5 (-) (2)	-	63.5 (-) (2)
Core	63.5 (-) (2)	-	63.5 (-) (2)
BrPsy Inception	98.6 (16.1) (13)	73.5 (-) (2)	103.2 (12.4) (11)
6 months	98.8 (18.5) (10)	73.5 (-) (2)	105.1 (14.2) (8)
Follow-up	109.8 (5.7) (4)	111.5 (-) (2)	108.0 (-) (2)
Core	108.0 (-) (2)	-	108.0 (-) (2)
SA Inception	95.5 (11.6) (6)	103.0 (-) (1)	94.0 (12.3) (5)
6 months	81.6 (33.0) (11)	71.2 (42.1) (6)	94.0 (12.3) (5)
Follow-up	85.2 (24.8) (27)	80.8 (29.5) (16)	91.6 (15.1) (11)
Core	95.5 (11.6) (6)	103.0 (-) (1)	94.0 (12.3) (5)
BD I Inception	97.1 (28.2) (29)	89.6 (33.1) (16)	106.2 (18.1) (13)
6 months	100.6 (22.9) (31)	96.1 (27.1) (16)	105.3 (17.0) (15)
Follow-up	100.7 (19.5) (33)	96.8 (22.3) (17)	104.9 (15.7) (16)
Core	104.3 (19.5) (24)	99.7 922.1) (12)	108.8 (16.2) (12)
BD II Follow-up	121.0 (-) (1)	-	121.0 (-) (1)
MDDP Inception	91.7 (28.4) (31)	83.6 (26.5) (13)	97.6 (29.1) (18)
6 months	95.2 (24.5) (31)	91.5 (17.6) (12)	97.5 (28.3) (19)
Follow-up	97.6 (24.4) (26)	92.8 (18.2) (12)	101.7 (28.8) (14)
Score	95.4 (26.7) (21)	88.1 (18.5) (9)	100.8 (31.2) (12)
DD Inception	84.7 (18.2) (13)	85.8 (17.2) (9)	82.3 (23.0) (4)

6 months	85.7 (19.2) (10)	88.0 (18.2) (6)	82.3 (23.0) (4)
Follow-up	105.3 (16.2) (3)	96.0 (-) (2)	124.0 (-) (1)
Core	96.0 (-) (2)	96.0 (-) (2)	-
PGMC Inception	64.0 (35.1) (4)	37.0 (-) (2)	91.0 (-) (2)
6 months	64.0 (35.1) (4)	37.0 (-) (2)	91.0 (-) (2)
Follow-up	80.0 (32.4) (3)	45.0 (-) (1)	97.5 (-) (2)
Core	77.0 (-) (2)	45.0 (-) (1)	109.0 (-) (1)
SIP Inception	101.8 (19.6) (10)	101.8 (19.6) (10)	-
6 months	104.0 (18.3) (10)	104.0 (18.3) (10)	-
Follow-up	113.5 (6.4) (8)	113.5 (6.4) (8)	-
Core	112.5 (7.0) (4)	112.5 (7.0) (4)	-
PNOS Inception	86.0 (20.4) (14)	86.4 (17.2) (10)	85.0 (30.3) (4)
6 months	84.6 (21.5) (12)	84.4 (18.2) (8)	85.0 (30.3) (4)
Follow-up	102.7 (17.9) (3)	100.5 (-) (2)	107.0 (-) (1)
Core	102.7 (17.9) (3)	100.5 (-) (2)	107.0 (-) (1)
SIM Inception	96.7 (21.5) (6)	95.3 (26.2) (4)	99.5 (-) (2)
6 months	96.7 (21.5) (6)	95.3 (26.2) (4)	99.5 (-) (2)
Follow-up	108.7 (9.9) (6)	112.7 (2.3) (3)	104.7 (-) (3)
core	103.0 (12.1) (3)	110.0 (-) (1)	99.5 (-) (2)
MGMC Inception	95.0 (-) (1)	-	95.0 (-) (1)
6 months	95.0 (-) (1)	-	95.0 (-) (1)
Follow-up	95.0 (-) (1)	-	95.0 (-) (1)
Core	95.0 (-) (1)	-	95.0 (-) (1)
SDD Inception	92.0 (-) (1)	92.0 (-) (1)	-
6 months	92.0 (-) (1)	92.0 (-) (1)	-
Alz Follow-up	62.0 (-) (1)	-	62.0 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BD II Bipolar disorder II
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder
Alz Alzheimer's disease
QLS Quality of Life Scale

Table 29b: QLS scores at six year follow-up for SZ, SA, BD and MDDP at follow-up

Diagnosis	All QLS scores (SD) (n)	Male QLS scores (SD) (n)	Female QLS scores (SD) (n)
SZ	70.2 (27.1) (60)	67.8 (27.2) (42)	75.8 (26.9) (18)
SA	85.2[a] (24.8) (27)	80.8 (29.5) (16)	91.6 (15.1) (11)
BD	100.7[c] (19.5) (33)	96.8 (22.3) (17)	104.9 (15.7) (16)
MDDP	97.6[c] (24.4) (26)	92.8 (18.2) (12)	101.7 (28.8) (14)

[a] $p<0.05$, [c] $p<0.001$ vs. SZ

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
QLS Quality of Life Scale

As indicated in Tables 29a/b, QLS scores show QOL to be lowest for SZ, slightly better for SA and better still for BD and MDDP. All four diagnoses show a similar pattern of higher scores (better QOL) among females at follow-up (effect of sex $p<0.05$; no diagnosis x sex interaction). Other diagnoses show QOL scores generally similar to or slightly better than those of BD and MDDP, with the exception of low QOL for the small number of cases of PGMC and MGMC.

WHOQOL-Bref scores

Table 30a: WHOQOL-Bref scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all three occasions

Diagnosis	All WHOQOL-Bref (SD) (n)	Male WHOQOL-Bref (SD) (n)	Female WHOQOL-Bref (SD) (n)
SZ Inception	94.2 (11.8) (18)	94.7 (12.7) (15)	91.3 (7.4) (3)

6 months	94.0 (10.5) (23)	94.4 (11.3) (19)	92.3 (6.3) (4)
Follow-up	94.1 (10.8) (35)	94.1 (10.5) (23)	94.1 (11.8) (12)
Core	93.1 (12.1) (16)	93.5 (13.1) (13)	91.3 (7.4) (3)
SF Inception	99.0 (13.2) (10)	101.6 (13.1) (8)	88.5 (-) (2)
6 months	94.2 (8.7) (5)	97.3 (6.2) (4)	82.0 (-) (1)
Follow-up	-	-	-
Core	-	-	-
BrPsy Inception	105.3 (15.2) (8)	82.0 (-) (1)	108.6 (12.9) (7)
6 months	102.7 (16.9 (6)	82.0 (-) (1)	106.8 (15.1) (5)
Follow-up	80.0 (-) (1)	-	80.0 (-) (1)
Core	80.0 (-) (1)	-	80.0 (-) (1)
SA Inception	90.0 (12.2) (6)	95.0 (-) (1)	89.0 (13.4) (5)
6 months	91.9 (12.2) (7)	99.0 (-) (2)	89.0 (13.4) (5)
Follow-up	94.8 (11.7) (16)	94.9 (9.0) (9)	94.7 (15.4) (7)
Core	90.0 (12.2) (6)	95.0 (-) (1)	89.0 (13.4) (5)
BD I Inception	99.6 (12.2) (22)	95.6 (14.3) (10)	102.9 (9.6) (12)
6 months	101.5 (13.2) (24)	97.6 (16.7) (10)	104.4 (9.7) (14)
Follow-up	98.8 (16.4) (24)	95.2 (20.0) (13)	103.1 (10.0) (11)
Core	99.3 (13.2) (19)	94.0 (15.7) (8)	103.1 (10.0) (11)
BD II Follow-up	122.0 (-) (1)	-	122.0 (-) (1)
MDDP Inception	100.4 (14.8) (22)	95.4 (15.9) (10)	104.6 (13.0) (12)
6 months	101.2 (15.0) (23)	97.5 (16.7) (11)	104.6 (13.0) (12)
Follow-up	100.4 (14.7) (21)	94.1 (15.4) (10)	106.2 (11.9) (11)
Core	99.5 (15.8) (17)	93.5 (17.4) (8)	104.8 (12.8) (9)
DD Inception	95.4 (6.6) (9)	97.0 (4.9) (6)	92.3 (9.6) (3)
6 months	95.6 (7.6) (7)	98.0 (6.0) (4)	92.3 (9.6) (3)
Follow-up	101.5 (-) (2)	91.0 (-) (1)	112.0 (-) (1)
Core	91.0 (-) (1)	91.0 (-) (1)	-
PGMC Inception	88.3 (3.1) (3)	87.0 (-) (2)	91.0 (-) (1)
6 months	88.3 (3.1) (3)	87.0 (-) (2)	91.0 (-) (1)
Follow-up	91.3 (2.5) (3)	89.0 (-) (1)	92.5 (-) (2)
Core	90.0 (-) (2)	89.0 (-) (1)	91.0 (-) (1)
SIP Inception	90.0 (19.6) (7)	90.0 (19.6) (7)	-
6 months	89.0 (18.4) (8)	89.0 (18.4) (8)	-
Follow-up	94.0 (9.4) (8)	94.0 (9.4) (8)	-
Core	88.8 (9.8) (4)	88.8 (9.8) (4)	-

PNOS Inception	92.2 (11.1) (10)	94.3 (10.7) (6)	89.0 (12.5) (4)
6 months	93.3 (11.2) (9)	96.8 (9.9) (5)	89.0 (12.5) (4)
Follow-up	100.0 (9.6) (3)	103.5 (-) (2)	93.0 (-) (1)
Core	100.0 (9.6) (3)	103.5 (-) (2)	93.0 (-) (1)
SIM Inception	103.0 (15.1) (3)	103.0 (15.1) (3)	-
6 months	103.0 (15.1) (3)	103.0 (15.1) (3)	-
Follow-up	110.5 (8.9) (4)	112.3 (9.9) (3)	-
Core	117.0 (-) (1)	117.0 (-) (1)	-
MGMC Inception	75.0 (-) (1)	-	75.0 (-) (1)
6 months	75.0 (-) (1)	-	75.0 (-) (1)
Follow-up	75.0 (-) (1)	-	75.0 (-) (1)
Core	75.0 (-) (1)	-	75.0 (-) (1)
SDD Inception	92.0 (-) (1)	92.0 (-) (1)	-
6 months	92.0 (-) (1)	92.0 (-) (1)	-
Alz Follow-up	79.0 (-) (1)	-	79.0 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BD II Bipolar disorder II
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder
Alz Alzheimer's disease

WHO-QOL Bref World Health Organisation Quality of Life Bref

Table 30b: WHOQOL-Bref at six year follow-up for SZ, SA, BD and MDDP at follow-up

Diagnosis	All WHOQOL-Bref scores (SD) (n)	Male WHOQOL-Bref scores (SD) (n)	Female WHOQOL-Bref scores (SD) (n)
SZ	94.1 (10.8) (35)	94.1 (10.5) (23)	94.1 (11.8) (12)
SA	94.8 (11.7) (16)	94.9 (9.0) (9)	94.7 (15.4) (7)
BD	98.8 (16.4) (24)	95.2 (20.0) (13)	103.1 (10.0) (11)

MDDP	100.4 (14.7) (21)	94.1 (15.4) (10)	106.2 (11.9) (11)

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
WHO-QOL Bref World Health Organisation Quality of Life Bref

As indicated in Tables 30a/b, WHOQOL-Bref data at follow-up are available for fewer of the total number of inceptees. While the lowest scores, reflecting poorest subjective QOL, are found in SZ and SA, with higher scores apparent for MDDP and BD, no significant differences between the diagnoses were evident at follow-up (no effect of diagnosis or sex; no diagnosis x sex interaction). Other diagnoses showed WHOQOL-Bref scores similar to those above, with the exception of low QOL for the small number of cases of PGMC and MGMC.

Service engagement

SES scores

Table 31a: SES scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all three occasions

Diagnosis	All SES (SD) (n)	Male SES (SD) (n)	Female SES (SD) (n)
SZ Inception	18.4 (11.9) (30)	18.4 (11.0) (24)	18.5 (16.2) (6)
6 months	19.5 (12.5) (42)	19.7 (11.6) (34)	18.5 (16.9) (8)
Follow-up	20.4 (12.5) (60)	21.9 (12.0) (42)	17.1 (13.3) (18)
Core	20.3 (11.5) (26)	19.9 (10.9) (21)	22.2 (15.0) (5)
SF Inception	16.2 (13.8) (21)	14.3 (13.2) (14)	20.0 (15.4) (7)
6 months	17.0 (13.9) (10)	13.4 (14.9) (5)	20.6 (13.5) (5)
Follow-up	27.7 (7.8) (3)	34.0 (-) (1)	24.5 (-) (2)
Core	27.7 (7.8) (3)	34.0 (-) (1)	24.5 (-) (2)

BrPsy Inception	15.2 (16.5)(13)	20.5 (-) (2)	14.3 (15.8) (11)
6 months	14.6 (17.6) (10)	20.5 (-) (2)	13.1 (16.6) (8)
Follow-up	19.5 (13.6) (4)	21.0 (-) (2)	18.0 (-) (2)
Core	18.0 (-) (2)	-	18.0 (-) (2)
SA Inception	4.7 (4.2) (6)	6.0 (-) (1)	4.4 (4.6) (5)
6 months	14.7 (14.6) (11)	23.3 (14.7) (6)	4.4 (4.6) (5)
Follow-up	13.3 (11.6) (27)	16.2 (11.0) (16)	9.1 (11.7 (11)
Core	4.7 (4.2) (6)	6.0 (-) (1)	4.4 (4.6) (5)
BD I Inception	12.4 (12.0) (29)	15.9 (11.8) (16)	8.0 (11.2) (13)
6 months	11.2 (11.5) (31)	14.1 (11.9) (16)	8.1 (10.6) (15)
Follow-up	12.2 (12.2) (33)	12.9 (10.6) (17)	11.6 (14.0) (16)
Core	10.9 (11.5) (24)	14.1 (10.9) (12)	7.7 (11.6) (12)
BD II Follow-up	0.0 (-) (1)	-	0.0 (-) (1)
MDDP Inception	11.9 (12.9) (31)	15.3 (14.9) (13)	9.4 (11.0) (18)
6 months	10.7 (11.5) (31)	10.5 (10.8) (12)	10.7 (12.2) (19)
Follow-up	8.7 (10.1) (26)	9.8 (9.9) (12)	7.8 (10.5) (14)
Core	9.3 (11.0) (21)	9.9 (11.6) (9)	8.8 (11.1) (12)
DD Inception	13.7 (10.2) (14)	13.9 (11.0) (10)	13.3 (9.2) (4)
6 months	10.8 (7.7) (11)	9.4 (7.2) (7)	13.3 (9.2) (4)
Follow-up	4.3 (4.5) (3)	6.5 (-) (2)	0.0 (-) (1)
Core	6.5 (-) (2)	6.5 (-) (2)	-
PGMC Inception	20.3 (13.2) (4)	26.0 (-) (2)	14.5 (-) (2)
6 months	20.3 (13.2) (4)	26.0 (-) (2)	14.5 (-) (2)
Follow-up	12.7 (8.4) (3)	18.0 (-) (1)	10.0 -) (2)
Core	10.5 (-) (2)	18.0 (-) (1)	3.0 (-) (1)
SIP Inception	15.5 (11.4) (10)	15.5 (11.4) (10)	-
6 months	14.5 (11.6) (10)	14.5 (11.6) (10)	-
Follow-up	7.4 (8.6) (8)	7.4 (8.6) (8)	-
Core	9.3 (12.0) (4)	9.3 (12.0) (4)	-
PNOS Inception	16.3 (12.5) (14)	15.2 (14.0) (10)	11.5 (9.7) (4)
6 months	15.3 (11.8) (12)	17.1 (12.8) (8)	11.5 (9.7) (4)
Follow-up	4.3 (5.1) (3)	6.5 (-) (2)	0.0 (-) (1)
Core	4.3 (5.1) (3)	6.5 (-) (2)	0.0 (-) (1)
SIM Inception	13.8 (7.9) (6)	16.3 (6.1) (4)	9.0 (-) (2)
6 months	13.8 (7.9) (6)	16.3 (6.1) (4)	9.0 (-) (2)
Follow-up	14.2 (11.4) (6)	20.0 (12.5) (3)	8.3 (8.1) (3)
Core	12.3 (9.9) (3)	19.0 (-) (1)	9.0 (-) (2)

MGMC Inception	13.0 (-) (1)	-	13.0 (-) (1)
6 months	13.0 (-) (1)	-	13.0 (-) (1)
Follow-up	13.0 (-) (1)	-	13.0 (-) (1)
Core	13.0 (-) (1)	-	13.0 (-) (1)
SDD Inception	17.0 (-) (1)	17.0 (-) (1)	-
Alz Follow-up	18.0 (-) (1)	-	18.0 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
PNOS Psychosis not otherwise specified
MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BD II Bipolar disorder II
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
BrPsy Brief psychotic disorder
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder
Alz Alzheimer's disease
SES Service Engagement Scale

Table 31b: SES scores at six year follow-up for SZ, SA, BD and MDDP at follow-up

Diagnosis	All SES scores (SD) (n)	Male SES scores (SD) (n)	Female SES scores (SD) (n)
SZ	20.4 (12.5) (60)	21.9 (12.0) (42)	17.1 (13.3) (18)
SA	13.3[a] (11.6) (27)	16.2 (11.0) (16)	9.1 (11.7) (11)
BD	12.2[b] (12.2) (33)	12.9 (10.6) (17)	11.6 (14.0) (16)
MDDP	8.7[c] (10.1) (26)	9.8 (9.9) (12)	7.8 (10.5) (14)

[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$ vs SZ

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
SES Service Engagement Scale

As indicated in Tables 31a/b, high SES scores show particularly poor SE in SZ, somewhat better engagement in SA and BD, and best engagement in MDDP. All four diagnoses show a similar trend for better engagement among females at follow-up (effect of sex, p=0.07; no diagnosis x sex interaction). Among other diagnoses, SE was also poor for SF and BrPsy, but better for DD, SIP and PNOS.

Principal component analysis

For two of the primary outcomes of interest (functioning, QOL), more than one scale was included in the assessments performed at follow-up: functioning is measured using the GAF, HoNOS, Strauss-Carpenter and SLOF; QOL is measured using the QLS and WHOQOL-Bref. In contrast, psychopathology and SE are each measured using a single scale (PANSS and SES respectively). For outcomes measured by more than one scale, principal component analysis was performed, to establish the extent to which the different scales map onto common principal components (PCs). A component matrix was constructed, to examine the extent to which each scale loads on each primary PC across diagnoses, by sex.

Table 32: Pearson correlations for scales measuring functioning

	Pearson correlations between each scale			
	HoNOS	Strauss-Carpenter	GAF	SLOF
HoNOS	1	-0.754[b]	-0.754[b]	-0.637[b]
Strauss-Carpenter	-0.754[b]	1	0.857[b]	0.773[b]
GAF	-0.754[b]	0.857[b]	1	0.632[b]
SLOF	-0.637[b]	0.773[b]	0.632[b]	1

[b] $p<0.01$

HoNOS Health of the Nation Outcome Scale
GAF Global Assessment of Functioning Scale
SLOF Specific Levels of Functioning Scale

As can be seen in Table 32, each of the scales measuring functioning is highly correlated with the other scales; the negative values in Table 32 reflect that for some of the instruments (GAF, SLOF, Strauss-Carpenter) a high score indicates better functioning, while in others (HoNOS) a low score indicates better functioning.

Table 33 shows that principal component analysis of the four instruments measuring functioning yields a 4-factor model. PC 1 is the key factor onto which the four scales load, explaining 80.2% of the variance. Thus, function PC 1 (Function 1) can be considered a unitary index that best captures what is measured by each of the different functioning scales and can be used in further analyses for predictors of functioning.

Table 33: Principal component loadings among HoNOS, Strauss-Carpenter, GAF and SLOF

	PC			
	1	2	3	4
HoNOS	-0.878	0.256	0.405	0.012
Strauss - Carpenter	0.948	0.022	0.186	-0.258
GAF	0.909	-0.260	0.266	0.189
SLOF	0.845	0.521	-0.074	0.099
% of variance explained	80.2%	10.1%	6.9%	2.8%

PC Principal component
HoNOS Health of the Nation Outcome Scale
GAF Global Assessment of Functioning Scale
SLOF Specific Levels of Functioning Scale

Table 34: Pearson correlations for scales measuring quality of life

	Pearson correlations calculated for each variable	
	QLS	WHOQOL-Bref
QLS	1	0.435[b]
WHOQOL-Bref	0.435[b]	1

[b] $p<0.01$
QLS Quality of Life Scale
WHOQOL-Bref World Health Organisation Quality of Life Bref Scale

As can be seen in Table 34, the two scales measuring QOL are also correlated significantly, albeit to a lesser extent than the scales measuring functioning. This might be expected, as the QLS involves more clinician input, while the WHOQOL-Bref is completed by the patient. Subjective and objective measures of QOL have been shown to differ to some extent (Whitty et al., 2004).

Table 35 shows that principal component analysis of the two instruments measuring QOL yields a 2-factor model. Quality of life PC 1 (QOL 1) explains 71.8% of the variance, indicating that the two scales may be meaningfully combined into this single principal component, QOL 1, in further analyses for predictors of QOL.

Table 35: Principal component loadings among QLS and WHOQOL-Bref

	PC	
	1	2
QLS	0.847	0.531
WHOQOL-Bref	0.847	-0.531
% of variance explained	71.8%	28.2%

PC Principal component
QLS Quality of Life Scale
WHOQOL-Bref World Health Organisation Quality of Life Bref Scale

Table 36: Scale loadings on Function 1 for major diagnostic groupings, by sex

	SZ Male	SZ Female	BD Male	BD Female	SA Male	SA Female	MDDP Male	MDDP Female
HoNOS	-0.889	-0.776	-0.856	-0.927	-0.753	-0.824	-0.885	-0.954
Strauss-Carpenter	0.953	0.903	0.950	0.873	0.904	0.904	0.949	0.977
GAF	0.916	0.871	0.915	0.938	0.904	0.836	0.873	0.909
SLOF	0.842	0.874	0.715	0.953	0.860	0.721	0.964	0.950

SZ Schizophrenia
BD Bipolar disorder
SA Schizoaffective disorder
MDDP Major depressive disorder with psychotic features
HoNOS Health of the Nation Outcome Scale
GAF Global Assessment of Functioning Scale
SLOF Specific Levels of Functioning Scale

Table 37: Scale loadings on QOL 1 for major diagnostic groupings, by sex

	SZ Male	SZ Female	BD Male	BD Female	SA Male	SA Female	MDDP Male	MDDP Female
WHOQOL-Bref	0.812	0.874	0.923	0.909	0.715	0.851	0.895	0.745
QLS	0.812	0.874	0.923	0.909	0.715	0.851	0.895	0.745

SZ Schizophrenia
BD Bipolar disorder
SA Schizoaffective disorder
MDDP Major depressive disorder with psychotic features
QOL Quality of life
WHOQOL-Bref World Health Organisation QOL Bref
QLS Quality of Life Scale

Tables 36 and 37 show that scale loadings on Function 1 and QOL 1 do not differ materially between the different diagnoses, by sex, and thus indicate that the use of Function 1 and QOL 1 in further analyses is appropriate.

Functioning

Function 1 scores

Table 38a: Function 1 scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all three occasions

	All Function 1 (SD) (n)	Male Function 1 (SD) (n)	Female Function 1 (SD) (n)
SZ Inception	-0.569 (1.08) (30)	-0.545 (0.16) (24)	-0.663 (0.75) (6)
6 months	-0.603 (1.02) (42)	-0.596 (1.07) (34)	-0.633 (0.85) (8)
Follow-up	-0.571 (0.97) (60)	-0.679 (1.02) (42)	-0.319 (0.80) (18)
Core	-0.731 (1.05) (26)	-0.735 (1.11) (21)	-0.712 (0.83) (5)
SF Inception	-0.205 (1.07) (20)	-0.009 (1.15) (13)	-0.570 (0.84) (7)
6 months	-0.19 (0.96) (9)	0.293 (1.12) (4)	-0.578 (0.69) (5)
Follow-up	-1.05 (-) (2)	-	-1.053 (-) (2)
Core	-1.05 (-) (2)	-	-1.053 (-) (2)
BrPsy Inception	0.507 (0.67) (13)	-0.405 (-) (2)	0.673 (0.52) (11)
6 months	0.554 (0.70) (10)	-0.405 (-) (2)	0.794 (0.46) (8)
Follow-up	0.718 (0.21) (4)	0.843 (- (2)	0.594 (-) (2)
Core	0.594 (-) (2)	-	0.594 (-) (2)
SA Inception	0.218 (0.38) (6)	0.038 (-) (1)	0.254 (0.42) (5)
6 months	-0.242 (1.12) (11)	-0.656 (1.39) (6)	0.254 (0.42) (5)
Follow-up	-0.520 (0.80) (27)	-0.252 (0.92) (16)	0.239 (0.50) (11)
Core	0.218 (0.38) (6)	0.038 (-) (1)	0.254 (0.42) (5)
BD I Inception	0.332 (1.01) (29)	0.034 (1.13) (16)	0.698 (0.73) (13)
6 months	0.432 (0.89) (31)	0.247 (1.01) (16)	0.630 (0.74) (15)
Follow-up	0.417 (0.84) (33)	0.221 (0.92) (17)	0.626 (0.72) (16)
Core	0.515 (0.87) (24)	0.266 (0.95) (12)	0.763 (0.72) (12)
BD II Follow-up	1.318 (-) (1)	-	1.318 (-) (1)
MDDP Inception	0.142 (1.06) (31)	-0.215 (1.03) (13)	0.400 (1.03) (18)

6 months	0.301 (0.91) (31)	0.121 (0.75) (12)	0.415 (1.01) (19)
Follow-up	0.373 (0.94) (26)	0.115 (0.76) (12)	0.595 (1.04) (14)
Core	0.264 (1.00) (21)	-0.083 (0.76) (9)	0.524 (1.11) (12)
DD Inception	0.024 (0.63) (13)	0.004 (0.61) (9)	0.067 (0.76) (4)
6 months	0.152 (0.55) (10)	0.209 (0.43) (6)	0.067 (0.76) (4)
Follow-up	0.814 (0.48) (3)	0.536 (-) (2)	1.371 (-) (1)
Core	0.536 (-) (2)	0.536 (-) (2)	-
PGMC Inception	-0.954 (1.26) (4)	-2.029 (0.26) (2)	0.120 (-) (2)
6 months	-0.954 (1.26) (4)	-2.029 (0.26) (2)	0.120 (-) (2)
Follow-up	-0.671 (1.09) (3)	-1.848 (-) (1)	-0.083 (-) (2)
Core	-0.769 (-) (2)	-1.848 (-) (1)	0.309 (-) (1)
SIP Inception	0.374 (0.66) (10)	0.374 (0.66) (10)	-
6 months	0.402 (0.63) (10)	0.402 (0.63) (10)	-
Follow-up	0.766 (0.26) (8)	0.766 (0.26) (8)	-
Core	0.735 (0.28) (4)	0.738 (0.28) (4)	-
PNOS Inception	-0.195 (0.91) (14)	-0.183 (0.68) (10)	-0.224 (1.48) (4)
6 months	-0.169 (0.98) (12)	-0.141 (0.75) (8)	-0.224 (1.48) (4)
Follow-up	0.662 (0.72) (3)	0.587 (-) (2)	0.811 (-) (1)
Core	0.662 (0.72) (3)	0.587 (1-) (2)	0.811 (-) (1)
SIM Inception	0.461 (0.70) (6)	0.358 (0.83) (4)	0.669 (-) (2)
6 months	0.461 (0.70) (6)	0.358 (0.83) (4)	0.669 (-) (2)
Follow-up	0.820 (0.35) (6)	0.830 (0.34) (3)	0.809 (0.44) (3)
Core	0.779 (0.41) (3)	1.00 (-) (1)	0.669 (-) (2)
MGMC Inception	-1.227 (-) (1)	-	-1.227 (-) (1)
6 months	-1.227 (-) (1)	-	-1.227 (-) (1)
Follow-up	-1.227 (-) (1)	-	-1.227 (-) (1)
Core	-1.227 (-) (1)	-	-1.227 (-) (1)
SDD Inception	0.183 (-) (1)	0.183 (-) (1)	-
6 months	0.183 (-) (1)	0.183 (-) (1)	-
Alz Follow-up	-2.11 3 (-) (1)	-	-2.11 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
PNOS Psychosis not otherwise specified
MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
BrPsy Brief psychotic disorder
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder

BD II Bipolar disorder II
DD Delusional disorder
Alz Alzheimer's disease
Function 1 Function principal component 1

Table 38b: Function 1 scores at six year follow-up for diagnoses of SZ, SA, BD and MDDP at follow-up

Diagnosis	All Function 1 scores (SD) (n)	Male Function 1 scores (SD) (n)	Female Function 1 scores (SD) (n)
SZ	-0.571 (0.97) (60)	-0.679 (1.02) (42)	-0.319 (0.80) (18)
SA	-0.520[a] (0.80) (27)	-0.252 (0.92) (16)	0.239 (0.50) (11)
BD	0.417[c] (0.84) (33)	0.221 (0.92) (17)	0.626 (0.72) (16)
MDDP	0.373[c] (0.94) (26)	0.115 (0.76) (12)	0.595 (1.04) (14)

[a] $p<0.05$, [c] $p<0.001$ vs. SZ
SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
Function 1 Function principal component 1

As indicated in Tables 38a/b, Function 1 scores show functioning to be poorest for SZ and SA and better for BD and MDDP. All four diagnoses show a similar pattern of better functioning among females at follow-up (effect of sex, $p<0.005$; no diagnosis x sex interaction). Other diagnoses show Function 1 scores similar to or slightly better than those for BD and MDDP, with the exception of poor functioning for the small numbers of cases of PGMC and MGMC.

Quality of life

QOL 1 scores

Table 39a: QOL 1 scores at six year follow-up in relation to diagnoses at onset, six months, six year follow-up and the 'core' group having that diagnosis on all these occasions

	All QOL 1 (SD) (n)	Male QOL 1 (SD) (n)	Female QOL 1 (SD) (n)
SZ Inception	-0.420 (0.96) (18)	-0.369 (1.04) (15)	-0.671 (0.26) (3)
6 months	-0.457 (0.91) (23)	-0.469 (0.97) (19)	-0.397 (0.59) (4)
Follow-up	-0.540 (0.92) (35)	-0.610 (0.91) (23)	-0.407 (0.95) (12)
Core	-0.556 (0.93) (16)	-0.530 (1.03) (13)	-0.671 (0.26) (3)
SF Inception	-0.068 (1.11) (10)	-0.031 (1.21) (8)	-0.211 (-) (2)
6 months	-0.26 (0.91) (5)	-0.118 (0.98) (4)	-0.845 (-) (1)
Follow-up	-	-	-
Core	-	-	-
BrPsy Inception	0.622 (0.93) (8)	-1.260 (-) (1)	0.891 (0.57) (7)
6 months	0.542 (1.07) (6)	-1.260 (-) (1)	0.903 (0.68) (5)
Follow-up	-0.264 (-) (1)	-	-0.264 (-) (1)
Core	-0.264 (-) (1)	-	-0.264 (-) (1)
SA Inception	-0.249 (0.69) (6)	0.145 (-) (1)	-0.328 (0.75) (5)
6 months	-0.432 (0.80) (7)	-0.693 (-) (2)	-0.328 (0.75) (5)
Follow-up	-0.121 (0.84) (16)	-0.244 (0.84) (9)	0.037 (0.88) (7)
Core	-0.249 (0.69) (6)	0.145 (-) (1)	-0.328 (0.75) (5)
BD I Inception	0.268 (1.00) (22)	-0.170 (1.16) (10)	0.632 (0.69) (12)
6 months	0.454 (0.93) (24)	0.159 (1.20) (10)	0.665 (0.65) (14)
Follow-up	0.278 (1.14) (24)	-0.088 (1.33) (13)	0.711 (0.67) (11)
Core	0.368 (0.98) (19)	-0.104 (1.17) (8)	0.711 (0.67) (11)
BD II Follow-up	1.755 (-) (1)	-	1.755 (-) (1)
MDDP Inception	0.341 (0.97) (22)	-0.010 (0.93) (10)	0.633 (0.94) (12)
6 months	0.367 (0.96) (23)	0.078 (0.93) (11)	0.633 (0.94) (12)
Follow-up	0.356 (0.89) (21)	-0.084 (0.88) (10)	0.755 (0.71) (11)
Core	0.296 (0.96) (17)	-0.157 (0.99) (8)	0.698 (0.78) (9)
DD Inception	-0.263 (0.65) (9)	-0.128 (0.43) (6)	-0.534 (1.04) (3)

6 months	-0.212 (0.72) (7)	0.030 (0.36) (4)	-0.534 (1.04) (3)
Follow-up	0.594 (-) (2)	-0.193 (-) (1)	1.382 (-) (1)
Core	-0.193 (-) (1)	-0.193 (-) (1)	-
PGMC Inception	-1.119 (1.10) (3)	-1.731 (-) (2)	0.107 (-) (1)
6 months	-1.119 (1.10) (3)	-1.73 (-) (2)	0.107 (-) (1)
Follow-up	-0.547 (0.81) (3)	-1.458 (-) (1)	-0.092 (-) (2)
Core	-0.676 (-) (2)	-1.458 (-) (1)	0.107 (-) (1)
SIP Inception	0.003 (1.25) (7)	0.003 (1.25) (7)	-
6 months	-0.048 (1.17) (8)	-0.048 (1.17) (8)	-
Follow-up	0.343 (0.49) (8)	0.343 (0.49) (8)	-
Core	0.088 (0.59) (4)	0.088 (0.59) (4)	-
PNOS Inception	-0.242 (0.92) (10)	-0.046 (0.69) (6)	-0.535 (1.24) (4)
6 months	-0.223 (0.97) (9)	0.027 (0.74) (5)	-0.535 (1.24) (4)
Follow-up	0.359 (0.76) (3)	0.464 (-) (2)	0.149 (-) (1)
Core	0.359 (0.76) (3)	0.464 (-) (2)	0.149 (-) (1)
SIM Inception	0.215 (1.34) (3)	0.215 (1.34) (3)	-
6 months	0.215 (1.34) (3)	0.215 (1.34) (3)	-
Follow-up	1.068 (0.37) (4)	1.135 (0.42) (3)	0.865 (-) (1)
Core	1.280 (-) (1)	1.280 (-) (1)	-
MGMC Inception	-0.924 (-) (1)	-	-0.924 (-) (1)
6 months	-0.924 (-) (1)	-	-0.924 (-) (1)
Follow-up	-0.924 (-) (1)	-	-0.924 (-) (1)
Core	-0.924 (-) (1)	-	-0.924 (-) (1)
SDD Inception	-0.241 (-) (1)	-0.241 (-) (1)	-
6 months	-0.241 (-) (1)	-0.241 (-) (1)	-
Alz Follow-up	-1.508 (-) (1)	-	-1.508 (-) (1)

SZ Schizophrenia
SF Schizophreniform disorder
SA Schizoaffective disorder
PNOS Psychosis not otherwise specified
MDDP Major depressive disorder with psychosis
BD I Bipolar disorder I
BD II Bipolar disorder II
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
BrPsy Brief psychotic disorder
SIM Substance induced mania
MGMC Mania due to a general medical condition
SDD Simple deteriorative disorder
Alz Alzheimer's disease
QOL 1 Quality of Life principal component 1

Table 39b: QOL 1 scores at six year follow-up for diagnoses of SZ, SA, BD and MDDP at follow-up

Diagnosis	All QOL 1 scores (SD) (n)	Male QOL 1 scores (SD) (n)	Female QOL 1 scores (SD) (n)
SZ	-0.540 (0.92) (35)	-0.610 (0.91) (23)	-0.407 (0.95) (12)
SA	-0.121[b] (0.84) (16)	-0.244 (0.84) (9)	0.037 (0.88) (7)
BD	0.278[c] (1.14) (24)	-0.088 (1.33) (13)	0.711 (0.67) (11)
MDDP	0.356[c] (0.89) (21)	-0.084 (0.88) (10)	0.755 (0.71) (11)

[b] $p<0.01$, [c] $p<0.001$ vs. SZ

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
QOL 1 Quality of Life principal component 1

As indicated in Tables 39a/b, QOL 1 scores show QOL to be lowest for SZ, slightly better for SA and better still for BD and MDDP. All four diagnoses show a similar pattern of better QOL among females at follow-up (effect of sex, $p=0.01$; no diagnosis x sex interaction). Other diagnoses show QOL1 scores similar to or slightly better than those for SA, BD and MDDP, with the exception of poor QOL for the small numbers of cases of PGMC and MGMC.

Correlations between outcome variables

Table 40: Correlations between outcome variables

	Pearson correlation coefficients					
Variables	PANSS pos	PANSS neg	PANSS gen	Function 1	QOL 1	SES
PANSS pos	1	0.541[b]	0.692[b]	-0.549[b]	-0.280[b]	0.506[b]
PANSS neg	0.541[b]	1	0.621	-0.717[b]	-0.580[b]	0.536[b]
PANSS gen	0.692[b]	0.621[b]	1	-0.755[b]	-0.616[b]	0.573[b]
Function 1	-0.549[b]	-0.717[b]	-0.755[b]	1	0.845[b]	-0.642[b]
QOL 1	-0.280[b]	-0.580[b]	-0.616[b]	0.845[b]	1	-0.520[b]
SES	0.506[b]	0.536[b]	0.573[b]	-0.642[b]	-0.520[b]	1

[b]p<0.01

PANSS Positive and Negative Syndrome Scale
pos positive subscale
neg negative subscale
gen general subscale
Function 1 Function principal component 1
QOL 1 Quality of life principal component 1
SES Service Engagement Scale

Table 40 shows that there are moderated to high correlations between many of the principal outcome measures.

Multiple linear regression modelling across all cases

Functioning

In order to build a model for predictors of functioning at follow-up, multiple linear regression analysis with Function 1 as the dependent variable and other measures as the independent variables (Table 41) was undertaken.

Table 41: Predictors of Function 1 entered into regression modelling

Sex
Age at presentation
Months to follow-up
1° vs. 2° education completed
1° vs. 3° education completed
Months to follow up
Marital status at follow-up [ever married vs. never married]
Substance abuse at follow up
Supported vs. unsupported living conditions
PANSS general at follow-up
PANSS positive at follow-up
PANSS negative at follow-up
SES at follow-up
QOL 1 at follow-up
PANSS Positive and Negative Syndrome Scale
SES Service Engagement Scale
QOL Quality of life

Three modes of multiple linear regression modelling were performed, in order to verify the consistency of any model generated, namely forced entry, forward and stepwise modelling. As can be seen in Table 42, there is a high level of agreement between the different regression models, particularly for prediction of Function 1 by PANSS general, PANSS negative, poor SE , never married and supported as opposed to unsupported living conditions. Substance abuse approached significance in the forced entry model ($p = 0.09$) and was therefore included in further analysis. Specific details for the forward entry model are given in Table 43.

Table 42: Multiple linear regression models for predictors of Function 1*

Forced entry	Forward	Stepwise
PANSS gen	PANSS gen	PANSS gen
PANSS neg	PANSS neg	PANSS neg
SES	SES	SES
Supp/unsupported	1° vs. LCert edu	1° vs. LCert edu
Months to f/u	Never married	Never married
Age at onset	Supp/unsupported	Supp/unsupported
Substance abuse	1° vs. 3° edu	1° vs. 3° edu

*Independent variables listed in descending order of significance; each $p<0.05$ except substance abuse ($p=0.09$)

PANSS gen	Positive and Negative Syndrome Scale, general subscale
PANSS neg	Positive and Negative Syndrome Scale, negative subscale
SES	Service Engagement Scale
Supp/unsupported	Supported rather than unsupported living conditions
1° vs. LCert edu	Primary rather than Leaving Certificate (secondary) standard of education completed
1° vs. 3° edu	Primary rather than tertiary education completed

Table 43: Forward regression model for predictors of Function 1

Independent variable	R^2	β	SEβ	T	P
PANSS gen	0.583	-0.077	0.005	-14.195	0.001
PANSS neg	0.692	-0.047	0.007	-7.114	0.001
SES	0.726	-0.019	0.005	-4.154	0.001
1° vs. LCert edu	0.749	-0.019	0.059	3.632	0.001
Never married	0.766	0.276	0.087	3.193	0.002
supp vs. unsupp	0.775	-0.126	0.052	-2.397	0.018
1° vs. 3° edu	0.782	0.148	0.074	1.985	0.031

PANSS gen	Positive and Negative Syndrome Scale, general subscale
PANSS neg	Positive and Negative Syndrome Scale, negative subscale
SES	Service Engagement Scale
1° vs. LCert edu	Primary rather than Leaving Certificate (secondary) education completed
Supp vs. unsupp	Supported than unsupported living conditions
1° vs. 3° edu	Primary rather than tertiary education completed

Quality of life

QOL 1 was adopted as the dependent variable in similar multiple linear regression modelling for predictors of QOL, using the same independent variables as in Table 41. Table 44 shows a high level of agreement between the different regression models, particularly for prediction of QOL 1 by PANSS gen, PANSS pos, never married and older age at presentation; additionally, forward and stepwise methods also selected poor SE. Specific details for the forward entry model are given in Table 45.

Table 44: Multiple linear regression models for predictors of QOL 1*

Forced entry	Forward	Stepwise
PANSS gen	PANSS gen	PANSS gen
PANSS pos	Never married	Never married
Age at presentation	Age at presentation	Age at presentation
Marital status	SES	SES
	PANSS pos	PANSS pos

* Independent variables listed in descending order of significance; each $p<0.05$

PANSS gen Positive and Negative Syndrome Scale, general subscale
PANSS pos Positive and Negative Syndrome Scale, positive subscale
SES Service Engagement Scale

Table 45: Forward regression model for predictors of QOL 1

Independent variable	R^2	B	SEβ	t	P
PANSS gen	0.384	-0.076	0.010	-7.648	0.000
Never vs. ever married	0.520	0.789	0.154	5.137	0.000
Age at presentation	0.580	-0.017	0.005	-3.641	0.000
SES	0.614	-0.023	0.008	-2.839	0.006
PANSS pos	0.635	0.044	0.019	2.277	0.025

PANSS gen Positive and Negative Syndrome Scale, general subscale
PANSS pos Positive and Negative Syndrome Scale, positive subscale
SES Service Engagement Scale

Multiple linear regression modelling in relation to diagnosis

To investigate whether these relationships, obtained across all cases, differed between the diagnoses, two approaches were adopted. Initially, interaction terms for the principal diagnoses (SZ, SA, BD and MDDP) were included in relation to the predictors for Function 1 identified in Tables 42 and predictors for QOL 1 identified in Table 44. Then, each of four primary diagnoses were examined separately. The only interactions attaining significance are indicated in Table 46: prediction of Function 1 by months to follow-up differed between SZ and MDDP; prediction of QOL 1 by substance abuse and PANSS general differed between SZ and BD; prediction of QOL 1 by substance abuse differed between SZ and MDDP. Thus, in general, predictors for Function 1 and QOL 1 are similar across the primary diagnostic groups.

Table 46: Significant interaction terms by diagnosis in multiple regression models for prediction of Function 1 and QOL 1

Dependent variable	Interaction	Significance
Function 1	Months to follow-up x SZ/MDDP	0.045
QOL 1	Substance abuse at follow-up x SZ/BD	0.039
	Substance abuse at follow-up x SZ/MDDP	0.040
	PANSS general x SZ/BD	0.036

QOL Quality of life
SZ/MDDP Major depressive disorder with psychosis compared to reference diagnosis of schizophrenia
SZ/BD Bipolar disorder compared to reference diagnosis of schizophrenia
PANSS Positive and Negative Syndrome Scale

Multiple linear regression modelling for each principal diagnosis

Functioning

In SZ, lower Function 1 was predicted by higher PANSS negative and PANSS general scores. In BD, lower Function 1 was predicted by substance abuse as well as higher PANSS general

and PANSS negative scores. In MDDP, lower Function 1 was predicted by dependent living conditions (those living alone or with flatmates doing worse than those living with spouse/children, all of whom were functioning more poorly than those living in supported conditions) and worse SE (Table 47).

Quality of life

In SZ, lower QOL 1 was predicted by never being married. No variables were identified as specifically predicting QOL 1 in SA. In BD, lower QOL 1 was predicted by higher PANSS general. In MDDP, lower QOL 1 was predicted by older age at presentation, longer time to follow-up, substance abuse, not living independently and worse SE (Table 47).

Table 47: Significant predictors of Function 1 and QOL 1 for each of the principal diagnoses of SZ, SA, BD and MDDP*

Function 1			QOL 1		
SZ	BD	MDDP	SZ	BD	MDDP
PANSS negative	Substance abuse at f/u	Dependent living	Never married	PANSS general	Living alone
PANSS general	PANSS general	Living alone			Substance abuse at f/u
	PANSS negative	Worse service engagement			Dependent living
					Older age at onset
					Longer time to f/u
					Worse service engagement
					No Leaving Cert

* Independent variables listed in descending order of significance; each $p<0.05$

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar disorder
MDDP Major depressive disorder with psychosis
PANSS Positive and Negative Syndrome Scale
f/u follow-up

Discussion

General methodological considerations in relation to population and case finding

The validity of the results presented here is predicated on the methodology of the study. The population chosen for this study is defined by a methodologically rigorous incidence study that has been carried out since 1995 in the Cavan/Monaghan area. An incidence study, and particularly a first episode psychosis study, is suitable for research focussing on clinical and functional outcomes in that it captures a population with this socially debilitating group of illnesses during a key period of their psychological, social and occupational development, during which the pattern of future illness starts to emerge. A prevalent population would introduce the difficulty of trying to draw conclusions based on people at very different phases of their illnesses, from the tumultuous early phase of illness to the more stable, later phases. First episode studies are now accepted to be the most satisfactory way of studying incidence populations in psychiatry, assuming they fulfil methodological criteria established by Poser (1994) for epidemiological studies of diseases diagnosed on the basis of clinical, rather than pathognomonic features. These include:

- That the study be located in a geographically defined area and that the possibility of missing cases which are treated in other areas is limited
- That the study be carried out in an area with maximal ethnic homogeneity
- That standardised diagnostic procedures are adhered to
- That diagnoses at the boundaries, with overlap in terms of symptomatology and hypothesised pathology, should be included in the study
- That individuals be retrospectively included if they are detected post first episode but have become symptomatic within the geographically defined [and in the case of a first episode study, time defined] study period

The Cavan/Monaghan First Episode Psychosis Study can be set against those criteria, as follows:

- The study is carried out within a specific geographical area that is clearly defined by the psychiatric service clinical catchment area, corresponding to the counties of Cavan and Monaghan; a geographically and administratively distinct 'panhandle' area of Cavan is included in an adjacent psychiatric catchment area. Efforts to detect individuals treated elsewhere are carried out by searching for cases in the two main private psychiatric hospitals in Ireland, both located in Dublin, as well as in the national forensic services.

- The area has significant ethnic homogeneity and demographic stability, with 90% of the population of the two counties being of Irish nationality according to the 2006 census (Central Statistics Office 2006), compared to 87% for the nation as a whole.

- With regard to diagnostic procedure the SCID-DSM diagnostic schedule has been used since the onset of the study; the six clinical researcher fellows to date have trained together and with their colleagues in the St. John of God First Episode Psychosis research group (Browne et al., 2000; Clarke et al., 2006).

- Regarding the inclusion of boundary diagnoses, the design of the study specifically includes a first episode of all of the psychosis spectrum disorders, to also include a first manic episode; thus, it does not limit itself, as some studies have, to the examination of, for example, only first episode SZ, SA and SF.

- Retrospective inclusion of late-detected cases is an integral aspect of the study design.

General methodological considerations in relation to follow-up

In order to draw conclusions on outcomes in the patient cohort identified, it was crucial to establish the maximum possible follow-up rate, so as to minimise the introduction of bias into the study. In general, patients with psychotic illness are notoriously difficult to follow-up, due to the common feature of 'recovery' from what is almost invariably a traumatic experience. The very high rate of follow-up of the Cavan/Monaghan study, based on the methodology described above, markedly increases confidence as to the representativeness of the data from the study. The relative demographic stability that characterises the population of this area made a significant contribution to the high rate of follow-up, as well as the strong community links present in this predominantly rural region. Home-based treatment delivered by the mental health service within this community, together with the service's strong primary care links, again facilitated the high rate of follow-up. The fact that information was drawn from multiple sources (patient, long-term case notes, family members, keyworkers) in order to complete follow-up assessment further strengthens the methodology and increases confidence for drawing conclusions from the data obtained.

Epidemiology

As incidence and prevalence data from this study have been published in recent years (Scully et al., 2002; Baldwin et al., 2005., Owoeye et al., 2010), and will continue to evolve, re-analysis is unnecessary here. However, it is pertinent to briefly summarise these figures, in order to better understand the population's epidemiological characteristics. Overall incidence rates of FEP range from 15/100 000 per year reported in a Brazilian study (Menezes et al., 2007) to 34.8/100 000 per year in the AESOP study (Kirkbride et al., 2006). The Cavan/Monaghan study lies at the upper end of this range, at 31.6/100 000 (Baldwin et al., 2005). With regard to SZ, a detailed overview of incidence is contained in the Introduction, with a meta-analysis of studies to date indicating mean incidence for schizophrenia spectrum disorders to be 15.2/100 000 (McGrath et al., 2004). In the present study, incidence (10.8/100 000) has been reported as being well within, but towards the lower end of, the range of values encompassed by the meta-analysis (Baldwin et al., 2005); this may in part reflect application

here of SCID-DSM IV criteria vis-à-vis many other studies utilising less restrictive criteria. Regarding BD, reported incidence ranges from 2.2-8.7/100 000, with the present study indicating a figure (5.2/100 000) towards the middle of this range (Baldwin et al., 2005). Regarding MDDP, incidence values reported in the literature have a relatively narrow range of 5.6-7.2/100 000; the present study gives a figure for MDDP of 6.4/100 000, in the middle of this range (Baldwin et al., 2005). The incidence of SA has been the subject of less extensive research, with the rate in Cavan/Monaghan (2.0/100 000) being typically lower than for SZ.

Demography of case cohort compared to population of origin and other study populations

The first part of the Results section describes the demographic characteristics of the population, in particular age, sex and marital status. Each of these characteristics was subdivided by diagnostic category for each of the three time points at which diagnosis was recorded, namely onset, six months and six year follow-up. The inclusion of all of these time points throughout the Results section adds to the richness of our understanding of the meaning of these diagnoses. Diagnosis at onset is important as it is clinically valuable to understand what predictive value the onset diagnosis has in terms of illness and outcome trajectory over the years; concerned patients and families are seeking information on prognosis in the early stages of a psychotic disorder and psychiatrists are seeking to chart a path through what can be a complex, fluid and often indistinct period of illness. Six month diagnosis is likely to be somewhat more robust than that made at onset, as clarity can emerge after the initial maelstrom of symptoms subsides. However, it is diagnosis at follow-up that is of most interest, being the diagnosis based on observation of course of illness over time. It is therefore the most reliable and that most likely to follow the person throughout the rest of their lives.

Age

Mean age at onset of FEP in this population was 36.1, which is somewhat higher than values reported in other FEP studies; for example, 25.6 years in Canada (Malla et al., 2002a) and

24.4 years in Australia (McGorry et al., 1998). However, median age at onset for the four primary disorders is 23 for SZ, 25 for SA, 27 for BD and 45 for MDDP (Baldwin et al., 2005). It is worth noting that many FEP studies take place in the context of a dedicated Early Psychosis service, most of which have an upper age limit for inclusion; such exclusion of those with later onset of illness will inevitably give a lower mean age at onset. As is found in other studies, overall age at onset is older in females than males, here by nine years. This difference is larger than that found between the sexes in the principal diagnoses (SZ, SA, BD, MDDP), and derives primarily from SF, BrPsy, PGMC, SIM and MGMC. Mean age at onset will be discussed further in relation to follow-up diagnoses. Among the principal diagnoses, SZ (31.7), SA (28.9) and BD (34.5) have generally similar mean ages at onset, this being somewhat later for MDDP (43.1). The finding for SA is somewhat unusual, with most studies finding an age at onset lying between those for SZ and BD (Abrams & Arcineagas, 2007). However, the older age at onset for MDDP is generally consistent with previous research (Drevets & Todd, 2005). The only other category sufficiently populous at follow-up is SIP, having a relatively young age at onset (27.0). When age at onset is examined from the perspective of diagnosis made at onset relative to that made at follow-up, there are no marked differences for the principal diagnoses.

Sex

The total number of participants followed up in this study gives an overall sex ratio within FEP of 59% male to 41% female. This makes sense given the range of conditions encompassed, from SZ, which has a marked male preponderance, to MDDP, which has a slight female preponderance.

The changes in sex ratios for SZ over the course of the study are interesting, with a four-fold male-female ratio at onset, dropping over the course of the follow-up period to approximately 2.5:1. Meta-analysis (Aleman et al., 2003) and systematic review (McGrath et al., 2004) yield a ratio of 1.4:1, however, many of the studies included in these analyses included less restrictive diagnostic criteria than those applied here. For BD, the sex ratio seen in this population is consistent with those seen in the literature (Robins et al., 1984), being more or

less equally distributed between males and females, with little change throughout the course of the study. Most research on sex ratios for depression does not specifically resolve MDDP. Therefore, it is difficult to clarify whether or not the finding here, namely of a slightly higher overall rate in females, is consistent or otherwise with the literature. However, a tentative summary of research findings (Bebbington, 1991) indicates that whilst the more neurotic types of depression appear to have a female:male ratio of approximately 2:1, the psychotic subtype probably has a more equal ratio; this would be consistent with the findings of the present study. While sex ratios for SA change markedly over the course of the study, the small number of individuals with this diagnosis at onset means interpretation of this finding must be cautious. At onset, far more females than males received this diagnosis (5:1, n=6); by six months, this ratio was almost equal (1:1.2 female:male, n=11), while by follow-up, the ratio indicates a slight male preponderance (1: 1.5). The literature, whilst again not extensive, would suggest that the ratio of females to males for SA is approximately 2:1 (Abrams et al., 2007), as here; these ratios are more similar to those found in BD than to those found in SZ (Winokur & Tsuang, 1996). Other findings worth noting are that both SF and DD have an initial male:female ratio of approximately 2:1, which shifts towards unity at six months, with loss of most of these males to other diagnoses at follow-up. SIP was diagnosed only in men at each of onset, six months and follow-up. This is consistent with the general excess of substance and alcohol misuse found in males. BrPsy shows a marked female excess at onset (5:1, n=13). By follow-up, most cases have evolved towards other diagnoses, making numbers too small to draw conclusions about later sex ratio.

Marital status

All of the major diagnostic groups compare very unfavourably with the general population on considering marital status figures from the 2006 census for the border region of Ireland, which includes counties Cavan and Monaghan. Among males, 85% of those with SZ were single at follow-up, compared to an overall figure of 29% for men of the same age distribution among the general population. Those with SA fare marginally less adversely, with 69% being single. Those with BD fare rather better, with 44% single. However, it is males with MDDP (mean age 46.9 at follow-up) who do worst of all, with 85% single,

compared to 18% of males aged 45 – 49 years in the region. Among females, those with psychosis are also much more likely to be single relative to the general population; 50% of women with SZ were single compared to 15% among the general population. As in men, women with BD fare rather better, with 35% single. 73% of women with SA were single at follow-up, compared to 23% of women of similar age in the region, while 21% of women with MDDP were single compared to 9% among the general population. With the exception of MDDP, these figures are similar to findings in studies in other parts of the world (Thara, 2004; Gureje & Bamidele, 1999; Muller et al., 1998), where research in general shows low rates of marriage in psychosis, with rates lowest in SZ, followed by SA and then BD (Tsuang et al, 1979;Tsuang & Dempsey 1979). Whilst women with psychosis were more likely to be married at follow-up, this was in part accounted for by their older age at first presentation and hence at follow-up; when men and women with psychosis are compared to their respective age- and sex-matched populations, rates of single marital status for females approach those for males. This is at odds with the idea that women are less socially disabled by psychosis, due to their generally older mean age at onset for these disorders. The exception to this finding is MDDP, where males are far more likely than females to be single when compared to the general population of similar age. Marital status is one of the key indicators of social functioning and differences of this magnitude are of enduring concern.

Diagnostic stability at follow-up

Diagnostic (in)stability over the follow-up period was one of the principal issues of interest in this study. An onset, diagnosis can contain such important prognostic implications that it is vital to establish the extent to which this diagnosis will endure over time. If diagnosis is unstable, it has important implications for the diagnostic system used and for our concepts of psychotic illness. Diagnosis was assessed at three points: at initial presentation with a first psychotic episode, six months after initial presentation and at a mean of 6.4 years after initial presentation. Of particular interest is the comparison between diagnosis at six months and that at follow-up. This is because of the difficulties inherent in making an emphatic diagnosis within the early weeks of presentation, for two main reasons: first, in many cases additional information emerges from a variety of sources during the first six months of illness

which clarify aspects of the illness which may have been obscured at onset; second, the relative importance of the myriad of symptoms that can characterise early illness may not become clear until several months following presentation.

Figure 2: Overall flow between diagnostic categories over six year follow-up

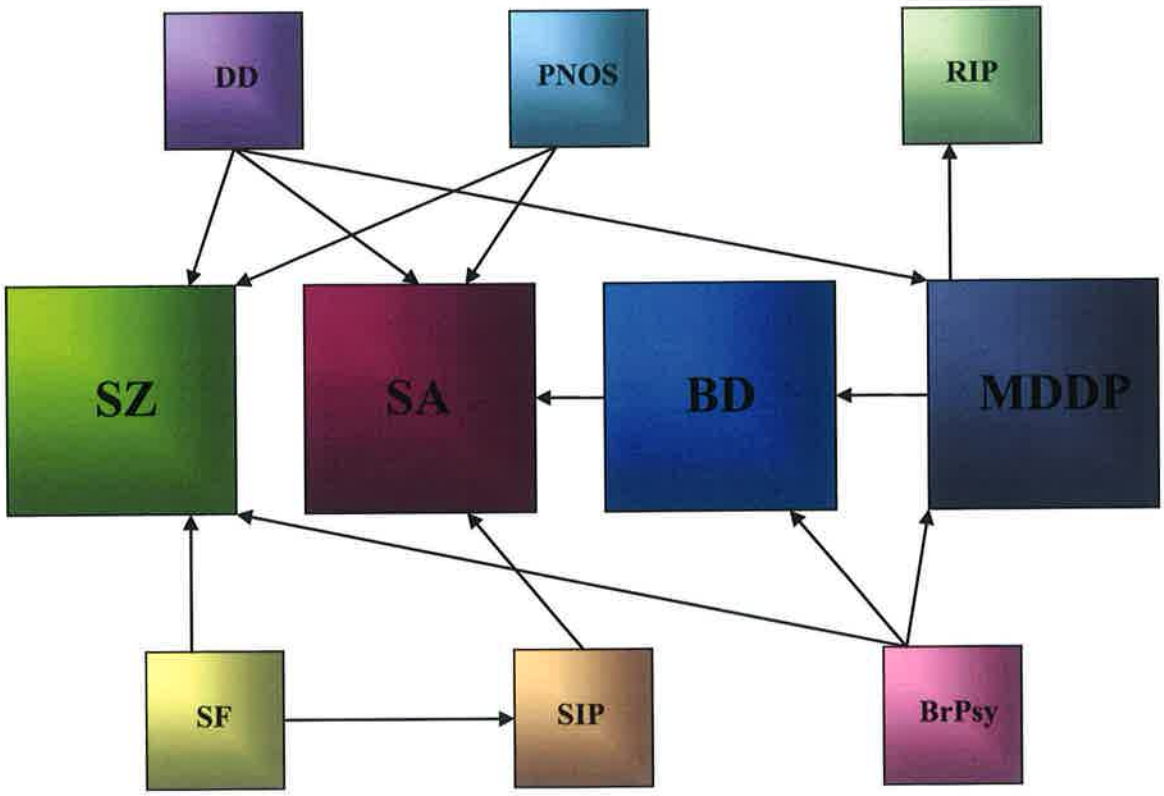
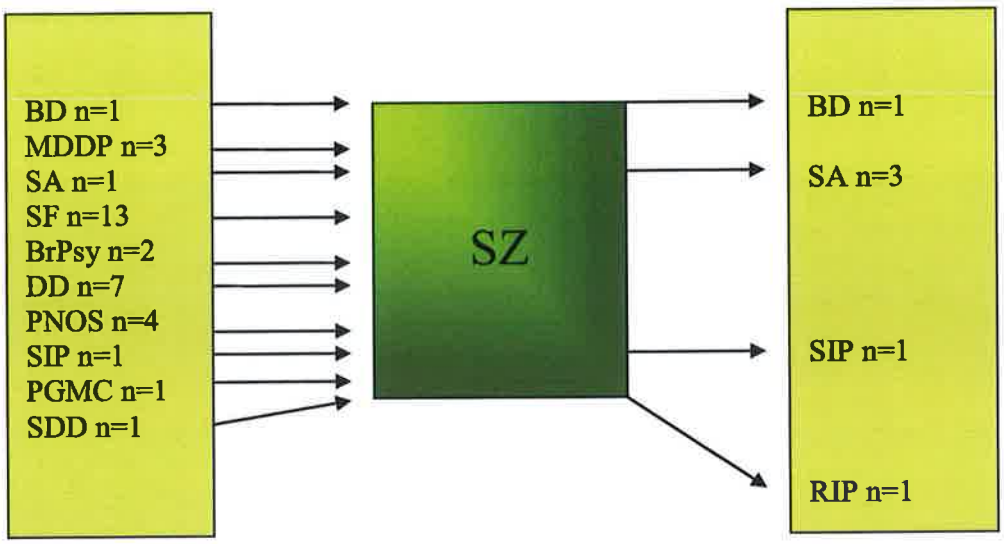


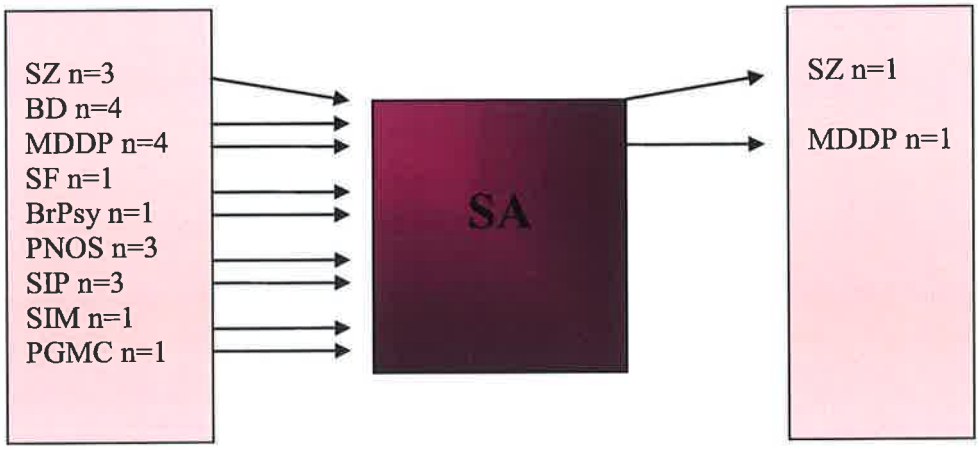
Figure 3: Diagnostic transitions over six years to and from SZ



Tables 9, 10 & 11 detail numbers in each diagnostic category at the different time points

Excluding those diagnostic categories containing very small numbers of cases, the most stable diagnosis followed prospectively over the follow-up period was SZ. This is very much in concordance with existing literature and indicates the concept of SZ as a reliable diagnostic category. Further examination of the data for SZ shows that over the follow-up period very few people flow out of this diagnosis, with a greater number flowing into this diagnosis over time after having received other psychotic diagnoses at onset. The main 'feeder' diagnoses for SZ are SF, DD, BrPsy and PNOS. This is consistent with the findings of previous studies, which also indicate SZ to be a stable diagnosis over time, with a positive predictive validity ranging from 80 – 98% (Tsuang et al, 1981; Forrester et al., 2001; Hoye et al., 2000; Schimmelmann et al., 2005; Naz et al., 2003; Veen et al., 2004; Whitty et al, 2005; Amin et al., 1999a; Hollis, 2000). Thus, SZ can be considered a diagnosis yet more likely to made over the long-term than in the short-term. Figure 2 summarises flow into and out of the main diagnostic categories over the follow-up period. These diagnostic transitions are detailed in Figure 3 for SZ and in subsequent figures for each diagnosis applying to more than one individual

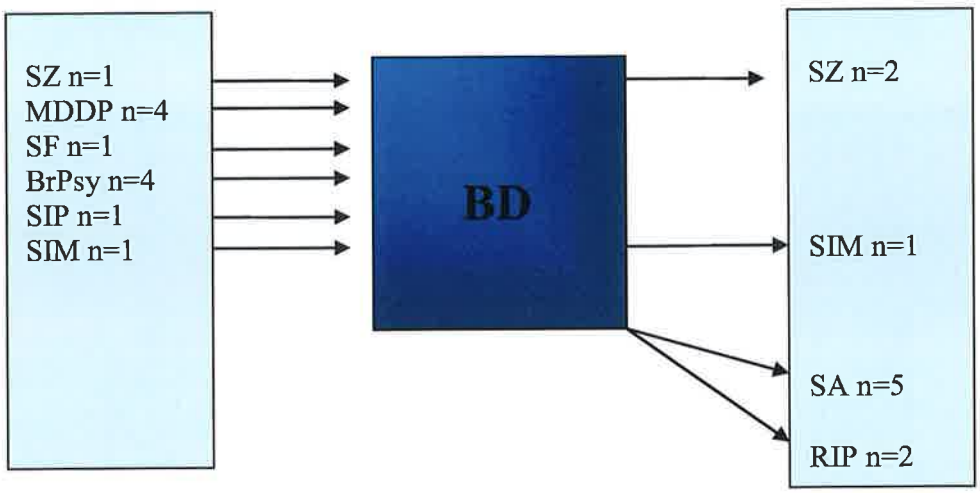
Figure 4: Diagnostic transitions over six years to and from SA



Tables 9, 10 & 11 detail numbers in each diagnostic category at the different time points

As indicated in Figure 4, from one perspective SA appears to be very stable, with most people who receive the diagnosis at onset retaining it at follow-up. However, when movement into the category is examined, it is found that this is very much a diagnosis that receives individuals largely from other principal diagnoses (SZ, BD, MDDP), as well as a number from PNOS. It makes intuitive sense that SA is a diagnosis more easily acquired than lost, as it encompasses a wider range of psychopathology than the other principal diagnoses and thus it may often take a longer period of illness for this to become clear. The diagnoses from which it receives people over time further supports its conceptualisation as a form between non-affective and affective psychotic illnesses. Much previous research has indicated SA to be a somewhat unstable diagnosis (Marneros et al., 1990; Hollis, 2000; Schwartz et al., 2000) compared to the other main diagnostic categories (SZ, BD, MDDP) and, as here, that it accrues rather than loses numbers over longer periods of follow-up (Zarate et al., 1997).

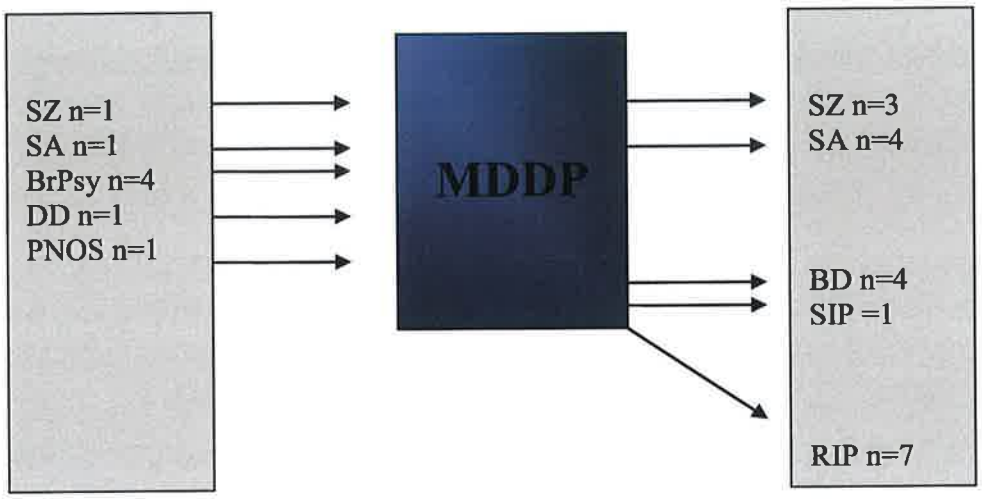
Figure 5: Diagnostic transitions over six years to and from BD



Tables 9, 10 & 11 detail numbers in each diagnostic category at the different time points

As indicated in Figure 5, BD is stable over time, losing few participants over the follow-up period. However, unlike SZ, BD does not accrue many cases from other onset diagnoses; those that transition to BD do so mainly from MDDP and BrPsy. BD has been shown previously to be a stable diagnostic entity over time, with stability estimates ranging between 56 – 100% for operationally defined BD (Tsuang et al., 1981; Amin et al., 1999a; Srinath et al., 1997; Schwartz et al., 2000; Forrester et al., 2001; Whitty et al., 2005).

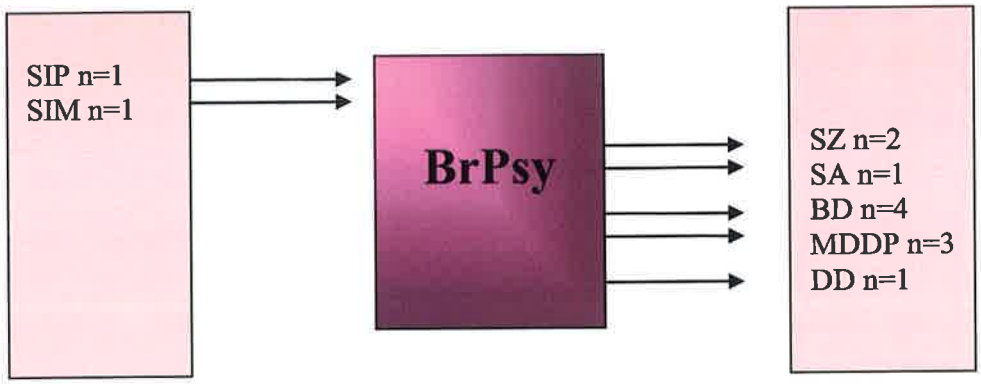
Figure 6: Diagnostic transitions over six years to and from MDDP



Tables 9, 10 & 11 detail numbers in each diagnostic category at the different time points

As indicated in Figure 6, MDDP is somewhat less stable than SZ, SA and BD. Other studies have reported similar findings (Maj et al., 1990; Goldberg et al., 2001; Whitty et al., 2005). A notable finding of concern in the present study is that five people with this diagnosis at first presentation died of natural or accidental causes over the follow-up period, with a further two individuals dying by suicide; thus, an initial diagnosis of MDDP has by far the highest mortality rate. This is partially, though not wholly, accounted for by the older age at first presentation for this diagnosis; the other principal diagnoses, such as SZ, also present throughout the lifespan with little evidence for similar mortality among those presenting at an older age (Table 15). There is also transition to this diagnostic category particularly from BrPsy, and transition out of this diagnostic category particularly to BD, SA and SZ. This suggests that what is diagnosed initially as MDDP may be the first indication of a number of other psychotic disorders, particularly those having an affective component, as well as of MDDP itself.

Figure 7: Diagnostic transitions over six years to and from BrPsy

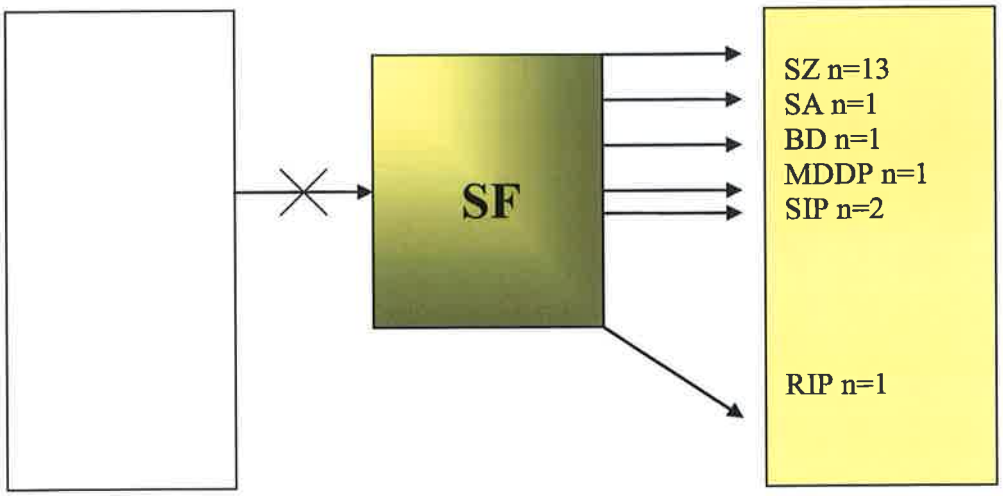


Tables 9, 10 & 11 detail numbers in each diagnostic category at the different time points

As indicated in Figure 7, BrPsy is of considerable interest. It is found here to be highly unstable over time, confirming the findings of other studies (Opjordsmoen, 1985; Jorgensen et al., 1997; Schwartz et al., 2000; Valevski et al., 2001). Most patients receiving this diagnosis at first presentation proceed to more severe forms of psychotic illness at follow-up, particularly SZ, BD and MDDP; by follow-up, only two of the original 11 cases retain the diagnosis, indicating that such an initial presentation is far from being as benign as is often thought. Here, as noted in some other studies with differing durations of follow-up (Valevski et al., 2001; Jorgensen et al., 1997; Sajith et al., 2002; Amini et al., 2005), the longer the follow-up period the greater the instability of this diagnosis; here, such transition to more severe diagnoses is little evident over the first six months. Also of note is that this diagnosis is markedly more common among women than men at initial presentation, with women also appearing more likely than men to go on to develop more severe psychotic diagnoses. BrPsy appears to be a deceptive entity that can be the

harbinger of long-term evolution to serious psychotic illness and may repay more vigorous, sustained intervention.

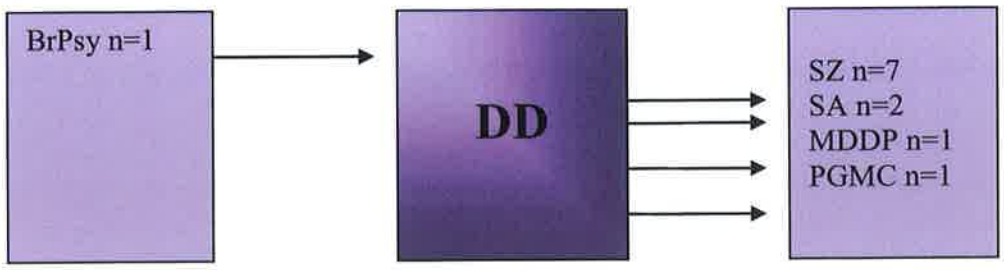
Figure 8: Diagnostic transitions over six years to and from SF



Tables 9, 10 & 11 detail numbers in each diagnostic category at the different time points

As indicated in Figure 8, diagnostic stability for SF is low, as most people with this diagnosis at first presentation go on to receive a diagnosis of SZ simply due to the passage of time necessary to satisfy the 'six month' criterion for this diagnosis. Other studies of diagnostic stability in SF have shown similar low rates of stability (Whitty et al., 2005; Naz et al., 2003; Iancu et al., 2002; Chinchilla Moreno et al., 1996; Marchesi et al., 2007; Zarate et al., 2000; Egea et al., 2004). Evidence for this diagnostic shift in the present study is already evident by six months and continues into the longer term follow-up period. Interestingly, another diagnostic category receiving those initially diagnosed as SF is SIP (n=2), indicating that undetected substance abuse may lead to a picture similar to that of SF. The two females who retained a diagnosis of SF at follow-up were aged 79 and 84 at first presentation, suggesting that the initial diagnosis may have been related to an undetected physical cause. This left just one male with an enduring diagnosis of SF at follow-up. These findings question the utility of an initial diagnosis of SF and suggest that it is a far from benign prognosticand.

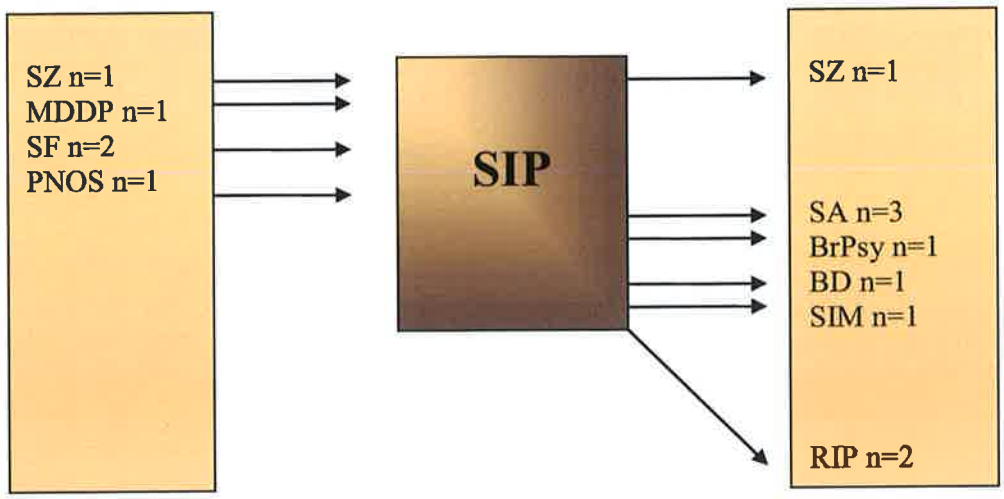
Figure 9: Diagnostic transitions over six years to and from DD



Tables 9, 10 & 11 detail numbers in each diagnostic category at the different time points

As indicated in Figure 9, DD also has low diagnostic stability over the follow-up period. Most cases evolve to SZ and a small number to SA. While little research has looked at DD longitudinally, one study found it to have a diagnostic stability of 53% (Debnath et al., 2006). However, the belief that monosymptomatic delusions may persist over time with little effect on a person's functioning may require re-evaluation, on the basis of poor levels of longer term functioning in the majority of patients who evolve from DD to SZ or SA.

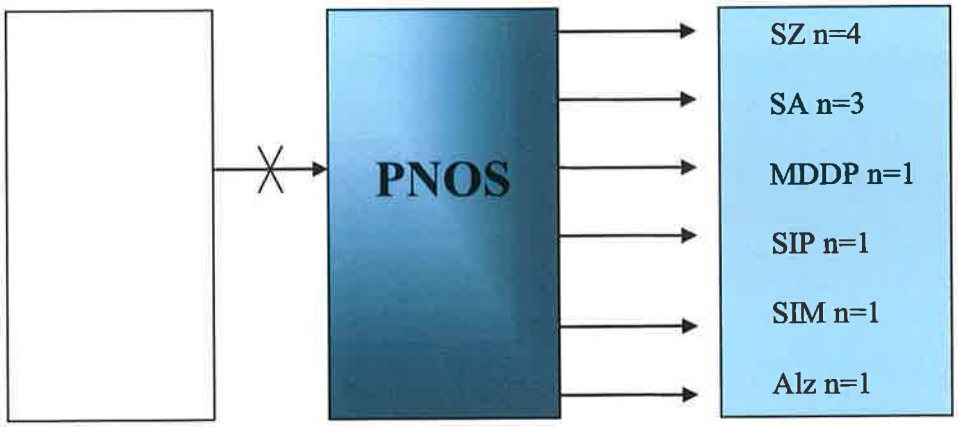
Figure 10: Diagnostic transitions over six years to and from SIP



Tables 9, 10 & 11 detail numbers in each diagnostic category at the different time points

As indicated in Figure 10, SIP is also an unstable diagnosis over time. It has 12 cases at onset; the substances involved included cannabis (n=5), alcohol (n=2) and polysubstance (n=5). It loses eight of these 12 initial members over the follow-up period but, unlike SF, BrPsy and DD, it also accrues some cases at follow-up from other initial diagnoses (SF, SZ, MDDP, PNOS). SIP has been found previously to be an unstable diagnosis (Whitty et al, 2005). This two-way traffic may make intuitive sense: what is assumed to be SIP at onset by virtue of the presence of substance misuse and more transient psychotic symptoms, may evolve into a more enduring illness over time that is unrelated to initial substance misuse and may be better considered in retrospect to have been precipitated rather than caused by substance misuse; conversely, information may emerge over time regarding substance misuse in enduring psychotic illness that, at onset, may have appeared unrelated to substance misuse.

Figure 11: Diagnostic transitions over six years to and from PNOS



Tables 9, 10 & 11 detail numbers in each diagnostic category at the different time points

As indicated in Figure 11, PNOS is, by virtue of its diagnostic criteria, a heterogeneous group consisting of individuals with illness that appears atypical and/or about whom insufficient information is available. As such, it is indispensable as a category, as higher levels of uncertainty will always exist where diagnosis is solely based on inference from an array of symptoms and course of illness rather than via any validating diagnostic test. It is therefore unsurprising that, over time, the majority of patients with this diagnosis at first presentation receive another diagnosis at follow-up; additional information is collected and the sometimes confusing array of symptoms that is common at the first presentation of psychotic illness can settle into a more stable phase. Of the 15 individuals with this diagnosis at first presentation, only four retain it at follow-up. Of these four, one was not available for follow-up; additional information that might have clarified that diagnosis was not available. Another study mentioning the diagnostic stability of PNOS found it to have one of the lowest levels of stability of all diagnoses within the psychotic spectrum (Whitty et al., 2005). It is interesting to consider what diagnosis those with PNOS at first presentation receive at follow-up, in order to establish whether it makes sense that there might have been diagnostic uncertainty at onset. Whilst eight

individuals went on to develop SZ, SA or MDDP, three went on to receive a diagnosis of either SIP, SIM or Alz, all diagnoses that point to the possibility of initial diagnostic uncertainty.

Figure 12: Diagnostic transitions over six years to and from PGMC

Tables 9, 10 & 11 detail numbers in each diagnostic category at the different time points

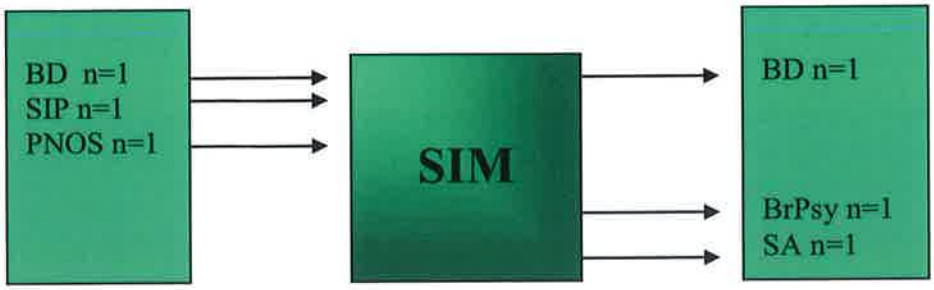
PGMC is the first of four diagnostic categories with very small numbers and, as such, it is better to consider the data as a case series (Table 48). As indicated in Figure 12, of the four individuals with PGMC at first presentation, two were given the same diagnosis at follow up, one SZ and one SA. There was one case where an initial diagnosis of DD evolved to a diagnosis of PGMC. This diagnosis may be more common than is captured up by most FEP studies, as many cases may not come to the attention of the incepting psychiatric services. PGMC has been found to be difficult to distinguish from SZ, often demonstrating the same 'nuclear' symptoms (Johnstone et al, 1988). Commoner causes include CVA, fronto-temporal dementia, thyroid disease, tumours of the brain, systemic lupus erythematosis (SLE), neurosyphilis, Parkinson's disease and multiple sclerosis (Johnstone et al, 1988). These organic phenocopies of psychosis have added to understanding of the anatomic basis of psychotic symptoms. In post-CVA psychosis for example, misidentification syndromes occur more frequently with right temporal lobe lesions (Hudson & Grace, 2000), manic symptoms with right sided thalamic infarcts (Carota et al., 2002), visual hallucinations with activation of regions near the occipital cortex (Carota et al.,

2002) and delusions with right-sided CVA in the presence of pre-existing diffuse brain atrophy (Levine & Grek, 1984).

Table 48: Physical causes to which PGMC was attributed

Case no.	Time of diagnosis of PGMC	Physical cause to which PGMC attributed
1	Presentation, follow-up	Korsakoff's psychosis
2	Presentation, follow-up	Cerebro-vascular accident
3	Presentation	Systemic lupus erythematosus
4	Presentation	Cerebro-vascular accident
5	Follow-up	Cerebro-vascular accident

Figure 13: Diagnostic shift over six year towards and away from SIM



Tables 9, 10 & 11 detail numbers in each diagnostic category at the different time points

SIM was diagnosed in six participants at onset; the substances involved included antidepressants (n=3), alcohol (n=2) and cannabis (n=1). As indicated in Figure 13, by follow-up three of these retained the diagnosis, with one each being reassigned to the diagnostic categories SA, BD and BrPsy. Three individuals with other diagnoses at onset (BD, SIP and PNOS) received a diagnosis of SIM at follow-up. Many drugs are capable of inducing mania, particularly antidepressants and steroids (Peet & Peters, 1995). Substances of abuse such as alcohol, amphetamines, hallucinogens and cannabis are also implicated (Hilty et al., 1999). The relationship between antidepressants, SIM and BD is complex and difficult to clarify in view of the high rates of co-morbidity of BD and substance abuse, the high rates of antidepressant use in BD and the unclear relationship between antidepressants and polarity switches in BD (Goldberg & Truman, 2003).

A diagnosis of MGMC was made in one individual at onset of illness, the cause being a cerebrovascular accident, and was unchanged at follow-up.

SDD was diagnosed in one individual at onset of illness, and was unchanged at follow-up. SDD (dementia simplex) was included by Kraepelin in his classification of SZ (1921). It was

understood as being characterised by a change in personality, loss of interest and decline in functional ability in the absence of florid psychotic symptoms. It has been criticised as being of uncertain nosological validity (Stone et al., 1968) and was omitted from DSM-III. DSM-IV, however, has included it as a 'criteria set for further study'. Psychometric assessment and functional neuroimaging suggest deficits consistent with those seen in typical SZ (Serra-Mestres et al., 2000).

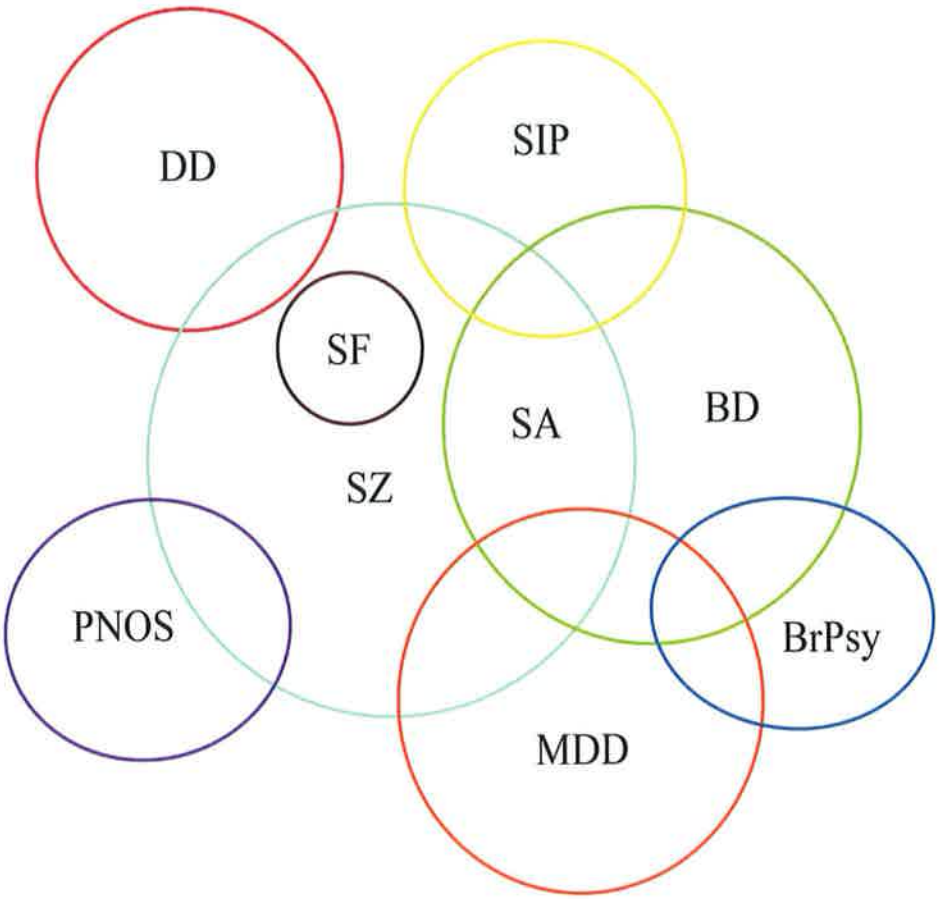
Conclusions

The above findings point towards a model that may be visualised as a Venn diagram having overlapping sets which possibly result from a number of related symptomatic profiles, in accordance with a dimensional rather than a categorical approach to diagnosis. Kupfer et al (2002) have summarised the increasing evidence for a dimensional approach as follows:

> 'Despite many proposed candidates, not one laboratory marker has been found to be specific in identifying any of the DSM-defined syndromes. Epidemiologic and clinical studies have shown extremely high rates of comorbidities among the disorders, undermining the hypothesis that the syndromes represent distinct etiologies. Furthermore, epidemiologic studies have shown a high degree of short-term diagnostic instability for many disorders. With regard to treatment, lack of treatment specificity is the rule rather than the exception' (p.xviii).

A simplified diagram is offered in Figure 14 for those diagnoses with 10 or more individuals at six month follow-up.

Figure 14: Putative inter-relationships between categorical psychotic diagnoses



In this diagram, there are three major diagnostic nodes, SZ, BD and MDDP, which are both (a) populous enough to suggest that they constitute substantive diagnostic entities, and (b) having high levels of prospective and retrospective stability. SA, another putative node, is populous only at follow-up and appears to inhabit the territory between the three other nodes. SF appears primarily a progenitor of SZ, while DD appears primarily a variant progenitor of SZ and SA. BrPsy appears to be related prospectively to BD and MDD, while SIP and PNOS appear to be related prospectively to SZ and SA. This summarises the transitions between the diagnoses over time and may prove useful, in combination with the section below on psychopathology, for further consideration of how psychotic illness might be conceptualised, given the essentially symptom-based nature of diagnosis.

Psychopathology at follow-up

It was considered very important when designing this study to look at psychopathology at follow-up. Whilst functioning and QOL have taken us beyond symptom severity and hospitalisation as key outcomes of interest, psychopathology remains an important variable in terms both of understanding the nature of psychotic illness and of establishing factors that moderate functional measures of outcome. The PANSS was chosen principally because, as an 'industry standard', it was used for baseline assessment; the aspiration was to compare PANSS at baseline to that at follow-up. However, this was not feasible due to the limited number who completed the PANSS at onset of illness. Other measures such as the Scale for the Assessment of Positive/Negative Symptoms (SAPS/SANS) are now also widely used, but as a single measure of psychopathology, the PANSS was deemed suitable for the purpose of this study in relation to function and QOL. As discussed in Results, PANSS scores at follow-up were considered by diagnostic category at the three times points, as well as for the sub-groups who possessed a given diagnosis at all three time points (called 'core' diagnoses). Results were also divided by sex for each diagnosis at each time point.

Schizophrenia

Among the more populous diagnostic groupings (i.e. SZ, SA, BD and MDDP), SZ has the highest level of positive, negative and general symptoms, making it the most severe diagnosis in terms of psychopathology across the psychotic spectrum. The findings in relation to positive and negative symptoms are not surprising, as a diagnosis of SZ is made on the basis of these, rather than affective symptoms. This conforms with the literature to date, which has found characteristically high rates of positive and negative symptoms in SZ compared to other psychotic diagnoses (Brockington et al., 1991; Crow, 1980; Andreasen, 1982; Carpenter et al., 1988). Perhaps more surprising is the finding that general psychopathology, which includes mood and anxiety symptoms, are also high relative to affective psychosis, which might be expected to have higher levels of such symptoms. However, research has shown that patients with SZ do experience high rates of both anxiety and depression, both of which are constituents of PANSS-general (Planansky & Johnston, 1978; Craig et al., 2002; Braga et al., 2004; Ciapparelli et al., 2007). Time at diagnosis makes little difference to positive or general symptoms. However, PANSS negative scores are somewhat higher when those who moved into this category from other diagnoses at follow-up are included, suggesting that diagnostic change toward SZ, and therefore away from other diagnoses, occurs more readily in the presence of severe negative symptoms.

Schizoaffective disorder

After SZ, SA has the highest levels of positive, negative and general symptoms, in accordance with the literature to date (van Os et al., 1999; Pini et al., 2004; Williams & McGlashan, 1987). Given the modest number of members in this diagnostic category at onset relative to follow-up, it is of interest to clarify if the large influx into this diagnostic category influences severity for these measures. This is not the case, with little relationship to time of diagnosis for either positive, negative or general symptoms.

Bipolar disorder

Total psychopathology scores are lower in BD than in SZ and SA, and are more similar to those found in MDDP. This pattern is particularly pronounced for positive and negative symptoms, and less so for general symptoms. This is not particularly surprising, given that negative symptoms are considered less characteristic of the affective psychoses and that positive symptoms are not necessary for a diagnosis of BD (Pini et al., 2004; McGorry et al., 1998). However, it is evident that negative symptoms are not exclusive to SZ-spectrum illness (Pini et al., 2004), as corroborated here. This is one of the findings that has lead to the suggestion that a dimensional rather than a categorical approach to classification may be more appropriate for this group of illnesses (Slade & Andrews, 2005; van Os et al., 1999; Peralta et al., 2002). As in SA, the time at which diagnosis was made does not in the main have a major impact on scores for any of these symptom domains. Future studies would benefit from the inclusion of a more incisive instrument for the assessment of affective, particularly manic, symptoms.

Major depressive disorder with psychotic features

Where to position MDDP in terms of diagnostic spectrum and psychopathology vis-à-vis the other principal diagnoses (SZ, SA, BD) is challenging, given the relative lack of research into this diagnosis. Most of the literature that exists highlights the importance of depressive, and to a lesser extent negative, symptoms in MDDP (Salvatore et al., 2007; van Os et al., 1999; Reischies et al., 1990; Peralta et al., 1997). Here, positive and general symptoms were present at levels slightly lower than those found in BD. Low levels of positive symptoms relative to SZ has been noted previously (McGorry et al., 1998). However, that positive symptoms occur at lower levels than in BD is interesting, in that inclusion in the study was possible with a diagnosis of BD in the clinical 'absence' of psychotic symptoms, but not with MDD (major depressive disorder without psychotic symptoms). This might occur because positive symptoms are not 'absent' or 'present' but, rather, distributed continuously in BD. Another possibility might be that patients with MDDP were less unwell at follow-up. However, negative symptoms in MDDP were found to be slightly more severe than in BD,

although less severe than in SZ or SA. This could in part reflect misinterpretation of depressive psychomotor retardation and social withdrawal as 'negative' symptoms, given the limited capacity of the PANSS to distinguish between and capture affective symptoms. In summary, MDDP appears closest to BD in terms of symptoms, with the somewhat unexpected finding that 'negative' symptoms are higher in MDDP than in BD. Future studies would benefit from the inclusion of a more incisive instrument for the assessment of affective, particularly depressive, symptoms.

Schizophreniform disorder

Symptom levels in SF are generally between those found in SZ and SA. Positive symptom level is similar to that in SZ, even in those with SF at follow-up who might be expected to have a less florid illness than those having evolved to SZ. This concurs with literature findings to date (Kendler & Walsh, 1995). When negative symptoms are considered, however, a greater separation is seen between SF and SZ; unsurprisingly, the small numbers with SF at follow-up have somewhat lower levels than those with this diagnosis at onset, again in accordance with previous research (Makanjuola & Adedapo, 1987). Together with the above findings regarding diagnostic stability, this suggests that SF as defined by DSM IV is very similar to SZ, other than that negative symptoms may be less pronounced. An interesting finding, and one that will be considered further below in relation to functioning, is that females with SF appear somewhat more symptomatic than males.

Brief psychotic disorder

Whilst numbers in this diagnostic category are small, and previous research findings are limited, some observations may be made; positive, negative and general symptoms occur at lower severity relative to SZ, SA, BD and MDDP. Marneros et al (2005) found that the most important feature differentiating between BrPsy and the other psychotic disorders were 'rapidly changing delusional topics', 'rapidly changing mood' and anxiety.

Delusional disorder

Like SF, numbers for DD at follow-up are modest and findings therefore need to be interpreted with caution. Research to date indicates that positive symptoms are prominent in DD but not to the extent found in SZ (Kendler & Walsh, 1995; McGorry et al., 1998). Here, symptoms occur generally at levels lower than for SZ but higher than for BD and MDDP. However, there is one key exception: negative symptoms are considerably lower than in any of the other main diagnostic categories. This is not surprising, as the presence of negative symptoms would likely change the diagnosis to that of SZ.

Substance-induced psychosis

Overall psychopathology in SIP is amongst the lowest of any of the diagnoses, with positive symptoms present at levels similar to those found in MDDP and BD. Little specific research into psychopathology in SIP has been carried out. However, it is accepted that positive symptoms qualitatively similar to those found in SZ predominate during the acute episode (Castellani et al., 1985). For SIP at follow-up, all symptoms, particularly negative and general symptoms, are markedly less severe. These findings extend a conceptualisation of SIP as a diagnosis that is largely characterised by positive symptoms which appear in the context of substance abuse. In the present study, this diagnosis was encountered only in men which undoubtedly reflects the overall higher level of substance abuse in males; however, one might speculate also on a greater sensitivity of males to development of psychotic symptoms in this context.

Psychosis not otherwise specified

It is of interest to consider here what pattern of symptoms remains difficult to classify over a six year follow-up period, during which this category reduces from 14 to 3 individuals. Firstly, at follow-up positive and negative symptoms are lower than for any other category. This may indicate that an initial episode, which either does not clearly fit an early pattern for any diagnosis, or about which there is inadequate information, is then followed by a

relatively symptom-free period. General psychopathology is, however, present at levels similar to those found in BD and MDDP, indicating that there is some ongoing process in these individuals, however unclear its nature. All of the symptoms domains are low for PNOS at follow-up, consistent with the evolution of individuals having this diagnosis at onset and six months towards other more categorical diagnoses over time. No literature was evident with which to compare these findings. Numbers at follow-up are too small to investigate possible sex differences.

Other diagnoses

The diagnostic groups of PGMC, SIM and MGMC are too small to allow any useful symptomatic characterisation; neither have they been the subject of specific research on psychopathology. However, some broad observations may be made: for example, they tend to have low levels of symptoms and these levels are lower for those retaining the diagnosis at follow-up than for those with the diagnoses at onset, as individuals migrate out of these diagnoses towards more symptomatic categories.

Conclusions

These findings should be considered in conjunction with those relating to diagnostic stability, to clarify relationship between diagnoses. SZ has the highest levels of positive, negative and general symptoms. SA lies closer to SZ in terms of positive symptoms but is approximately midway between SZ and BD/MDDP in terms of negative symptoms. BD and MDDP have relatively lower levels, being similar to each other in overall symptom severity but with higher levels of negative symptoms in MDDP. While SF is closest to SZ, BrPsy lies closer to BD and MDDP. DD also evidences symptom severity similar to SZ and SA, whilst SIP has lower severity of symptoms. Lastly, PNOS has a low level of symptoms by follow-up. This is largely supports the diagnostic conceptualisation offered in Figure 14, with addition of the concept that the centre of the diagram generally represents more severe symptomatology.

Functioning at follow-up

Functioning is possibly the most important measure of outcome in any study of illness, in particular psychiatric illness, where functioning is often closely allied to severity. As summarised in Introduction, functioning in some disorders in the psychotic spectrum, such as SZ and BD, has been relatively well described. However, there is less evidence and much uncertainty with regard to many other psychotic diagnoses. This description of the levels of functioning found across the diagnoses in the present study will start by considering those for which there is greater clarity, in order to establish whether this study shows results consistent with those reported previously. In some other studies, social and occupational functioning have been considered separately. However, here it was decided to consider them in a composite fashion for the following reasons:

1. The high level of correlation between social and occupational functioning in other studies (Samele et al., 2001; Mantonakis et al., 1982);
2. To conceptually focus consideration of functioning to that of an individual's ability to operate in society in the general sense, which may give a clearer picture of impairment/non-impairment;
3. To reduce to a manageable number the variables being considered.

Methodological considerations

Several measures of functioning were used in this study, each of which makes a particular contribution towards capturing the breadth of function-dysfunction. The GAF is useful in that it allows the rater to create an overall perspective on functioning; whilst it asks the rater to consider particular domains, it is not bound by a potentially limiting set of questions. The Strauss-Carpenter Scale is particularly relevant to functioning in SZ and related psychoses, as it focuses on the functional deficits which may be associated with negative symptoms. The HoNOS is a good general global measure of functioning which has been used in population studies and is therefore designed to be more sensitive to gradations of functioning at the

higher end of the spectrum (Wing et al., 1996; 1998); the SLOF has the reverse property, with questions aimed at picking up differences in functioning at the disability end of this spectrum (Schneider & Struening, 1983). Having used each of these measures in order to create a comprehensive assessment of functioning, they were then subjected to principal component analysis in order to distil the findings of the study into a manageable set of results. The resultant PC, 'Function 1', explaining over 80% of the variance, was then used for logistic regression modelling. Here, Function 1 will be discussed rather than considering the findings on each of the measures.

Functioning in relation to diagnosis and sex

Schizophrenia

As has been found in the vast majority of studies carried out around the world (Johnstone et al., 1992; Lauronen et al., 2005), functioning in SZ is markedly impaired and compares unfavourably to that found in other psychotic disorders. It has the most severely impaired level of functioning of any of the diagnoses, with the exception of two of the uncommon diagnoses, PGMC and MGMC; the reasons why these surpass even SZ in terms of impairment will be discussed below. Of interest is that those with 'core' SZ, i.e. those who received a diagnosis of SZ at onset, six months and follow-up, appear to have the worst outcome. It might be speculated that those who have the purest form of the illness, with few of the affective symptoms that might cloud the diagnostic picture and with prominent negative symptoms that clarify a diagnosis of SZ, do worse than those who inhabit the 'overlap' sections of the Venn diagram representing diagnosis (Figure 14). Men with SZ function somewhat worse than women, confirming the majority of previous reports (Thara, 2004; Beiser et al., 1994). However, the present effects of sex appear not as marked as those found in some other studies.

Schizoaffective disorder

Because of the small number of participants with SA at onset (n=6) and the considerably larger number at follow-up (n=27), it is perhaps most useful to focus on the follow-up diagnosis of SA when considering functioning in this group. Though SA lies somewhere between SZ and BD/MDDP in terms of psychopathology, it is much closer to SZ in terms of functional impairment. While this concurs with some previous findings (Tsuang & Dempsey, 1979b; Lay et al., 1997), other studies have located it closer to the affective psychosis (Nardi et al., 2005; Marneros et al., 1990). In SA, functional outcome is worse in men than in women, as is the case for SZ. If functioning at follow-up is so impaired in SA, perhaps measuring functioning at onset might give more prognostic information than a classification system that concentrates primarily on symptoms.

Bipolar disorder

Functioning in BD lies somewhere in the middle if an ordinal ranking of the diagnoses is created. However, the actual values for each diagnosis indicated greater separation of BD from SZ and SA than from diagnoses with better functional outcomes. Previous research has also indicated considerable separation between functioning in BD relative to SZ (Grossman et al., 1991; Morgan et al., 2005; Depp et al., 2006). To gain a concept of the relative severity of these diagnoses, a mean GAF score of 68.5 at follow-up indicates functioning at the top of the range described thus: 'Some mild symptoms OR some difficulty in social, occupational, or school functioning, but generally functioning pretty well, has some meaningful interpersonal relationships' (First et al., 2002). This score is very similar to that found by Hajek et al (2005). Thus, whilst impairment is present at follow-up, it is not in the severe range. Given that the diagnosis of BD accrues more cases than it loses over time, and that the general pattern is of loss to diagnoses with worse functional impairment (SZ, SA) and to gain from diagnoses with better functioning (BrPsy, MDDP, SIP), this might be expected. Again, males fare worse than females with respect to functioning in BD, in accordance with previous findings (Tohen et al, 1990; Morgan et al., 2005).

Major depressive disorder with psychotic features

This is a particularly interesting entity to study, as its status within the spectrum of psychotic illnesses and its relationship to other diagnoses, particularly BD, is unclear. To date, there has been very little work on functioning in MDDP. That which exists points towards functioning in MDDP being either similar to or somewhat better than in BD (Haglund et al., 1998; Kettering et al., 1987; Tsuang et al., 1979). However, in the present study functioning in those with MDDP at follow-up appears slightly worse than that found in BD, despite the fact that symptoms, as determined by PANSS total, are very similar for these two disorders. Males with MDDP show worse functioning than females. Those with a diagnosis of MDDP at follow-up show somewhat better functioning than those in whom the diagnosis was made at onset, which may be accounted for by the diagnostic exodus over time towards diagnostic categories characterised by worse functioning and the influx of individuals from better functioning categories.

Schizophreniform disorder

Limited research on functioning in SF has found this to be less impaired than in SZ (Sautter et al, 2006; Benazzi, 2003; Zarate et al, 2000). Since the majority of cases at inception go on to develop SZ or SA, little may be said about the functioning of the few who retain this diagnosis. Numbers at follow-up are too small to clarify any sex differences but results suggest that SF may be one of the few disorders where women function more poorly than men in the long-term. Onset diagnoses of SZ and DD in women also show somewhat poorer functioning, suggesting that an episode of psychotic illness without a material affective component may be associated with adverse functional outcome in women.

Brief psychotic disorder

For BrPsy, numbers are relatively small, particularly so at follow-up, thus limiting conclusions that can be drawn. This diagnosis might well be expected to show generally better functioning than other diagnoses in that, by definition, symptomatic episodes are time-

limited and good inter-episode levels of functioning might be expected. Research on BrPsy over the period immediately following onset also indicates that this is the case (Jauch & Carpenter, 1988; Pillmann et al, 2002); this is confirmed by the present findings, which place it into a better-functioning cluster, along with SIP and PNOS. While BrPsy at follow-up shows better functioning than the same diagnosis at onset, this is due to the exodus over time of those functioning most poorly to more severe diagnostic categories. Males with BrPsy appear to do worse than females but numbers at follow-up are too small to allow systematic comparisons.

Delusional disorder

This diagnosis is underpopulated at follow-up, such that it is difficult to draw any firm long-term conclusions. DD at onset can be compared to SZ, the diagnostic category that at follow-up is the biggest recipient of cases among those with an onset diagnosis of DD. It is found that DD at onset has a functional outcome at follow-up similar to that for SF at onset; both fare better than SZ but worse than those with a diagnosis, at any time, of BD or MDDP. Only three people were diagnosed with DD at follow-up and, unsurprisingly, a follow-up diagnosis of DD entails better functioning than among those with DD at onset. This may be due partly to the presence of negative symptoms that make it unlikely a diagnosis of DD would be retained at follow-up, and partly to the exodus of those cases developing an alternative diagnosis with worse functional outcome. As for SF, DD is one of the few disorders for which females with this diagnosis at onset have worse functioning at follow-up than their male counterparts. There is little literature with which to compare these present findings.

Substance-induced psychosis

Certain characteristics of SIP make it difficult to understand fully its functional status: first, only four of those with this diagnosis at onset retained it at follow-up; second, no women received this diagnosis at any time. Nonetheless, functioning is relatively high in this group, particularly at follow-up, which might be predicted in a group hypothesised to be at lower

genetic risk for developing psychosis. This is in line with the limited amount of research on functioning in SIP (Gersabeck, 1999).

Psychosis not otherwise specified

PNOS is another diagnosis with very few cases at follow-up. Thus, we know more about the prognostic implications of this diagnosis at onset than in the long-term. Those few who retain this diagnosis at follow-up have relatively good functioning. However, having this diagnosis at onset has more severe implications, as many such cases go on to develop SZ or SA. At follow-up, numbers with PNOS are too small to allow conclusions as to sex differences. However, for onset and six month diagnoses of PNOS, functional outcome appears marginally worse in females. Because of the heterogenous nature of this category, it is difficult to generalise these findings to any group beyond the individuals concerned.

Psychosis due to a general medical condition

This is one of the smallest diagnostic categories, with only four individuals having a diagnosis of PGMC at onset. As such, it is more usefully considered as a series of case studies rather than a group from whom more global interpretations of outcome may be made. These four individuals are found to have particularly poor functional outcomes at follow-up, which reflects their ongoing poor physical health interfering with functioning in a manner that extends beyond the presence of psychiatric illness; this can be seen from their relatively low positive and negative symptom scores. There is little literature with which to compare the present findings.

Substance induced mania

The few individuals with SIM have good functioning, as do those with SIP. There is little literature with which to compare the present findings.

Mood disorder due to a general medical condition

One individual received a diagnosis of MGMC at onset and retained it throughout the study. This individual showed particularly poor functioning throughout the study, for reasons likely similar to those suggested above for PGMC.

Simple deteriorative disorder

The single individual with SDD at onset went on to receive a diagnosis of SZ at follow-up but showed higher functioning than the mean for SZ.

Conclusions

The findings in this study regarding diagnoses for which functional outcome has already been the subject of substantive previous research, i.e. SZ, SA and BD, elaborates those findings through systematic comparison: follow-up functioning is particularly poor in SZ; whilst there is less impairment in BD, functioning is still impaired in the majority of individuals; outcome in SA lies between SZ and BD, although closer to that for SZ. Functioning in MDDP is slightly worse than for BD, despite the latter having been considered a more severe illness entailing greater likelihood of inter-episode impairment. Among the less populous diagnostic groupings, DD at onset and SF at onset lie close to SA at onset with regard to functioning at follow-up. BrPsy, SIP, PNOS and SIM all have functional outcomes at the better end of the spectrum indicated across the study. PGMC and MGMC both have very poor functional outcomes, which is probably due to poor physical health leading to low function scores. The overall pattern is for those diagnoses with generally better outcomes to have functional outcome scores by diagnosis at onset that are lower than by diagnosis at follow-up, with the reverse being found for those diagnoses with generally worse outcomes. Men are found almost invariably to function more poorly than women at follow-up, the exception being for diagnoses of SZ, SF and DD at onset; this indicates that in women, the absence of affective symptoms at the onset of their illness is a negative prognosticand.

Quality of life at follow-up

To date, the majority of research on QOL in psychosis has looked at correlates and predictors within a given diagnosis, rather than comparing QOL between different psychotic diagnoses. Poor premorbid functioning, higher levels of negative and depressive symptoms, fewer psychological resources and poor social supports have all been associated with worse outcomes in terms of QOL (Malla et al., 2002a; Svirskis et al., 2007; Melle et al., 2005b), which is generally impaired in psychosis relative to the normal population (Hakkaart-van Roijen et al., 2004; Bechdolf et al.. 2005; Sierra et al., 2005; Depp et al., 2006; Svirikis et al., 2007). We might assume that diagnoses with poorer premorbid adjustment and more negative symptoms, such as SZ, might have the most impaired QOL. However, as most research is based on SZ individuals alone, it does not necessarily follow that this is the case. So little research has been carried out on diagnostic groups other than SZ that the findings presented here provide a useful starting point for future exploration of the area.

Methodological considerations

Here, two measures of QOL of life were used, one of which is a clinician-rated semi-structured interview (QLS), the other being subjective (WHOQOL-Bref). As the QLS is quite disease specific, with a focus on the deficit syndrome in SZ, it was felt to be important to include another subjective measure of QOL which is designed for more general use across populations. The WHOQOL-Bref was designed as 'an international cross-culturally comparable quality of life assessment instrument. It assesses the individual's perceptions in the context of their culture and value systems, and their personal goals, standards and concerns' (World Health Organisation, 2009). Thus, two measures designed with very different populations in mind, one being administered by a clinician and one self-rated by the patient, were used in order to gain a broader perspective on QOL. As with measures of functioning, principal component analysis was then performed on the data yielded by the two instruments, in order to see if any PC(s) exist(s) which might provide a useful composite measure of QOL. Such a PC was found and QOL 1 is the resultant index, as defined in

Results. It is important to consider that because fewer participants completed the QOL measures than other assessments, numbers are smaller and thus conclusions drawn on the basis of these data are more limited. However, when age and sex for the groups completing and not completing QOL measures are compared, they are found to be generally similar.

Quality of life in relation to diagnosis and sex

Schizophrenia

The results of the study confirm findings relating to QOL in SZ, namely that it is considerably impaired (Bechdolf et al., 2005). SZ has the poorest QOL of any of the principal or moderately populous diagnostic categories. At follow-up, SZ diagnosed at onset has marginally better QOL than SZ diagnosed at follow-up, with 'core' SZ having the poorest QOL of all. It is interesting to reflect on these findings in the light of the notion that in SZ there can be a discrepancy between subjective and objective QOL, whereby people with SZ rate their QOL higher than clinician ratings (Eklund & Hansson, 2001; Sainfort et al., 1996; Gorna et al., 2007; Kusel et al., 2007; Tomotake et al., 2006). The composite QOL 1 measure does not capture this notion. However, when the QLS (objective) data are compared to the WHOQOL-BREF (subjective) data, it can be seen that SZ is less isolated towards the bottom of the ranking when subjective rather than objective measures are considered. This suggests that subjective and objective measures of QOL may be more in agreement for some diagnostic categories than others. Sex effects on QOL in SZ do not follow a clear pattern; males do variously better or worse on this measure depending on when the diagnosis was made, with no clear trend in favour of either males or females.

Schizoaffective disorder

SA is the second most impaired of those diagnostic groups with sufficient numbers to draw conclusions. It is interesting that impairment in QOL for SA is less than for SZ. This is despite the fact that, in addition to relatively high levels of negative symptoms (a correlate of poor QOL), this group could also be expected to have higher levels of depressive and other

affective symptoms which might have a negative impact on QOL. Indeed, if QLS and WHOQOL-Bref measures are compared, it can be seen that SA appears lower in the ranking by diagnoses for subjective than it does for objective QOL. Men with SA have poorer QOL than women, no matter when the diagnosis was made. There is little literature with which to compare the present finding.

Bipolar disorder

Little has been known about QOL in BD, other than that it is more impaired than in the normal population (Sierra et al., 2005; Hakkaart-van Roijen et al., 2004; Depp et al., 2006). In this study QOL in BD was found to be at the upper end of the range encountered across psychotic diagnoses. Given that there is little literature systematically comparing QOL across the diagnoses, this is useful information. It also appears that the point at which the diagnosis was made has little impact on QOL at follow-up. Again, QOL is found to be poorer in men than in women.

Major depressive disorder with psychotic features

Little is known about QOL in MDDP, particularly how QOL for this diagnosis compares to other diagnoses such as SZ and BD. The present data indicates that in MDDP QOL is similar to that in BD, being towards that end of the range across diagnoses where QOL is less impaired and therefore possibly closer to normal population values. Consistent with the pattern of sex differences discussed above for SZ, SA and BD, males with MDDP also show poorer QOL. However, inspection of QOL 1 values by sex across diagnoses indicates than male-female differences are in the rank order SZ<SA<BD=MDDP. Thus, a greater affective component to psychotic illness may have a more adverse impact on QOL in males than in females.

Schizophreniform disorder

No individuals with SF at follow-up completed QOL measures at follow-up, so it is only possible to examine QOL at follow-up for a diagnosis of SF at onset. It is found that QOL in SF lies somewhere between SZ and BD/MDDP. Many individuals with SF go on to develop more serious psychotic illness, primarily SZ; when they do so, they retain better QOL than the overall mean for the diagnosis of SZ to which most evolve. No meaningful analysis of any sex differences is possible.

Brief psychotic disorder

Numbers are sufficient only to comment on QOL at follow-up for a diagnosis of BrPsy at onset and six months. It is found to be substantially at the better end of the spectrum, with values higher than those for MDDP or BD. Most individuals with BrPsy at onset go on to develop more serious psychotic illness; when they do so, as for SF, they retain better QOL than the overall mean for the diagnoses to which BrPsy evolves. No meaningful analysis of any sex differences is possible.

Delusional disorder

Numbers are sufficient only to comment on QOL at follow-up for a diagnosis of DD at onset and six months. QOL in those with an onset diagnosis of DD is quite poor and close to that for SA. No meaningful analysis of any sex differences is possible.

Substance-induced psychosis

QOL in SIP is somewhat poorer than in BD/MDDP. This is interesting when considering that SIP shows better functioning; thus, whilst function and QOL are generally related, there can be exceptions. As for SZ, there is greater discrepancy between subjective and clinician-rated QOL; those with SIP rate their QOL lower than do clinicians, whereas those with SZ rate their QOL as higher than do clinicians. One might speculate that a dysphoric tendency

might lead to both greater risk for substance abuse as well as lower subjective QOL. No sex comparisons are possible, given that no women received this diagnosis.

Psychosis not otherwise specified

QOL at follow-up appears to vary markedly between PNOS at onset and at follow-up, the latter experiencing generally better QOL. However, numbers are sufficient only to consider PNOS at onset, where QOL is similar to that for SA. Interestingly, diagnosis of PNOS at onset entails worse QOL in females than in males, though this must be interpreted cautiously given the small numbers.

Psychosis due to a general medical condition

For the few individuals with PGMC who completed assessment, QOL is very poor, considerably lower even than for SZ. The impact of ongoing poor physical health is likely to contribute to such poor QOL, in particular when considered with the findings for MGMC.

Substance-induced mania

The small number of individuals with a diagnosis of SIM at onset have QOL similar to SIP. Those with SIM at follow-up have the highest QOL for any group.

Mood disorder due to a general medical condition

For the single individual with MGMC who completed assessment, QOL is very poor. This is in agreement with the findings for PGMC.

Simple deteriorative disorder

The single individual with SDD at onset went on to receive a diagnosis of SZ at follow-up but showed better QOL than the mean for SZ.

Conclusions

For QOL, a close relationship with symptoms is less evident than is the case for functioning; QOL appears to vary in a more independent way. Previous research has indicated QOL to be reduced in the presence of higher symptom ratings (Huppert et al., 2001; Voruganti et al., 1998; Ritsner et al., 2002; Savilla et al., 2008; Perlick et al., 2008). Whilst there is considerable overlap between patient- and clinician–rated QOL, this is less so for SZ. This has been noted in previous studies, where patient-rated QOL tends to be lower in SZ (Gorna et al, 2007; Kusel et al., 2007; Tomotake et al., 2006). However, principal component analysis indicates that a unitary construct can be derived from the two measures that places SZ at the lower end of a spectrum, closely followed by SA, with BD and MDDP at the higher end together with BrPsy; SF, DD, SIP and PNOS all lie somewhere in the middle, though small numbers make it difficult to draw substantive conclusions. Also, differences between the sexes, in favour of females, appears more evident for diagnoses having more prominent affective symptoms.

Service engagement at follow-up

It is clear from the literature that SE is important in governing outcome in psychosis (Kissling, 1994). There is evidence that adherence and engagement in SZ are similar to chronic physical illnesses (McPhillips & Sensky, 1998). While there is little information on engagement in BD, adherence appears to be similar to that in SZ. Engagement appears to be good in MDDP, with levels of adherence similar to those in BD. Aside from the above diagnoses, other psychotic diagnoses have received little investigation; nor have there been many studies that have sought to compare levels of SE between the diagnoses.

Methodological considerations

SE was measured at follow-up using the SES, the only instrument available which quantifies this concept. There are many instruments which aim to measure adherence. However, the aim here is to take a broader perspective on SE, encompassing attitude towards illness and

treatment, adherence to treatment and alliance with service providers. The use of this single, straightforward instrument with good face validity is less problematic than trying to create, using principal component analysis, a measure of SE which would be constructed from conceptually heterogenous scales.

There are striking variations in SE across many diagnostic groups, such that rankings differ substantially depending on whether diagnosis at onset or diagnosis at follow-up is considered. Thus, it is only possible to comment on relative SE between diagnoses for which there is less variation over time and sufficient numbers to allow inter-group comparisons, namely SZ, BD and MDDP. Follow-up diagnoses have been used as the principal reference point when discussing SE outside of these more stable groups.

Service engagement in relation to diagnosis and sex

Schizophrenia

SE in SZ is found here to be particularly low. Other studies have indicated better SE in this disorder (Cohen & Teresi, 1996; Berghofer et al., 2002, Morgan et al, 2003). Whilst there is no literature comparing SZ to other diagnoses in this regard, there is a general clinical and research impression that people with SZ are relatively difficult to engage and that a combination of poor motivation and poor insight may contribute to this picture. There are no studies that have applied this scale to chronic physical illnesses, so it is not possible to make such comparisons. Men and women do not differ substantially on this measure, whereas one study (Miner et al., 1997) found better engagement in women than men. Whilst there are some sex differences on several measures considered here (psychopathology, function, QOL, SE), these appear smaller for SZ than for other psychotic diagnoses.

Schizoaffective disorder

SE in SA is in the middle of the range encountered across the different diagnoses at follow-up. Females with SA show considerably better SE than do males. This is a pattern that

applies to most other diagnoses, with a few exceptions such as SZ. There is little literature with which to compare these findings.

Bipolar disorder

SE in BD is generally similar to that found in SA, indicating perhaps that the presence of more affective symptoms in psychosis results in improved SE. SE has not been a focus of research in BD to date. However, previous research has pointed to poor adherence to medication and low rates of help-seeking behaviour in BD (Keck et al., 1997; ten Have et al., 2002; Coletti et al., 2005; Fleck et al., 2005; Wang et al., 2005; Sajatovic et al., 2006a). Women with BD again show better SE than do men, to an extent similar to that found in SA.

Major depressive disorder with psychotic features

MDDP shows SE towards the upper end of the range encountered across the diagnoses. This adds weight to the hypothesis that increasing levels of affectivity, especially depression, may lead to improved SE in psychotic illness. High rates of SE in MDDP have been noted previously (Sparr et al., 1993; Menchetti et al., 2006). Interestingly, for MDDP there is little difference in SE between the sexes, when it might have been expected that women would be more likely to engage with services.

Schizophreniform disorder

For SF, SE appears to be particularly poor, lower even than for SZ. It is important to note the low numbers with this diagnosis at follow-up. Nevertheless, poor SE at follow-up may reflect those with a more benign illness course, i.e. those with SF at follow-up who have not evolved to SZ, being less in need of services. Females with SF at onset show poorer SE than do males, which diverges from the prevailing pattern. However, males with SF at follow-up show poorer SE than do females.

Brief psychotic disorder

For BrPsy there is little research on SE with which to compare the present findings. Here, SE at follow-up is generally poor in BrPsy, with values similar to those found in SZ. This may reflect those with a more benign illness course, i.e. those with BrPsy at follow-up who have not evolved to a more serious diagnosis, being less in need of services or deeming themselves less in need of services as an adaptive response to less severe illness. Females with BrPsy appear to engage better than do males in this group.

Delusional disorder

Diagnosis of DD at follow-up is associated with good SE. This is somewhat unexpected, as DD clustered more with SF in relation to the variables discussed previously. Negative symptoms might impact negatively on SE, to result in relatively higher SE in DD at follow-up; DD is to some extent distinguished psychopathologically from SZ by fewer negative symptoms. No meaningful analysis of any sex differences is possible.

Substance induced psychosis

In contrast to one study on the adverse impact of SIP on SE (Krebbin et al, 2009), as well as the adverse impact of substance abuse in general on SE in psychosis (Marshall et al., 1994; Olfson et al., 2000; Verdoux et al., 2000; Coodin et al., 2004; Hudson et al., 2004; Elbogen et al., 2005; Kamali et al., 2006; Valenstein et al., 2006; Ascher-Svanum et al., 2006; Schimmelmann et al., 2006; Tunis et al., 2007;Perkins et al., 2008) the present finding of good SE in SIP relative to other diagnoses is surprising. SIP at follow-up is associated with higher SE than for SIP at onset. Those with substance abuse at onset, whether or not they go on to retain the diagnosis of SIP or to develop a non-substance-induced psychosis by follow-up, may be more likely to engage poorly than those who evolve to a diagnosis of SIP. This would be consistent with the finding that for those with SIP at onset, the majority had a co-morbid diagnosis of substance abuse at follow-up, whereas for those with SIP at follow-up

only half continued to abuse substances. No sex comparisons are possible, given that no women received this diagnosis.

Psychosis not otherwise specified

While PNOS at onset shows relatively poor SE, PNOS at follow-up shows better SE. That PNOS is by its nature heterogenous hinders conceptualisation of SE for this disorder, other than that females show somewhat better SE than do males.

Psychosis due to a general medical condition

PGMC at onset demonstrates poor SE, while the few individuals with PGMC at follow-up show better SE. Small numbers again confound interpretation, though females with PGMC appear to engage better than do males.

Substance-induced mania

SIM demonstrates generally moderate SE. It is of interest that SE in SIM appears lower than in SIP, despite their evidencing similar values for other measures discussed above. However, care must be taken not to over-interpret the findings in view of the small numbers in this category. Again, women appear to engage better than do men.

Mood disorder due to a general medical condition

The single female with MGMC showed SE in the middle of the range encountered across the diagnoses.

Simple deteriorative disorder

The single male with SDD at onset showed poor SE and evolved to a diagnosis of SZ at follow-up.

Conclusions

Whilst SE follows the general trend for SZ to be at the lower end for each index, BD and MDDP at the upper end and SA in between, that SIP shows good SE is surprising. As for other indices, males show generally poorer SE than females, though for SZ, SF and MDDP this effect appears less pronounced.

Predictors of functioning and quality of life across psychotic illness

One of the aims of this study was to establish whether significant predictors of key outcome variables across psychotic illness, i.e. function and QOL, could be identified. The previous sections explore relationships within each diagnosis and quantify differences between them, in terms of symptomatology, function, QOL and SES. Here, it is hoped to uncover more about the reasons for variation in outcome and, hopefully, identify ways in which it might be possible to intervene in order to improve these outcomes. Candidate predictors of function and QOL in linear regression modelling included sex, age at onset of psychosis, duration of illness, educational level, marital status, substance abuse at follow-up, months to follow-up, unsupported vs. supported living conditions, PANSS positive, negative and general scores and SES scores.

Predictors of functioning

Among these variables, the most prominent in predicting variation in Function 1 is general symptoms, followed by negative symptoms. This is interesting, given that the majority of research to date has focussed on negative symptoms as a consistent predictor of poor social and occupational functioning (Charisiou et al., 1989; Anashkin, 1992-1993; Ho et al., 1998; Hofer et al., 2005; Voges & Addington, 2005; Svirkis et al., 2007), with positive symptoms being a weaker predictor (Johnstone et al., 1995; Harrow et al., 2004). Total symptom levels have generally not been found to predict outcome (Geddes et al., 1994; Vetter & Koller, 1996). It is somewhat surprising that general symptoms, being less specific diagnostically, exert greater prediction of functioning; indeed, SZ, which has the poorest level of functioning,

has positive and negative symptoms at the core of its diagnostic criteria. This could be due to the inclusion of depression in general symptoms, as some studies have shown depression to impact adversely on functioning (Tohen et al., 1990; Blanchard et al., 1998; Eklund et al., 2003). This indicates that, in addition to specific aspects of psychopathology that we often consider the most adverse prognoticands, general symptoms may be of unappreciated significance. It may be relevant that general symptoms are higher in SZ than for any other diagnosis, suggesting further that they are of more prognostic significance than is generally held to be the case. This has important implications for the treatment of psychotic illness, as general symptoms are not normally prioritised as key treatment targets by clinicians. The finding that negative symptoms are also important in terms of predicting function is unsurprising and well-documented in the literature (Charisiou et al., 1989; Anashkin, 1992-1993; Ho et al., 1998; Voges & Addington, 2005; Hofer et al., 2005; Svirskis et al., 2007).

SE is the next most important statistical predictor of functional outcome. A previous study has reported adherence to medication to be positively associated with good functioning (Rzewuska, 2002). Whilst these finding do not allow us to make any statements regarding causation, it may make intuitive sense that good SE might be associated with better functioning: good SE may improve outcome via a better therapeutic alliance and adherence to medication; alternatively, or additionally, SE may be related to other factors possibly associated with better functioning, such as agreeableness or insight.

Research to date has pointed to the importance of education in predicting function (Mechanic, 2002; Ruesch et al, 2002; McGurk & Meltzer, 2000). Completion of primary education only, as compared to completion of Leaving Certificate (secondary) education, was also found to be a strong predictor of poor functioning at follow-up. To a somewhat lesser extent, completion of primary education only, as compared to completion of tertiary (university/college) education, was also found to predict poor functioning. However, whether educational attainment impacts in a positive way on functioning or better functioning allows a higher level of educational attainment remains unclear.

Marital status at follow-up was examined in a binary fashion: 'never married' vs. 'ever married', i.e. married, separated/divorced, living with partner or widowed. The rationale for this was that the capacity to enter into such a relationship demonstrates a certain set of social/emotional skills that can be negatively affected by psychotic illness, in particular SZ, which has been shown to have particularly low rates of marriage relative to the general population. Marital status has been little considered as a predictor of functioning in research to date. It is therefore interesting to consider why 'ever married' marital status is indeed a predictor of functioning. It might be hypothesised either that the ability to marry could reflect a higher level of functioning or that the married state might improve ability to function; it is less likely that retaining single marital status might protect someone with psychotic illness from exposure to a potentially stressful interpersonal situation.

The last variable found to predict better functioning is unsupported as opposed to supported living conditions. Whilst research to date has identified good family and social support as an important predictor of good functioning (Erickson et al., 1998; Evert et al., 2003; Giron & Gomez-Beneyto, 2004), living conditions have not been specifically identified as important. In the present study, unsupported living conditions included living either alone, with a partner (either with or without children), with a sibling, or with housemates; supported living conditions included living with parents, in a hostel or in a nursing home. This would be consistent with poor functioning resulting in a need for supported living conditions.

It is interesting that sex was not found to be a predictor of functioning, given that many studies, particularly in SZ, have shown outcome to be better in females than in males (Beiser et al., 1994. However, some studies in SZ have shown the reverse (Thara, 2004; Hofer et al., 2005; Morgan et al., 2008) and studies in BD indicate similar levels of functioning between the sexes (Morgan et al., 2005; Hajek et al., 2005). It may be that across the full spectrum of psychotic diagnoses, sex differences become increasingly less significant. This has implications for how we think of those with first episode psychosis, as male sex is so often held to have a worse prognosis. This may not hold for the indices of functioning considered here.

Predictors of quality of life

As with functioning, one of the aims of this study was to identify variables that predict QOL.

Interestingly, general symptoms are the most significant predictor of QOL, as found for functioning. Previous research has found that high overall (and therefore less specific) measures of psychopathology have a negative impact on QOL (Voruganti et al., 1998; Huppert et al., 2001; Ritsner et al., 2002; Savilla et al., 2008; Perlick et al., 2008). This strengthens the argument for a need to pay greater attention to the less specific symptoms of psychotic illnesses which appear to have an important relationship with QOL as well as functioning. As for functioning, this could be due to the inclusion of depression in general symptoms, as some studies have shown depression to impact adversely on QOL (Malla et al., 2002a; Sim et al., 2004; Melle et al., 2005b; Wegener et al., 2005; Ruhrmann et al., 2008).

In contrast to functioning, negative symptoms do not predict QOL, whereas some other studies have identified negative symptoms as an important predictor of QOL (Browne et al., 1996; Katschnig, 2000; Norman et al., 2000; Rudnick, 2001; Fitzgerald et al., 2001, 2003; Kennedy, 2003; Aki et al., 2008). Positive symptoms, however, do predict poor QOL in the present study. Some other studies have also identified positive symptoms to impact adversely on QOL (Norman et al., 2000; Ritsner, 2003; Mohamed et al., 2008). It may be that the unpleasant subjective experience of positive symptoms has a particularly adverse impact on QOL.

Marital status is found to be the next most important predictor of QOL, with the 'ever married' group demonstrating better QOL than the 'never married' group. Though marriage may be protective in determining QOL, it may be that those with better QOL are more likely to enter into relationships that lead to marriage. Other studies have shown a similar relationship between good QOL and married status (Pinikahana et al., 2002; Kovess-Masfety et al., 2006).

Older age at onset also predicts better QOL; interestingly, prediction of functioning by age at onset fell just short of statistical significance. It might be that those who have a later onset of illness have more time to establish those aspects of their lives which contribute to QOL than those who are affected earlier.

The last variable shown to predict better QOL at follow-up is greater SE. As for functioning, SE may have a positive effect on QOL, those with better QOL may be more likely to engage with services, or SE and QOL may both be associated with another variable such as agreeableness or insight.

Predictors of functioning and quality of life for principal diagnoses

Predictors of functioning

There are some differences between the principle diagnoses, i.e. SZ, BD and MDDP, in terms of predictors of outcome. Substance abuse appears to particularly predict poor function at follow-up for BD. If this relationship were causative, it would have implications for prioritisation of treatment of substance abuse in this disorder. MDDP differs from the general pattern of prominence for general and negative symptoms in predicting functional outcome. Here, it is unsupported living that appears to best predict good functioning. It is plausible that those with better functioning are more likely to need lower levels of support or, equally, that unsupported living might have a positive impact on mood via self-efficacy. SE also appears to be an important predictor of function in MDDP; in this disorder, reliance on services might be indicative of higher levels of general dependence, and thus poorer functioning.

Predictors of quality of life

Similarly, differences between these principle diagnoses emerge in terms of predictors of QOL. 'Ever married' marital status is a strong positive predictor of QOL in SZ. Given the particularly low rate of marriage in this diagnostic group, those who marry may have

particular characteristics mediating both ability to form such a relationship and capacity to enjoy a better QOL. Unsupported living and SE predict QOL as well as functioning in MDDP. Substance abuse predicts QOL in MDDP, while it predicts functioning in BD. Unexpectedly, younger age at onset predicts better QOL in MDDP, as does shorter time to follow-up; QOL may decrease more prominently over time for MDDP than for other psychotic diagnoses. Finally, completion of Leaving Certificate education compared to completion of primary education predicts QOL in MDDP. Leaving Certificate education may have a particularly protective effect on QOL in MDDP, independent of the effect of age as those with primary education only are likely to be older.

Synthesis

The present study provides a detailed analysis of the six year outcome of the entire spectrum of FEP, and in addition presents factors which predict these outcomes. Many other studies reporting outcomes in FEP have restricted these to non-affective psychoses. As such, the present study adds to our understanding of the affective and other psychoses, and allows direct comparison of their outcomes with those disorders, such as SZ, about which more is known.

The FEP studies which are closest to the Cavan/Monaghan study in methodology, focus and reported findings are the EPPIC study based in Melbourne, the Suffolk County study based in Long Island, New York, and the DETECT study based in Dublin. Other large FEP studies such as the AESOP and Hillside studies (based in London/Nottingham/Bristol and New York, respectively) have focused their attention on epidemiology/ethnicity (AESOP) and biology/pharmacological treatment (Hillside). Below, are tables comparing the findings of the Cavan/Monaghan study with its closest counterparts.

Table 49: Diagnostic stability across First Episode Psychosis studies

Study	SZ	SA	BD	MDDP	SF	BrPsy	DD	PNOS	SIP
Cavan/Monaghan 6 years	88%	82%	76%	55%	27%	20%	20%	30%	36%
Suffolk County									
2 years[1]	92%	12%	83%	76%	55%	27%	67%	44%	64%
10 years[2]	94%	29%	-	-	7%	-	-	-	-
EPPIC									
18 mths[3]	97%	94%	83%	-	40%	-	-	-	-
DETECT									
4 years[4]	96%	-	80%	73%	33%	-	42%	0%	0%

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar affective disorder
MDDP Major depressive disorder with psychosis
SF Schizophreniform disorder
BrPsy Brief psychotic disorder
DD Delusional disorder
PNOS Psychosis not otherwise specified
SIP Substance induced psychosis

1. Schwartz et al, 2000
2. Bromet et al, 2005
3. Schimmelmann et al, 2005
4. Whitty et al, 2005

As shown in Table 49, there is general agreement in relation to diagnostic stability across FEP studies of the larger diagnostic categories, with the exception of SA in the Suffolk County study. It is also clear that the longer the follow-up period, the lower the degree of stability of SF. DD has lower diagnostic stability in the present study but this may also be attributed to the longer follow-up period.

Table 50: Psychopathology across First Episode Psychosis studies

Study	SZ	SA	BD	MDDP	SF	BrPsy	DD	PNOS	SIP
Cavan/Monaghan 6 years*									
PANSS total	65	57	45	44	54	45	41	38	38
PANSS pos	13	12	9	8	12	9	9	7	8
PANSS neg	20	16	10	11	13	11	8	8	8
PANSS gen	33	30	26	25	30	26	23	24	22
Suffolk County	-	-	-	-	-	-	-	-	-
EPPIC 2 years[1, 2]									
PANSS total	38	-	-	-	-	-	-	-	-
PANSS gen	20	-	-	-	-	-	-	-	-

DETECT									
4 years[3]									
PANSS pos	10	-	-	-	-	-	-	-	-
PANSS neg	14	-	-	-	-	-	-	-	-

*subgroups do not add up to total due to rounding

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar affective disorder
MDDP Major depressive disorder with psychosis
SF Schizophreniform disorder
BrPsy Brief psychotic disorder
DD Delusional disorder
PNOS Psychosis not otherwise specified
SIP Substance induced psychosis

1. Kirkpatrick et al, 1996
2. Henry et al, 2008
3. Whitty et al, 2008

As shown in Table 50, the literature available on the other FEP studies has not reported detailed psychopathology across the diagnoses. Only the EPPIC and DETECT studies have reported psychopathology scores, and only for SZ. PANSS total and general scores in the EPPIC study are lower than in the present study, and PANSS positive and negative scores in the DETECT study are also somewhat lower. Thus, only the Cavan/Monaghan study allows systematic comparison of psychopathology between the disorders. It is clear that SZ has the highest symptom ratings both overall and for each subscale; this is followed by SF and SA, and then by BD and MDDP

Table 51: Functioning across First Episode Psychosis studies

Study	SZ	SA	BD	MDDP	SF	BrPsy	DD	PNOS	SIP
Cavan/Monaghan									
6 years									
GAF	53	59	67	67	68	69	75	72	75
Paid employment	-	-	-	-	-	-	-	-	-
Suffolk County									
10 years[1]									
GAF	43	-	-	-	-	-	-	-	-
Paid employment	-	-	-	-	-	-	-	-	-
EPPIC									
GAF 2 years[2]	75	-	-	-	-	-	-	-	-
Paid employment 10 years[3]	57%	54%	-	-	-	-	-	-	-
Detect 4 years[4]									
GAF	59	-	-	-	-	-	-	-	-
Paid employment	47%	-	-	-	-	-	-	-	-

SZ Schizophrenia - BrPsy Brief psychotic disorder

1. Bromet et al, 2005

SA Schizoaffective disorder
BD Bipolar affective disorder
MDDP Major depressive disorder with psychosis
SF Schizophreniform disorder
DD Delusional disorder
PNOS Psychosis not otherwise specified
SIP Substance induced psychosis

[2] Sim et al, 2006
[3] Henry et al, 2008
[4] Whitty et al, 2008

As shown in Table 51, GAF levels are reported only for SZ in the other studies, with the Suffolk County study observing a particularly low score, the EPPIC study a particularly high score, and the DETECT study a score similar to that reported here. In the present study, the four main diagnostic categories are found to have the poorest functioning, with affective psychoses appearing somewhat less severely impaired. Aspects of societal integration, including SE, higher educational attainment, 'ever married' status and unsupported living conditions are all found to be predictors of good functioning in the Cavan/Monaghan study.

Table 52: Quality of life across First Episode Psychosis studies

Study	SZ	SA	BD	MDDP	SF	BrPsy	DD	PNOS	SIP	Non-affective psychosis
Cavan/Monaghan 6 years										
QLS	70	85	101	98	64	110	105	103	109	-
WHO-QOL Bref	94	95	99	100	-	80	102	100	94	-
Suffolk County	-	-	-	-	-	-	-	-	-	-
EPPIC	-	-	-	-	-	-	-	-	-	-
Detect 8 years[1]										
QLS	-	-	-	-	-	-	-	-	-	84

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar affective disorder
MDDP Major depressive disorder with psychosis
SF Schizophreniform disorder
BrPsy Brief psychotic disorder
DD Delusional disorder
PNOS Psychosis not otherwise specified
SIP Substance induced psychosis

[1] Crumlish et al, 2009

As shown in Table 52, there are very few data from other FEP studies with which to make direct comparisons of the QOL findings reported here. The DETECT study consolidates SZ, SF, DD and PNOS in their category 'non-affective psychosis'; thus, the QLS figure reported is probably similar to that which would be found for the same combination of diagnoses in the present study. SZ has the lowest ratings for both subjective and objective QOL. However, it appears that there is greater discrepancy between subjective and objective measures for the non-affective psychoses among the major diagnostic groupings. Here, low

ratings for general and positive symptoms, 'ever married' status, older age at onset and good SE all predict better QOL. These variables may relate to the illness having less impact on a 'normal' experience of development throughout the lifespan.

Table 53: Service engagement across First Episode Psychosis studies

Study	SZ	SA	BD	MDDP	SF	BrPsy	DD	PNOS	SIP	Overall
Cavan/Monaghan 6 years SES	20	13	12	9	28	20	4	4	7	-
Suffolk County [1] 1 year										
good	-	-	-	-	-	-	-	-	-	37%
moderate	-	-	-	-	-	-	-	-	-	47%
poor	-	-	-	-	-	-	-	-	-	15%
EPPIC[2]										
Engaged	67%	-	-	-	-	-	-	-	-	-
Disengaged	33%	-	-	-	-	-	-	-	-	-
Delta 6 mths[3]										
Adherent	67%	-	-	-	-	-	-	-	-	-
Non adherent	33%	-	-	-	-	-	-	-	-	-

SZ Schizophrenia
SA Schizoaffective disorder
BD Bipolar affective disorder
MDDP Major depressive disorder with psychosis
SF Schizophreniform disorder
BrPsy Brief psychotic disorder
DD Delusional disorder
PNOS Psychosis not otherwise specified
SIP Substance induced psychosis

1. Mojtabai et al, 2002
2. Schimmelmann et al, 2006
3. Kamali et al, 2006

Lastly, as shown in Table 53, in comparable FEP studies SE has been studied only in terms of adherence to medication or binary engagement/non-engagement. The EPPIC and DETECT studies, although using differing measures, show similar rates of individuals who appear to have 'bought into' treatment. The SES score (where low scores reflect better engagement) shows that for the major diagnostic groupings, an affective component appears to have a positive effect on engagement.

It is important to bear in mind the possibility that findings in each of these studies may be affected by the differing characteristics of mental health services in the area under investigation. Systematic evalution of these differences however, presents particular challenges.

Limitations

The main limitation of the study relates to the small numbers in some of the diagnostic categories for which little information exists regarding outcome. A multicentre study of similar design to the present study would be better placed to answer the multitude of unanswered questions that remain about diagnoses such as BrPsy, DD, PNOS, SIP, SIM, PGMC and MGMC. Additionally, data collected in relation to many of the variables measured at onset of illness (e.g. insight, cognitive function, neurological soft signs, duration of untreated illness, family history) were incomplete and thus did not allow them to be entered into statistical models for prediction of outcome. It should be mentioned also that the use of an objective as well as a subjective measure of QOL may have impacted on assessments of outcomes, as objective measures generally yield lower estimates of QOL than do subjective measures, which are the more meaningful outcome.

Implications

As might be expected, an overall picture emerges of SZ having the most adverse outcome of all the diagnoses within the psychotic spectrum. However, the main strength of this study is its ability to make systematic comparisons with, and document the interplay between, SA, BD and MDDP. Additionally, the study illuminates rarely considered aspects of SF, DD, BrPsy, PNOS, SIP, SIM, PGMC and MGMC. Psychopathology has a notably adverse effect on outcome for all diagnoses, whereas an ability to maintain social integration and a more 'normal' life course appears to have a positive effect on outcomes. This should be reflected in the approach to treatment across psychotic disorders: on the one hand broader symptom management, whether via pharmacological or psychotherapeutic approaches, may prevent particularly adverse outcomes, whereas interventions that promote occupational and social integration are key in raising outcomes beyond the level achievable by symptom management alone.

Future research directions

One important issue, beyond the scope of this thesis, is to explore the impact of an urban vs a rural population on outcome in psychosis. Systematic comparison between such populations would make an important contribution to understanding of these illnesses. Another issue that would merit exploration is rate of recovery in psychosis. However, considerable problems exist in defining recovery psychopathologically, clinically and functionally in individuals with psychotic illness.

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Appendix

Table A1: Age distribution of population in Ireland/Cavan/Monaghan in 2006

Area	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+
Ireland	13.9%	13.3%	17.0%	15.8%	13.6%	11.1%	7.7%	5.0%	2.7%
Cavan	15.1%	14.1%	14.1%	14.8%	13.7%	11.5%	7.7%	5.8%	3.4%
Monaghan	14.0%	14.6%	15.2%	14.6%	13.6%	11.6%	7.7%	5.5%	3.1%

Table A2: Place of residence of population in Ireland/Cavan/Monaghan/Dublin one year previous to 2006 census

				% outside Ireland	
Area	% at same address	% in same county	% in another county	Born in Ireland	Born outside Ireland
Ireland	89.2	5.7	2.1	0.6	2.4
Cavan	90.0	4.2	3.2	0.5	2.2
Monaghan	92.2	3.8	1.3	0.5	2.3
Dublin	87.5	7.2	1.5	0.7	3.1

Table A3: Country/continent describing nationality of population in Ireland/Cavan/Monaghan in 2006

Area	% Ireland	% UK	% Europe	% US	% Africa	% Asia	% Other
Ireland	88.8	2.7	4.5	0.3	0.8	1.1	1.7
Cavan	90.0	3.0	4.2	0.3	0.5	0.6	1.5
Monaghan	90.0	2.0	6.3	0.2	0.3	0.4	1.1

Table A4: Percentage of population in Ireland/Cavan/Monaghan whose birthplace is Ireland (north/south) in 2006/2002/1996

Year	Area	%	Year	Area	%	Year	Area	%
2006	Ireland	86.5	2002	Ireland	90.9	1996	Ireland	94.1
	Cavan	87.9		Cavan	94.0		Cavan	95.7
	Monaghan	88.2		Monaghan	94.1		Monaghan	96.1

TableA5: Socio-economic grouping in Ireland/Cavan/Monaghan in 2006

Area	A-employer/manager	B-higher professional	C-lower professional	D-non-manual	E-skilled manual	F-semiskilled manual	G-unskilled manual	H-own account worker	L-farmer	J-agricultural worker	Z-unknown
Ireland	15.3	5.8	10.7	19.3	10.1	8.4	3.8	4.3	3.9	0.6	17.8
Cavan	13.7	3.4	8.8	18.0	12.1	9.2	4.1	5.3	8.2	1.2	15.9
Monaghan	13.7	3.0	10.1	17.4	12.9	10.1	4.1	5.0	8.0	1.7	14.1

Table A6: Single marital status in Ireland/Cavan/Monaghan in 2006

Age	Area	Gender	%single	Age	Area	Gender	%single
15-19	Ireland	M	99.7	55-59	Ireland	M	15.5
		F	99.5			F	10.1
	Border	M	99.8		Border	M	17.5
		F	99.7			F	8.4
20-24	Ireland	M	97.3	60-64	Ireland	M	14.7
		F	95.1			F	9.8
	Border	M	97.7		Border	M	17.6
		F	94.6			F	8.7
25-29	Ireland	M	84.2	65-69	Ireland	M	16.4
		F	76.3			F	11.0
	Border	M	80.9		Border	M	20.6
		F	70.0			F	10.2
30-34	Ireland	M	54.0	70-74	Ireland	M	18.7
		F	45.0			F	13.1
	Border	M	48.5		Border	M	23.8
		F	37.3			F	12.7
35-39	Ireland	M	32.6	75-79	Ireland	M	20.8
		F	26.6			F	15.4
	Border	M	29.6		Border	M	26.5
		F	22.6			F	15.7
40-44	Ireland	M	22.4	80-84	Ireland	M	21.9
		F	17.8			F	17.6
	Border	M	21.7		Border	M	28.0
		F	15.1			F	17.0
45-49	Ireland	M	17.8	85+	Ireland	M	22.5
		F	13.7			F	20.2
	Border	M	18.2		Border	M	25.8
		F	11.6			F	20.4
50-54	Ireland	M	16.0				

Border	F	11.4
	M	16.4
	F	9.0

Table A7: Unemployment figures for Ireland/Border Counties first quarter 2007

Area	% unemployment
Ireland	4.2
Border Counties	5.5

Table A8: Age at which full-time education ceased in those no longer in education in Ireland/Cavan/Monaghan in 2006

Area	<15	15-16	17-18	19-20	21-22	23-24	25+	Unknown
Ireland	11.3	18.6	25.9	9.4	9.9	5.0	5.2	14.7
Cavan	15.4	20.6	24.4	9.8	7.9	3.1	3.0	15.8
Monaghan	15.8	23.9	24.6	8.9	7.5	3.1	2.7	13.4

Table A9: Number of people in single/family unit by size of family unit in Ireland/Cavan/Monaghan/Dublin City in 2006

Area	1	2	3	4	5	6+
Ireland	19.7	19.5	17.0	21.0	14.1	8.7
Cavan	16.7	18.4	16.0	20.0	16.0	13.0
Monaghan	16.0	17.1	16.3	20.7	16.8	13.0
Dublin City	32.4	21.8	15.1	15.8	9.4	5.5

Table A10: Sex and marital status at onset by diagnostic category at onset

Gender	Diagnosis	Single n (%)	Married/living as if married n (%)	Separated/ Divorced n (%)	Total n (%)
Male	SZ	24 (96%)	1 (4%)	-	25
	SF	13 (93%)	1 (7%)	-	14
	BrPsy	-	2 (100%)	-	2
	SA	1 (100)%	-	-	1
	BD	11 (65%)	6 (35%)	-	17
	MDDP	14 (78%)	4 (22%)	-	18
	DD	8 (89%)	-	1 (11%)	9
	PGMC	2 (100%)	-	-	2
	Sip	11 (92%)	1 (8%)	-	12
	PNOS	9 (90%)	1 (10%)	-	10
	SIM	1 (25%)	3 (75%)	-	4
	SDD	1 (100%)	-	-	1
	Total	95 (83%)	19 (16%)	1 (1%)	115
Female	SZ	4 (67%)	2 (32%)		6
	SF	4 (50%)	4 (50%)		8
	BrPsy	2 (18%)	9 (82%)		11
	SA	4 (80%)	1 (20%)		5
	BD	11 (73%)	4 (27%)		15
	MDDP	8 (36%)	14 (64%)		22
	DD	2 (50%)	2 (50%)		4
	PGMC	1 (50%)	1 (50%)		2
	PNOS	2 (40%)	3 (60%)		5
	SIM	1 (50%)	1 (10%)		2
	MGMC	-	1 (100%)		1
	Total	39 (48%)	42 (52%)		81

SZ Schizophrenia
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
MDDP Major depressive disorder
BD Bipolar disorder
DD Delusional disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified
SIM Substance induced mania
MGMC Mania due to a general medical condition

Table A11: Gender and marital status at six month follow-up by diagnostic category at onset

Gender	Diagnosis	Single	Married/living as if married	Widowed	Separated/ Divorced	Total
		n (%)	n (%)	n (%)	n (%)	n (%)
Male	SZ	21 (84%)	3 (12%)	-	1 (4%)	25
	SF	11 (79%)	3 (21%)	-	-	14
	BrPsy	-	2 (100%)	-	-	2
	SA	1 (100%)	-	-	-	1
	BD	10 (59%)	6 (35%0	-	1 (6%)	17
	MDDP	13 (72%)	4 (22%)	-	1 (6%)	18
	DD	7 (78%)	-	-	2 (22%)	9
	PGMC	2 (100%)	-	-	-	2
	SIP	10 (83%)	2 (17%)	-	-	12
	PNOS	9 (90%)	1 (10%)	-	-	10
	SIM	1 (25%)	2 (50%)	1 (25%)	-	4
	SDD	1 (100%)	-	-	-	1
	Total	86 (75%)	23 (20%)	1 (1%)	5 (4%)	115
Female	SZ	5 (83%)	1 (17%)	-	-	6
	SF	6 (74%)	1 (13%)	1 (13%)	-	8
	BrPsy	2 (18%)	6 (55%)	-	3 (27%)	11
	SA	4 (80%)	1 (20%)	-	-	5
	BD	7 (47%)	5 (33%)	3 (20%)	-	15
	MDDP	7 (32%)	13 (59%)	2 (9%)	-	22
	DD	1 (25%)	2 (50%)	1 (25%)	-	4
	PGMC	1 (50%)	-	1 (50%)	-	2
	PNOS	2 (40%0	2 (40%)	1 (20%)	-	5
	SIM	1 (50%)	-	-	1 (50%)	2
	MGMC	-	-	1 (100%)	-	1
	Total	36 (45%)	31 (38%)	10 (12%)	4 (5%)	81

SZ Schizophrenia
SA Schizoaffective disorder
BrPsy Brief psychotic disorder
PGMC Psychosis due to general medical condition
SIP Substance induced psychosis
PNOS Psychosis not otherwise specified

MDDP Major depressive disorder
BD Bipolar disorder
DD Delusional disorder
SIM Substance induced mania
MGMC Mania due to a general medical condition