Structural violence and schizophrenia: psychosocial, economic and cultural impacts on the onset of psychosis

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By

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As the candidate’s supervisor, I agree to the submission of this dissertation.

Supervisor: Prof. R.A. Emsley
DECLARATION

I, Jonathan Kenneth Burns, declare that:

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ABSTRACT

Schizophrenia is a common and serious mental disorder affecting approximately 1% of the population (WHO, 1973). That genetic and other developmental factors give rise to a predisposition or vulnerability to schizophrenia is well recognized. However, the role of the environment in conferring risk for the disorder is now indisputable. Psychosocial, economic and cultural factors all impact on risk as evidenced by recent epidemiological studies reporting variable incidence in relation to factors including unemployment, urbanicity, migration and trauma. Complex gene-gene and gene-environment (GxE) interactions lie at the origin of this common human disorder and account for the diversity of epidemiological findings and clinical presentations that we encounter in research and clinical practice.

This thesis comprises of six research papers and includes data from two separate studies of first-episode psychosis (FEP) conducted in KwaZulu-Natal, South Africa. The first study (Chapter 2) explored the impact of income inequality and poverty on the incidence of FEP and the results provide the first evidence for an association between increasing income inequality and increased incidence of FEP.

The second study (Chapter 3) investigated the impact of a number of psychosocial, economic and cultural factors on the clinical presentation of FEP. Previous experiences of trauma were associated with positive and affective symptoms at psychosis onset, while cannabis use was associated with clinical features of FEP that previously have been associated with better outcome. Cultural factors such as spiritual attributions of cause and
previous consultation with traditional healers may delay entry to psychiatric care and thereby negatively impact on prognosis of FEP.

Chapter 4 addresses the issue of how the environment acts through GxE interactions to modify risk and alter the clinical presentation and course of schizophrenia. In this paper, new epidemiological findings are integrated with an evolutionary genetic theory of schizophrenia.

In Chapter 5, I present a human rights perspective on the inequities and inequalities that characterize the lives of those with serious mental disorders such as schizophrenia, resulting from psychosocial, political, economic and cultural forces in the environment.

The concluding chapter draws all of the data together, highlights key findings and conclusions from the thesis, addresses weaknesses and limitations of these conclusions and identifies priority areas for future research in this field.
DEDICATION

For Eliza, Noah, Aidan and Luke and my mother Sarah – my wild and crazy family.
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<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>AO</td>
<td>Age of onset</td>
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<td>CCU</td>
<td>Current cannabis users</td>
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<td>CDSS</td>
<td>Calgary Depression Scale for Schizophrenia</td>
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<td>CNV</td>
<td>Copy number variation</td>
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<td>CT</td>
<td>Childhood trauma</td>
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<td>DSA</td>
<td>Developmental systems approach</td>
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<tr>
<td>DSM-IV-TR</td>
<td>Diagnostical and Statistical Manual, 4th edition (text revision)</td>
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<tr>
<td>DUP</td>
<td>Duration of untreated psychosis</td>
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<td>EEG</td>
<td>Electro-encephalogram</td>
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<td>FEP</td>
<td>First-episode psychosis</td>
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<td>GxE</td>
<td>Gene-environment</td>
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<td>GWAS</td>
<td>Genome-wide association scans</td>
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<td>HPA</td>
<td>Hypothalamic-pituitary-adrenal</td>
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<td>HIC</td>
<td>High-income country</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<td>II</td>
<td>Inequality Index</td>
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<td>LIC</td>
<td>Low-income country</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>LMIC</td>
<td>Low- and middle-income country</td>
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<td>MDGs</td>
<td>Millennium Development Goals</td>
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<td>MGMH</td>
<td>Movement for Global Mental Health</td>
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<td>MVR</td>
<td>Multivariate regression analysis</td>
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<td>NCU</td>
<td>Non-cannabis users</td>
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<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
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<td>PCU</td>
<td>Previous cannabis users</td>
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<td>PTSD</td>
<td>Post-traumatic stress disorder</td>
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<td>SA</td>
<td>Susceptibility allele</td>
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<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<td>WHO</td>
<td>World Health Organization</td>
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LIST OF PAPERS PUBLISHED OR ACCEPTED FOR PUBLICATION


CHAPTER 1
INTRODUCTION

1.1 THE ENVIRONMENT AND THE ONSET OF PSYCHOSIS

Schizophrenia is a common and serious mental disorder affecting approximately 1% of the population (WHO, 1973). Its onset is typically between ages 18 and 30 years of age – a period when individuals are becoming socially and economically independent and productive. The impact of the disorder is massive in the lives of individuals, with loss of social supports, disruption of studies and occupation, and growing social alienation, being frequent consequences of illness onset. Those with schizophrenia are at increased risk of both substance abuse and co-morbid physical illness and life expectancy is substantially reduced (Prince et al, 2007). Suicide is not an infrequent outcome (approximately 10%) (Saha et al, 2007). Schizophrenia also places a considerable burden on families and caregivers who often forgo employment to care for an affected family member while bearing financial responsibility for such care in addition to costly treatments. At a community or societal level, the burden of this illness is felt in terms of lost earnings as well as the demand on health and social services (Knapp, 1997).

The psychological, social, economic and cultural environment plays an important role in the onset of psychotic illness and schizophrenia in particular. Specifically, a number of environmental factors are now known to increase individual risk for psychosis and schizophrenia, especially in genetically vulnerable individuals. Complex gene-gene and gene-environment (GxE) interactions lie at the origin of this common human disorder.
(Van Os and Sham, 2003) and account for the diversity of epidemiological findings and clinical presentations that we encounter in research and clinical practice (McGrath et al, 2004; McGrath et al, 2008). There is also increasing evidence that environmental factors impact on and may alter the trajectory of the disease, giving rise to significant variability in individual course and outcome (Burns, 2009).

The focus of this thesis is the impact of the environment on the onset of psychosis. Specifically, the findings of two separate studies on first-episode psychosis (FEP) are reported; and several key issues related to the role of the environment in mental disorders are addressed. The first study, reported in Chapter 2 (Paper 1), set out to investigate the impact of income inequality, measured at the ecological level, on the treated incidence of FEP. While a variety of socioeconomic factors have been associated with increased incidence of FEP, the role of Income Inequality remains largely unknown. The second study, reported in Chapter 3 (Papers 2, 3 and 4) was prospective in nature and set out to investigate the impact of psychosocial and cultural factors on the clinical presentation of FEP. The rationale for this latter study will be discussed further on in this introductory chapter. Chapter 4 (Paper 5) addresses the issue of how the environment acts through GxE interactions to modify risk and alter the clinical presentation and course of schizophrenia. In Chapter 5 (Paper 6), I present a human rights perspective on the inequities and inequalities that characterize the lives of those with serious mental disorders such as schizophrenia, resulting from psychosocial, political, economic and cultural forces in the environment. Finally, Chapter 6 draws all of the data together, highlights key findings and conclusions from the thesis, addresses weaknesses and
limitations of these conclusions and identifies priority areas for future research in this field.

1.2 INCOME INEQUALITY AS A RISK FACTOR FOR PSYCHOSIS

Known socioeconomic risk factors for psychosis include unemployment (Marwaha and Johnson, 2004), urbanicity (Krabbe and Van Os, 2005), low socio-economic status (Byrne et al, 2004) and migration (Selten et al, 2007). However, another socioeconomic measure that is of considerable relevance and interest – notably an ecological rather than individual measure – is that of income inequality. Income inequality is a measure of the ‘rich-poor gap’ in any given society. It reflects the extent to which a society is unequal in terms of income distribution. This is a concept of great relevance to South Africa as that country ranks among the most inequitable in the world (Leibbrandt et al, 2010). The Gini coefficient is a common measure of income inequality but other measures exist also.

There are well-recognised associations between poverty, income inequality and health status. Wilkinson demonstrated in the 1980s and 1990s that the relative distribution of income in a society matters in its own right for population health (Wilkinson, 1992; 1996) and this has been supported by subsequent research (Subramanian and Kawachi, 2004). Ecological studies have shown that increasing income inequality between neighbourhoods predicts increased infant mortality rates (Wilkinson, 1996) increased risk for cardiovascular disease (Diez-Roux et al, 2000) and reduced life expectancy (Kennedy et al, 1996). Several studies have demonstrated a relationship between inequality and
psychiatric disorders, including anxiety and depression (Kahn et al, 2000; Weich et al, 2001) as well as suicide (Gunnell et al, 2003). One previous study examined the association between income inequality and the incidence of schizophrenia (Boydell et al, 2004). This ecological study by Boydell and colleagues looked at incidence rates of schizophrenia over a 10-year period across electoral wards in South London and correlated these rates with measures of ward deprivation and income inequality. Although they found no significant effect of inequality overall, the authors demonstrated that in the most deprived wards, the incidence of schizophrenia increased with increasing inequality. In the South African context, it seems highly relevant to investigate income inequality, measured at an ecological level, as a risk factor for first-episode psychosis.

1.3 PREDICTORS OF OUTCOME

Historically, a diagnosis of schizophrenia conferred a pessimistic view of course and outcome for patients. Schizophrenia was viewed as a chronic condition associated with a steady deterioration in occupational, social and cognitive functioning (De Lisi, 2008). This view of the disorder helped to distinguish it as a diagnostic entity from other serious mental illnesses such as Bipolar Disorder. However, this view has proved to be a generalization, as we now know that some patients with schizophrenia have a favourable outcome and maintain premorbid levels of functioning (Myin-Germey and Van Os, 2007; Petersen et al, 2008). With respect to a disorder that is so frequently associated with devastating deterioration in social and occupational functioning at the individual level, and with considerable burden at the familial and societal level, it is of utmost
importance to identify factors that are predictive of both positive and negative outcome (Emsley et al, 2008a). Interventions aimed at modifying such factors might yield profound individual and public health effects. And indeed, a significant proportion of the global research effort focused on schizophrenia, is preoccupied with understanding better the various predictors of outcome and with developing and testing novel interventions (Wyatt and Henter, 2001; Keshavan and Amirsadri, 2007).

Within this research context, there has been increasing interest in several baseline variables that appear to predict response to treatment, time to remission, relapse rates, course of the illness and functional and social outcome. These variables include: the age of onset (AO); the duration of untreated psychosis (DUP); and the pattern of symptoms manifest at illness onset during the first episode of psychosis (Marshall et al, 2005; White et al, 2009). Despite a number of methodological concerns that limit the comparability of studies (Verdoux and Cougnard, 2003), certain features of first-episode psychosis (FEP) have been shown to predict a poorer response to treatment, persistence of symptoms, a poorer course and worse outcome. These include: early age of onset, long DUP and a predominance of negative symptoms (see the following systematic reviews and meta-analyses for reviews of this literature: Perkins et al, 2005; Marshall et al, 2005; Norman et al, 2005). Conversely, the presence of positive and affective symptoms at onset is associated with a better treatment response, course and outcome (Emsley et al, 1999; Malla et al, 2006). This has been reported from both high and low-and-middle income country (LMIC) contexts (Emsley et al, 2007; Farooq et al, 2009). The evidence-base supporting a link between DUP and outcome is significant enough to have modified
clinical practice. In many parts of the world, clinicians and researchers alike are turning their attention to developing strategies for early intervention in treating first-onset psychosis (McGorry and Killackey, 2002; Drake and Lewis, 2005).

1.4 DEFINING ONSET

It is often difficult to confirm a diagnosis of schizophrenia during the first episode of psychosis, since a number of other disorders may present with similar symptoms. Mood disorders such as Bipolar Disorder and Major Depressive Disorder, substances such as cannabis and cocaine, organic brain syndromes such as epilepsy and HIV psychosis, and metabolic disorders may all present with psychotic symptoms indistinguishable from schizophrenia. It is therefore common practice to speak of ‘first-episode psychosis’ (FEP) rather than ‘first-episode schizophrenia’, especially in terms of research. In researching the onset of schizophrenia, we are forced to study the broader spectrum of first-episode psychotic disorders. In the context of this thesis, “First-Episode Psychosis” is defined as the first episode of psychotic illness, meeting DSM IV-TR criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder. This cluster of diagnoses is sometimes referred to as “schizophrenia-spectrum disorders.”

Defining onset itself is by no means an easy task as this is usually a retrospective clinical decision and a variety of prodromal symptoms may herald onset. Various definitions exist, but in common with a number of previous studies (Morgan et al, 2006), onset of psychosis is defined in this thesis as the presence for at least a week of one or more of the
following positive psychotic symptoms: hallucinations; delusions; thought disorder; and disorganized or bizarre behaviour with a marked deterioration in function.

1.5 DUP, AO AND SYMPTOMS AS PROXIES FOR OUTCOME

As DUP, AO and symptoms at onset have been shown to be predictive of course and outcome, it is feasible to treat these clinical features as proxies for course and outcome (Harrigan et al, 2003). Thus, if certain environmental factors are found to be associated with early AO, long DUP and negative symptoms at onset, it seems reasonable to argue that these same factors may be to some extent predictive of poorer course and outcome. It is well recognized that genetic and other developmental factors give rise to a predisposition or vulnerability to psychosis and schizophrenia (Gejman et al, 2010). But we also know that the maximum heritability in schizophrenia is only 80% (in monozygotic twins), thus implicating non-genetic environmental factors also in the genesis of the disorder. Clearly, the environment plays a role in enhancing risk for psychotic illness itself. But if specific environmental factors can also be shown to predict DUP, AO and specific symptoms at onset, then we will have evidence that the role of the environment extends beyond merely altering individual risk for psychosis, to also impacting on course and outcome of this disorder. This would be an important step forwards in terms of guiding the development of interventions that might positively alter the trajectory of disease; thereby giving rise to a more favourable course and outcome for those with schizophrenia and other psychotic disorders.
Prospective longitudinal studies of patients with first-episode psychosis are obviously the preferred method for investigating associations between environmental factors and course and outcome (Van Os et al, 2008; Van Os and Rutten, 2009). However, in many parts of the world (especially within developing countries where resources are limited, geographical catchment areas are large, and communication systems between researchers and study participants are often inadequate) prospective follow-up studies of outcome are fraught with difficulties. Loss to follow-up is a major problem. In such environments, it seems reasonable to approach this issue from a different angle. Specifically, if DUP, AO and symptoms at onset are associated with course and outcome (and studies of actual course and outcome are practically difficult to execute), then it seems reasonable to focus on these clinical features as proxies for course and outcome, while acknowledging the limitations of this strategy. Importantly, in the absence of the actual measurement of outcome itself (in a longitudinal cohort design), these baseline clinical features can only be regarded as proxies for outcome and not as real measures of outcome. Given this obvious limitation, it is still important, I argue, to investigate associations between environmental factors and these clinical features of FEP that can be considered to have prognostic value. Where such associations are shown to exist, it is likely that gene-environment interactions are implicated. In such cases, we can legitimately hypothesize that specific environmental factors mediate gene expression, not only to increase risk for psychosis itself (Van Os and Sham, 2003; Krabbendam and Van Os, 2005), but also to give rise to a clinical presentation of the illness at onset that is associated with better or worse course and outcome.
1.6 PREDICTORS OF DUP, AO AND SYMPTOMS AT ONSET

While there is a mass of research examining the putative consequences of early or late AO, long or short DUP and positive, negative and affective symptoms at illness onset, there is a corresponding dirth of studies addressing possible predictors of these same clinical variables (Peralta et al, 2005). Understanding, for example, risk factors for untreated psychosis, is important since DUP is a potentially modifiable prognostic factor (Birchwood et al, 1998; Perkins et al, 2005). A few international studies have looked at risk factors for prolonged DUP, focusing on premorbid adjustment (MacBeth and Gumley, 2008), social support networks (Horan et al, 2006; Peralta et al, 2005; Thorup et al, 2006) and pathway to care (Skeate et al, 2002; Compton et al, 2006; Johannessen et al, 2005; Chong et al, 2005), however this is a largely unresearched field.

In considering possible predictive factors of DUP, AO and symptoms at onset, it is relevant to consider a range of environmental factors that are recognized risk factors for psychosis itself. Earlier, in the introductory discussion of risk factors for psychosis, the following socioeconomic factors were cited: unemployment (Marwaha and Johnson, 2004), urbanicity (Krabbendam and Van Os, 2005), low socio-economic status (Byrne et al, 2004) and migration (Selten et al, 2007). Early trauma (Bendall et al, 2008; Krabbendam, 2008) and cannabis use (Compton et al, 2007) are also recognized risk factors. In view of the fact that environmental factors such as exposure to trauma and cannabis use are associated with increased incidence of psychosis, it is appropriate to hypothesize that these same factors may also impact on course and outcome.
1.7 TRAUMA AND PSYCHOSIS

Early traumatic experiences in childhood (especially early sexual abuse) are associated with an increased risk of psychosis (Morgan and Fisher, 2007; Read et al, 2005). Similarly, it is clear from case controlled studies that the prevalence of early trauma is higher in patients with psychosis than in the general population (Üçok and Bikmaz, 2007). Importantly, reviews of the association between childhood trauma (CT) and psychosis highlight the difficulties related to establishing a causal link between CT and psychosis (Morgan and Fisher, 2007; Bendall et al, 2008; Krabbendam, 2008). Prevalence rates of CT in people with psychosis vary considerably and methodological inconsistencies make it difficult to be conclusive regarding the relationship between these phenomena. Furthermore, most studies rely on retrospective reports of CT using differing instruments which further blurs the issue.

Not surprisingly, most research on the relationship between trauma and psychosis has been conducted in developed countries. Within the South African context, where levels of poverty and violence are high (Doolan et al, 2007), it is important to revisit this relationship. Specifically, it is relevant to ask the important question of whether exposure to significant trauma, at any point premorbidly, impacts on and modifies the clinical features of FEP that have been shown to predict outcome. We know from studies in developed countries that there is good evidence for an association between childhood trauma and abuse and the experience of positive psychotic symptoms (especially
command hallucinations) in adulthood (Read et al, 2005; Bebbington et al, 2004). Furthermore, CT is associated with subclinical positive symptoms in both individuals at high-risk for psychosis (Thompson et al, 2009) and non-clinical samples (Lataster et al, 2006). While childhood sexual abuse appears to have the greatest effect size (Krabbendam, 2008), the risk-increasing effects of early trauma seem to be related to interpersonal events in particular (Üçok and Bikmaz, 2007). At least six large, well-controlled population-based studies now support the role of developmental trauma in the emergence of psychotic symptoms (Bebbington et al, 2004; Janssen et al, 2004; Whitfield et al, 2005; Spauwen et al, 2006; Scott et al, 2007; Shevlin et al, 2007); and this relationship seems to refer exclusively to positive and affective symptoms rather than to negative symptoms (Read et al, 2005).

Investigating this issue in the context of South Africa, where rates of interpersonal violence and trauma are shockingly high, it is arguably of importance to consider exposure to trauma at any point premorbid to the onset of psychotic illness. Since onset of the first psychotic episode is typically during late adolescence or early adulthood, any trauma experienced premorbid to that first episode could be considered ‘developmental trauma’ (albeit a broader definition of ‘developmental trauma’ than is typical of this literature) (See Yurgelun-Todd, 2007 for a review of the neurobiological vulnerabilities of adolescence). In terms of the current thesis, one might anticipate that FEP patients with a significant history of interpersonal trauma would be more likely to manifest positive and affective symptoms.
1.8 CANNABIS USE AND ONSET OF PSYCHOSIS

Cannabis use and abuse is widespread in South Africa with 8.4% lifetime prevalence in the general population (Van Heerden et al, 2009). The prevalence of cannabis use/abuse in individuals with FEP is generally high and in previous African studies appears to be in the region of 35-40% (Rolfe et al, 1993; Roos et al, 2006; Koen et al, 2007). Importantly, co-morbid cannabis use/abuse is a clear predictor of worse long-term outcome in individuals with schizophrenia spectrum disorders (Compton et al, 2004; Linszen et al, 2004). However, both anecdotal clinical experience and empirical research indicate that a prominent history of recent cannabis abuse in patients presenting with first-episode psychosis (FEP), is associated with rapid resolution of acute symptoms. In terms of the clinical features of psychosis onset, international studies show that cannabis use/abuse in FEP is associated with early AO, prominent positive symptoms and a relative absence of negative symptoms (Compton et al, 2004; Van Mastrigt et al, 2004; Stirling et al, 2005; Sugranyes et al, 2009). Clearly then, the relationship between the clinical presentation of FEP and cannabis abuse is complex and warrants further investigation, especially within the South African context where this pattern of co-morbidity is so prevalent (Koen et al, 2007). Specifically, it is relevant to explore any associations that may exist between recent/current cannabis use/abuse and clinical features of FEP that have prognostic value.
Causal beliefs about psychotic symptoms and culturally determined help-seeking practices are likely to impact on pathway to care. In all societies there are folk (rather than scientific) understandings of mental phenomena. Strongly-held beliefs about causal attributions of mental distress and abnormal experiences may delay access to medical care (Razali et al, 1996; Kurihara et al, 2006a). In the case of psychotic illness, any delays which increase the DUP will, as previously discussed, impact negatively on course and outcome. It is therefore of interest and indeed of great relevance within the South African context, to examine the relationship between specific causal beliefs, pathway to care and DUP. Of course, these causal beliefs may be culturally determined, religious in nature or simply socially prevalent.

Surprisingly, there is a limited literature base on causal beliefs, help-seeking practices, pathway to care and DUP in FEP. According to Moss and colleagues (2006), their study of religious affiliation and its impact on DUP, is the first of its kind. They showed that FEP patients of Protestant faith had a longer DUP than those of Catholic faith. These authors note that in many religious communities, stigma concerning mental illness remains relatively strong. They also suggest that some fundamentalist and evangelical Protestants may delay seeking psychiatric treatment, viewing psychotic symptoms as exclusively spiritual problems or weaknesses rather than a mental health disorder.
In low- and middle-income country (LMIC) contexts, where typically large numbers of people subscribe to culturally specified traditional and religious beliefs and practices (Adebowale and Ogunlesi, 1999; Kurihara et al, 2006a), the role of individual causal attributions is likely to be of major importance in relation to the onset and course of mental disorders such as psychoses. For example, help-seeking behaviours that direct individuals to first consult traditional healers within their communities, may lead to delays in the initiation of medical treatment in FEP (Kurihara et al, 2006b). Such behaviour must be understood within a context where very often formal mental health services are not readily available and accessible to the populace, especially within rural communities (WHO, 2004; Saxena et al, 2007). In such contexts, traditional healers perform a vitally important role for individuals in physical, psychological or spiritual distress. They are very often the first port of call for patients and caregivers alike.

In the South African context, the question of causal beliefs, help-seeking practices and pathway to care is particularly interesting and warrants investigation. A large proportion of the population subscribe to a religious belief system, whether that be monotheistic or traditional ancestor-based (Mkize and Uys, 1994). Similarly, there is widespread use of non-medical forms of healing and treatment (eg. faith healing, herbalism, meditation and traditional healing practices). In many of these contexts, psychotic phenomena may be invested with strong culturally determined meanings or ‘idioms of distress.’ Individual and community causal attributions and help-seeking practices are likely to play a significant role in modifying pathway to care and accessing treatment (Haley et al, 2003). This can have major consequences for subsequent response to treatment, course and
outcome of psychotic illness. One might also hypothesise a relationship between causal beliefs and other baseline determinants of course and outcome (such as AO and predominant symptoms.)

1.10 GENE-ENVIRONMENT INTERACTIONS AND PSYCHOSIS

The central focus of this thesis concerns the impact of psychosocial, socioeconomic and cultural factors on both the epidemiology and the clinical presentation of first-episode psychosis (FEP). As mentioned earlier, there is good evidence that environmental factors play a significant role in altering risk for psychosis through complex gene-gene and gene-environment interactions (Van Os and Sham, 2003; Krabbendam and Van Os, 2005). In the context of this thesis, it is relevant to examine in some detail the mechanisms by which environmental factors alter gene expression and thereby increase risk for the disorder itself and possibly also impact on the clinical manifestation of the illness at onset. Any discussion of gene-environment interactions in relation to schizophrenia must address a key genetic question which increasingly is a focus of debate and investigation – and that is the question: Is there an evolutionary basis for the spectrum of genetic susceptibility to psychosis that is apparent in human populations? Several authors have argued in favour of an evolutionary approach to the genetic epidemiology of schizophrenia (Crow, 1995; Burns, 2007) and recent research supports this paradigm (Khaitovich, 2008). A major conceptual challenge is to integrate data supporting an evolutionary genetic basis for schizophrenia with new epidemiological findings that suggest marked variability in prevalence and incidence in relation to environmental
variables. The key to reconciling these two seemingly discordant sets of evidence lies in the adoption of a developmental systems approach to gene-environment interactions in the genesis of psychosis.

1.11 MENTAL ILLNESS AND HUMAN RIGHTS

In focusing on the role of the environment in the onset and clinical manifestation of psychosis and schizophrenia, it is relevant to address the issue of human rights. Specifically, the experience of living with a serious mental disorder such as schizophrenia in South Africa is arguably one characterized by multiple levels of inequality and discrimination. Social, economic, political and cultural factors contribute to gross inequities in access to care, availability of services and opportunities for social and economic engagement in society. Environmental factors, as we have already seen, may enhance risk for psychotic illness and impact negatively on course and outcome. These facts call for a human rights response to what Paul Farmer has termed the ‘structural violence’ inherent in the socioeconomic and political dynamics of unequal societies. Kelly (2005) has argued that social, economic and political factors such as poverty and income inequality “shape both the landscape of risk for developing [schizophrenia] and the context in which health-care is provided”. He suggests that these odious forces constitute a form of ‘structural violence’ (see Farmer, 2005) that impacts on the development and course of schizophrenic illness. In Chapter 5 of this thesis, I adopt a human rights framework to formulate a response to the multiple ways in which inequality
and discrimination characterize the lives of persons with mental disabilities such as schizophrenia.

1.12 FEP RESEARCH IN THE SOUTH AFRICAN CONTEXT

Finally, the vast majority of research on first-episode psychosis comes from the developed regions of North America, Europe, East Asia and Australasia. There is relatively little data regarding this important and common disorder from developing countries. Emsley’s group in Cape Town recruited a cohort of 48 FEP patients and examined correlations between DUP and symptoms as well as outcome (Oosthuizen et al, 2005). They reported that depressive and anxiety symptoms at baseline are associated with positive symptoms (Emsley et al, 1999) and may predict a better outcome with lower negative symptom scores at 6, 12 and 24 week follow-up (Oosthuizen et al, 2002). Furthermore, depressive symptoms in the acute episode appear to differ from those in the post-psychotic period in terms of their phenomenology, temporal relationship to psychosis and treatment response (Oosthuizen et al, 2006). In terms of remission, Emsley and his group showed that shorter duration of untreated psychosis (DUP) and significant symptom reduction at 6 weeks was predictive of remission; while remitters experienced greater symptom improvements, better quality of life, fewer relapses, had a more favorable attitude towards medication, had less extrapyramidal side-effects and received lower doses of antipsychotic medication (Emsley et al, 2006; 2007; 2008b). A separate
Zambian study reported on the clinical and basic demographic features of a cohort of 160 FEP patients (Mbewe et al, 2006).

Thus, the extant literature on FEP in Africa is limited and none of it has investigated previously the role of important psychosocial, socioeconomic and cultural factors in shaping the incidence and clinical presentation of the disorder. In a South African context, characterized by high levels of poverty, inequality, trauma, substance abuse and significant adherence to traditional health beliefs and practices, it is important to determine the impact of these environmental factors on the onset of psychosis.
CHAPTER 2
INCOME INEQUALITY AND RISK FOR PSYCHOSIS

This chapter reports on a study that investigated the relationship between Income Inequality (measured at the ecological level) and treated incidence of first-episode psychosis at a psychiatric hospital in KwaZulu-Natal, South Africa. The study is reported in Paper 1, “Poverty, inequality and the treated incidence of first-episode psychosis: An ecological study from South Africa”, published in the journal Social Psychiatry and Psychiatric Epidemiology in 2008.
Poverty, inequality and the treated incidence of first-episode psychosis
An ecological study from South Africa

Abstract
Introduction It is now commonly accepted that a range of psychosocial and environmental factors interact with genetic vulnerability in the genesis of psychotic illness. The aim of this study was to investigate whether measures of poverty and income inequality impact upon the treated incidence of first-episode psychosis (FEP) in the District of Umgungundlovu, South Africa. Methods Clinical and demographic data was collected from hospital records on all people aged 15–49 years from the District who presented to psychiatric services with FEP (DSM IV criteria) during 2005 (n = 160). All incident cases were grouped by municipality according to their recorded address. Measures of poverty and income inequality were calculated for each of the seven municipalities using data from the Statistics SA online database for the National Census 2001. Correlations were performed using SPSS to determine the relationships between treated incidence of FEP and poverty and inequality indices per municipality. Results There was a significant positive relationship between treated incidence and Inequality Index (Partial correlation coefficient 0.840; P = 0.036) and a non-significant negative relationship between treated incidence and Poverty Measure per municipality (Partial correlation coefficient −0.660; P = 0.154). These findings remained significant after adjusting for gender, age, ethnicity, urbanicity and employment status. Importantly, these results were not adjusted for individual level poverty. Discussion/Conclusion These findings lend support, in an African context, to increasing evidence that social, economic and political factors such as poverty and income inequality “shape both the landscape of risk for developing (psychosis) and the context in which health-care is provided” (Kelly in Soc Sci Med 61:721–730, 2005). These complex environmental factors appear to impact on the development and course of psychotic illness.

Key words first-episode psychosis – income inequality – poverty – treated incidence – structural violence

Introduction
It is now commonly accepted that a range of psychosocial and environmental factors interact with genetic vulnerability in the genesis of psychotic illness [28]. Recent meta-analyses [11, 24] show differences in both prevalence and incidence of schizophrenia in relation to variables such as: urban versus rural status [19]; social class [1, 6, 13]; migration [4]; unemployment [22] and homelessness [10]. While the biological basis of schizophrenia is indisputable, we know that socio-economic factors mediate the expression of the disorder [3, 30] and impact on outcome. Kelly [17] has argued that social, economic and political factors such as poverty and income inequality “shape both the landscape of risk for developing (schizophrenia) and the context in which health-care is provided”. He argues that these forces constitute a form of “structural violence” (see [9]) that impacts on the development and course of schizophrenic illness.

The associations between poverty, inequality and health are well-recognised. The seminal work of Wilkinson in the 1980s and early 1990s [31, 32],
demonstrating that the relative distribution of income in a society matters in its own right for population health, has since been well supported [27]. Ecological studies have shown that increasing income inequality between neighbourhoods predicts increased infant mortality rates [32], increased risk for cardiovascular disease [8] and reduced life expectancy [18]. Importantly there is also increasing evidence that individual level income inequality shows an even greater effect on individual health than does inequality at the ecological level [21]. Several studies have demonstrated a relationship between inequality and psychiatric disorders. For example, in a large UK survey of 8,191 adults, Weich et al. [29] found a positive association between income inequality and anxiety and depression, but only among people with high income. A US ecological study of 8,060 women, showed a positive correlation between state income inequality and risk for depression in low-income women [14]. And a study by Gunnell and colleagues [12] in England, Scotland and Wales of suicide trends between 1950 and 1998 found a positive association between country income inequality and suicide in men aged 25–34 years. Other studies have failed to demonstrate an association between inequality and mental disorders (e.g. [26]). Finally, a strong positive correlation has been demonstrated between income inequality and levels of social violence [33].

One previous study has examined the association between income inequality and the incidence of schizophrenia [1]. This ecological study by Boydell and colleagues looked at incidence rates of schizophrenia over a 10-year period across electoral wards in South London and correlated these rates with measures of ward deprivation and income inequality. Although they found no significant effect of inequality overall, the authors demonstrated that in the most deprived wards, the incidence of schizophrenia increased with increasing inequality.

The objective of this study is to partially replicate the study by Boydell and colleagues [1] but within an African context. Specifically it sought to investigate whether measures of poverty and income inequality impact upon the treated incidence of first-episode psychosis in a South African legislative district. A second objective was to compare the unemployment rate of the first episode sample with the general unemployment rate for the district.

### Methods

Clinical and demographic data was collected on all people aged 15–49 years from the District of uMngundlovu in KwaZulu-Natal Province who presented to psychiatric services with a first episode of psychosis during 2005. This district is made up of seven municipalities and has both rural and urban regions. The district has a total population of 927,833, while those aged 15–49 years number 508,275.

Clinical records of all admissions during 2005 to psychiatric services within the catchment area were checked by an experienced psychiatrist (JB). Individuals aged 15–49 years with a confirmed first-episode of psychosis and meeting DSM-IV criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder or psychotic disorder not otherwise specified, were included in the sample. Individuals with documented substance abuse within the last week prior to presentation for treatment were specifically excluded. The investigator was blinded to municipality of residence during this stage of the study. All incident cases were grouped by municipality according to their recorded residential address at the time of presentation to psychiatric services. Data pertaining to ethnic group, gender, urban versus rural location and employment status was recorded.

Measures of poverty and income inequality were calculated for each of the seven municipalities using data from the Statistics South Africa online database for the National Census 2001 [25]. The Poverty Measure equaled the percentage of households whose annual household income fell below the National Poverty Line of R9600 per household per annum [25]. Inequality Index (II) was calculated as a ratio of the mean income of the highest earners to the mean income of the lowest earners according to the following formula:

\[
II = \frac{\text{Mean annual income of the top 10% wage earners}}{\text{Mean annual income of the bottom 10% wage earners}}
\]

Finally, the unemployment rate for the district was calculated from National Census 2001 data as the number of people unemployed as a percentage of the total labour force.

Data were analysed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Partial Pearson’s correlation coefficients were generated to examine relationships between incidence, poverty and inequality, to control for confounding effects of urbanisation. The analysis was done at the level of the municipality. A P value of <0.05 was considered as statistically significant.

### Results

One hundred and sixty people aged 15–49 years presenting from the catchment area during 2005 with first episode psychosis were identified. One hundred and thirteen (71%) were male and forty-seven (29%) were female. The ratio of urban to rural location was 50:50. Table 1 details the results by municipality.

There was a significant positive relationship between treated incidence and Inequality Index per

<p>| Table 1 | Treated incidence, Poverty measures and Inequality Indices by Municipality of Residence |
|-----------------|---------------------------------|-----------------|------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Municipality</th>
<th>Number of incident cases</th>
<th>Total population (aged 15–49 years)</th>
<th>Treated incidence (per 100,000 population)</th>
<th>Poverty Measure (%)</th>
<th>Inequality Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umgeni</td>
<td>22</td>
<td>41,519</td>
<td>52.98</td>
<td>44.6</td>
<td>45.0</td>
</tr>
<tr>
<td>Umzumuzi</td>
<td>106</td>
<td>314,340</td>
<td>33.72</td>
<td>45.0</td>
<td>32.4</td>
</tr>
<tr>
<td>Mooi Mpofana</td>
<td>6</td>
<td>20,611</td>
<td>29.11</td>
<td>58.6</td>
<td>28.9</td>
</tr>
<tr>
<td>Richmond</td>
<td>8</td>
<td>33,006</td>
<td>24.24</td>
<td>66.3</td>
<td>20.4</td>
</tr>
<tr>
<td>Umshwathi</td>
<td>11</td>
<td>54,157</td>
<td>20.31</td>
<td>66.2</td>
<td>15.5</td>
</tr>
<tr>
<td>Impendle</td>
<td>3</td>
<td>14,781</td>
<td>20.29</td>
<td>78</td>
<td>12.7</td>
</tr>
<tr>
<td>Mkhambatin</td>
<td>4</td>
<td>29,861</td>
<td>13.39</td>
<td>66.3</td>
<td>14.7</td>
</tr>
</tbody>
</table>
municipality after controlling for urbanicity (Partial correlation coefficient 0.840; \( P = 0.036 \)). Thus increased municipal income inequality was associated with increased treated incidence of first-episode psychosis (FEP). There was a non-significant negative relationship between treated incidence and Poverty Measure per municipality after controlling for urbanicity (Partial correlation coefficient \(-0.660; \ P = 0.154\)). Thus there was a trend towards an association between increasing levels of poverty and decreased treated incidence of FEP. These results are shown in Table 2. The positive relationship between treated incidence of FEP and inequality index is shown in Fig. 1, while the negative relationship between treated incidence of FEP and poverty is shown in Fig. 2.

The unemployment rate for the whole cohort of FEP patients was 78\% while the unemployment rate for the entire population (aged 15–49 years) was 41\%.

### Discussion

#### Methodological issues

This study was based on a review of clinical records and therefore diagnostic variability may have been a factor affecting our results. However, since the same clinical hospital teams were responsible for all patients, irrespective of municipality of residence, there is unlikely to be any bias in clinical records. Case identification was performed by a single experienced psychiatrist using standardised diagnostic criteria who was blinded to municipality of residence. It is therefore unlikely that any bias existed in case identification. Of course, as with any study based on retrospective chart analyses, there are other limitations such as missing or inadequate records.

Although attempts were made to access FEP cases from private sector psychiatrists within the catchment area, very few cases were provided. However, since all private psychiatrists are located in the municipalities with the highest incidences (Umgeni and Umsunduzi) any bias resulting from “missed cases” from this sector would be in the direction of our findings. Furthermore, patients with acute psychoses represent a very small proportion of clients treated in the private sector. Thus, had these cases been included, they were unlikely to have comprised more than 5\% of the sample.

Another issue concerns the fact that this was a study of treated incidence rather than true incidence of FEP. True incidence is likely to be greater than that reported in this study (due to some psychotic individuals not entering the hospital system). Related to this is a further limitation, namely the small sample size in this study.

A final potential confounder concerning the study sample relates to the issue of comorbid HIV infection in participants. HIV status was not determined in this study and in the context of the current HIV pandemic engulfing Southern Africa; it is likely that some of the cases included were HIV-positive. A recent study conducted in the same hospital reported a prevalence rate of 24\% HIV seropositivity in a sample of 63 pa-

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**Table 2** Partial correlation between treated incidence of FEP and poverty index and inequality index, controlling for percentage of urbanicity

<table>
<thead>
<tr>
<th>Control variables</th>
<th>Incidence per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage urban</td>
<td>0.660</td>
</tr>
<tr>
<td>Percentage of households in poverty</td>
<td>0.154</td>
</tr>
<tr>
<td>Correlation</td>
<td>0.840</td>
</tr>
<tr>
<td>Significance (2-tailed)</td>
<td>0.036</td>
</tr>
<tr>
<td>df</td>
<td>4</td>
</tr>
</tbody>
</table>

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**Fig. 1** Scatter plot showing the positive relationship between treated incidence of FEP and Inequality Index (per municipality)

**Fig. 2** Scatter plot showing the negative relationship between treated incidence of FEP and Poverty Measure (per municipality)
tients with FEP [23]. Those participants in our study who were HIV-positive were likely to have been asymptomatic as psychosis secondary to a general medical condition was an exclusion factor in this study.

The Inequality Index and Poverty Measure used in the study are not the only indices used to measure these variables; other indices such as the GINI coefficient and the “index of inequality” and “composite deprivation score” (used in the Boydell et al. 2004 study [1]) are available. However, there is good support from the literature for using the indices chosen in this study.

Urbanicity is a recognised risk factor for schizophrenia and therefore results were controlled for urban residential status in this study. We therefore believe that the positive association demonstrated between treated incidence and increasing inequality is a genuine relationship and not a function of urbanicity. However, the relationship between incidence of FEP and inequality cannot be interpreted as causal as there are a number of other potential intermediary variables that were not assessed in this study (e.g. substance abuse, access to medical services, etc.).

This is an ecological study and therefore the “ecological fallacy” must be taken into account in the interpretation of the results, i.e. it is not appropriate to generalise the results to the individual level since the analysis was conducted on the municipality level. Furthermore, the small sample size of seven municipalities gave the analysis low power to detect clinically significant correlations, especially after controlling for a confounding variable like urbanicity decreased the degrees of freedom of the test even further. For this reason multiple linear regression analysis could not be performed.

Finally, the study is limited by our inability to adjust for individual level poverty measures. However, this limitation is true of many ecological studies.

### Inequality and psychosis

This study, conducted in a mixed urban and rural region of South Africa, showed an increased incidence of first-episode psychosis (FEP) in municipalities that had higher levels of income inequality and lower levels of poverty. Interestingly, there was an inverse relationship between measures of inequality (Inequality Index) and measures of poverty (Poverty Measure) for a municipality. One interpretation of this latter finding is that the rich–poor gap increases as the overall wealth of a population increases. This phenomenon is well recognised by economists as the Kuznets hypothesis, first formulated by Simon Kuznets during the 1950s [20]. This hypothesis suggests that, in regions with low levels of per capita income, inequality initially increases with rising per capita income and only decreases at later stages of economic development. Kuznets predicted that the poorest group’s share of overall income would decrease as economic growth takes off and would only be restored to initial levels after 60 years [7]. Although this hypothesis has many critics today, it is perhaps useful in the context of a developing country such as South Africa in trying to interpret our finding of an inverse relationship between poverty and inequality. A further explanation may be that social cohesion appears to be linked to income inequality and is of relevance to psychosis. If increasing inequality is associated with increasing social cohesion, and if social cohesion protects against poverty, this may explain the inverse relationship between income inequality and poverty.

The positive association between neighbourhood income inequality and rates of treated FEP supports the finding of Boydell and colleagues [1] in South London. These authors demonstrated an increased incidence of schizophrenia with increasing inequality but only in the most deprived group of electoral wards. It could be argued that the District of umgungundlovu, our study region, is representative of a generally deprived population when viewed from an international perspective. Certainly, in terms of per capita income, unemployment rates (41%), average household size, etc., this District is significantly deprived. Perhaps then it is only accurate at present to claim a positive relationship between increasing inequality and FEP incidence in regions of high deprivation; and that further studies are indicated to clarify the relationship in more affluent contexts.

Our findings also add to the existing evidence for an association between health status and income inequality (rather than levels of poverty). This work is most closely identified with Wilkinson, but has been replicated in many subsequent studies internationally. The “income inequality” or “relative income” hypothesis asserts that health depends not just on one’s own income but also on the incomes of others in society [15]. While individual rank within the income distribution is undoubtedly important, it seems that a large rich–poor gap in a community is bad for everyone in that community regardless of rank and not just for those at the bottom end.

The link between inequality and health has led to a search for possible mechanisms underlying this relationship. Wilkinson and others have argued that the causal relationship between income inequality and ill-health is mediated by various psychosocial stressors such as multiple life events, job insecurity, poor social networks and cohesion, low social capital, low self-esteem and fatalism [2, 16]. However, other authors such as Lynch maintain that this psychosocial interpretation raises several conceptual and empirical problems [21]. These authors argue that income inequality is accompanied by many material differences in condition of life at the individual and population levels, which may adversely influence health.
Thus, the “interpretation of links between income inequality and health must begin with the structural causes of inequalities, and not just focus on perceptions of that inequality” [21].

Cohen [5] argues that psychiatry has failed to focus on issues pertaining to social inequality despite the growing evidence for a strong association. This is in part due to the historical absence of a solid research and clinical base. In the case of psychotic disorder, where genetic and developmental vulnerability is mediated by psychosocial precipitants of disease, it is no longer tenable to ignore important ecological variables such as income inequality. Recent demonstrations of worldwide variability in the incidence of schizophrenia [11, 24], suggest that psychosocial and environmental factors play a critical role in the genesis of psychosis. As with urbanicity and employment status, there is now growing evidence for income inequality as an important variable in determining local incidence rates of psychotic disorders.

References

CHAPTER 3
THE IMPACT OF PSYCHOSOCIAL AND CULTURAL FACTORS ON THE CLINICAL PRESENTATION OF FIRST-EPISTODE PSYCHOSIS

This chapter reports results of a prospective study of first-episode psychosis conducted at a psychiatric hospital in KwaZulu-Natal, South Africa. The study objectives were to investigate the impact of psychosocial and cultural factors on clinical features of psychosis onset that can be considered ‘proxies’ for outcome. The study is reported in 3 papers, all of which have been accepted for publication in peer-reviewed journals (see Appendix A). Paper 2, “Exposure to trauma and the clinical presentation of first-episode psychosis in South Africa” is to be published in the Journal of Psychiatric Research; Paper 3, “Cannabis predicts shorter duration of untreated psychosis and low negative symptoms in first-episode psychosis: a South African study” is to be published in the African Journal of Psychiatry; and Paper 4, “Causal attributions, pathway to care and first-episode psychosis: a South African perspective” is to be published in the International Journal of Social Psychiatry.
Exposure to trauma and the clinical presentation of first-episode psychosis in South Africa

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Abstract – 137
Text Body – 3261
ABSTRACT

Objective:
To evaluate the relationship between a history of traumatic experiences and the clinical features of first-episode psychosis (FEP).

Method:
We tested associations between trauma variables and duration of untreated psychosis (DUP), age of onset (AO), PANSS-rated positive and negative symptoms and depressive symptoms (Calgary Depression Scale) in a sample of 54 FEP patients.

Results:
Mean DUP was 34.4 weeks, while mean AO was 24.7 years. Witnessing a seriously violent assault (49%) was associated with high positive symptoms ($p=0.002$), while a significant personal experience of racism and discrimination (39%) was associated with high depressive ($p=0.042$) symptoms. Previous sexual assault (44% of females) was associated with high positive ($p=0.028$) and negative ($p=0.035$) symptoms with a trend association with depressive symptoms ($p=0.092$).

Conclusion:
Our findings suggest that previous traumatic experience is associated with positive and affective symptoms in FEP.
KEYWORDS:

First-episode psychosis

Trauma

Duration of untreated psychosis

Symptoms
1. Introduction

There is increasing evidence that individuals experiencing a first episode of psychotic illness have a variety of clinical presentations and outcomes. Features of first-episode psychosis (FEP) that have been shown in previous research to predict outcome include: age of onset (AO); duration of untreated psychosis (DUP); and symptoms at onset. For example, long DUP and negative symptoms are associated with poorer outcome (Marshall et al., 2005; White et al., 2009), while later AO and positive and affective symptoms are associated with better outcome (Emsley et al., 1999; Malla et al., 2006). Given the potential public health advantages of better predicting course and outcome of psychotic disorders, it is important to explore whether certain risk factors for psychosis are predictive of specific patterns of clinical presentation at first episode.

Recent epidemiological research has identified a number of environmental risk factors for psychosis that interact with genetic and developmental liability to the disorder (Van Os et al., 2005). These risk factors include exposure to early traumatic experiences (Morgan and Fisher, 2007; Read et al., 2005). Reviews of the association between childhood trauma (CT) and psychosis highlight the difficulties related to establishing a causal link between CT and psychosis (Morgan and Fisher, 2007; Bendall et al., 2008; Krabbendam 2008). Nevertheless, it is clear from case controlled studies that patients with psychosis report more CT than general population controls (Üçok and Bikmaz, 2007). Similarly, in respect of traumas experienced during adolescence and adulthood, there is good empirical support for an association between later trauma and risk of psychotic symptoms.
(Bechdolf et al., 2010; Gracie et al., 2007; Shevlin et al., 2008). For example, there are clear links between post-traumatic stress disorder (PTSD) and secondary psychotic symptoms (Lindley et al., 2000; Seedat et al., 2003).

This brings us to the important question of whether certain environmental risk factors for psychosis (such as trauma) predict a cluster of clinical features of FEP that previously have been shown to predict outcome (e.g. positive and affective symptoms, short DUP, etc). In fact, there is good evidence for an association between childhood trauma and abuse and the experience of positive psychotic symptoms (especially command hallucinations) in adulthood (Bebbington et al., 2004; Read et al., 2005; Shevlin et al., 2007; Spauwen et al., 2006; Whitfield et al., 2005). While childhood sexual abuse appears to have the greatest effect size (Krabbendam 2008), the risk-increasing effects of early trauma seem to be related to interpersonal events in particular (Üçok and Bıkmaz, 2007). Furthermore, CT is associated with subclinical positive symptoms in both individuals at high-risk for psychosis (Thompson et al., 2009) and non-clinical samples (Lataster et al., 2006). Myin-Germeys and Van Os (2007) have suggested that there are at least two different dimensions in schizophrenia, each with its own risk factors, demography and symptoms. They propose that developmental trauma is on the “affective pathway” and is associated with female gender, less cognitive impairment and positive symptoms (Krabbendam 2008). If this is the case, one might then speculate that FEP patients with a significant history of early trauma would be more likely to manifest other positive prognostic features of psychosis onset (such as later AO and shorter DUP.)
With respect to adult traumas, the question is best addressed by examining the literature on PTSD and ‘secondary’ psychosis. The commonest psychotic symptoms in combat veterans with PTSD in a US study were auditory and visual hallucinations and delusions (Lindley et al., 2000), suggesting that later experiences of trauma may also be associated with positive symptoms at onset of psychosis. Since acute positive symptoms are very often associated with behavioural disorganization and significant distress, it seems reasonable to speculate that individuals with a history of exposure to significant trauma may tend to present earlier to psychiatric services (i.e. with shorter DUP).

Importantly, this study is located in South Africa which is a developing country with a predominantly non-Caucasian population. Furthermore, South Africa is characterized by high levels of poverty and violence – during both childhood and adulthood (Doolan et al., 2007). The vast majority of research on trauma and FEP has been conducted in developed countries with majority Caucasian patients and relatively lower levels of poverty and violence. It is therefore important to revisit the relationship between both early and later experiences of trauma and FEP within a developing context.

1.1. Aims of the study
Within a context where trauma is so pervasive, we sought to investigate the relationship between individual exposure to serious traumatic events and features of first-episode psychosis (FEP) that have previously been shown to have prognostic value – namely DUP, AO and symptoms at onset. Specifically, we sought to test the hypothesis that short
DUP, later AO, low negative symptoms and high positive, general and affective symptoms would be independently associated with a history of personal trauma.

2. Material and methods

2.1. Participants

The study was conducted at Town Hill Hospital, the main psychiatric referral hospital in the Province of KwaZulu-Natal, South Africa. Over a period of one year, all new admissions with a first episode of psychotic illness were screened for possible inclusion in the study. Those meeting DSM-IV-TR clinical criteria for Schizophreniform Disorder, Schizophrenia and Schizoaffective Disorder and for whom first-episode status was confirmed were invited to participate in the study. Written informed consent was obtained in each participant’s first language and permission was obtained to interview a close relative. Exclusion criteria were: age younger than 15 years or older than 47 years; intellectual disability; confirmed history or EEG evidence of epilepsy; evidence of psychotic illness precipitated by a general medical condition; and recent substance abuse (within the last week) or dependence.

2.2. Procedures and instruments

The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal and patients provided written, informed consent. Within 24 hours of admission, participants were interviewed by a psychiatrist (JKB or KJ) and rated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) as well as the Calgary
Depression Scale for Schizophrenia (CDSS) (Addington and Addington, 1990). Both these investigators had received prior training in the administration of these instruments and inter-rater reliability was good ($r = 0.88$ and 0.84 respectively). Basic demographic data as well as data on substance abuse and previous serious traumatic experiences was obtained from interviews with the patient and a close relative of the patient (for verification), as well as from clinical notes. Information relating to the onset of psychosis was also obtained from interviews with the patient and relatives and from clinical notes.

2.3. Definitions of outcome variables of interest

Duration of untreated psychosis (DUP) was defined as the period in weeks between the first appearance of positive psychotic symptoms and the initiation of treatment in hospital. In common with previous studies (Morgan et al., 2006), onset of psychosis was defined as the presence for at least a week of one or more of the following positive symptoms: hallucinations; delusions; thought disorder; disorganized or bizarre behaviour with a marked deterioration in function. Age of onset (AO) was calculated as the age when positive psychotic symptoms lasting more than a week first occurred. Positive, negative and general symptom scores were derived from the PANSS positive, negative and general psychopathology total scores respectively, while depressive scores were derived from the CDSS total score.

2.4. Statistical analysis

The data were analysed in SPSS version 15.0 (SPSS Inc., Chicago, Illinois). A p value <0.05 was considered as statistically significant. Characteristics of FEP (AO, DUP,
CDSS depressive symptoms and positive, negative and general psychopathology PANNS symptoms) were treated as continuous variables. Univariate analyses were performed using non-parametric methods due to the non-normal distributions of some of the dependent variables. Mann-Whitney U statistics were computed for dichotomized independent variables. Adjustment for confounding was achieved using regression modeling. DUP and AO were treated as time to event outcomes and predictors were modeled using Cox Proportional Hazards models. Multiple linear regression modeling was used for the outcomes of positive, negative and general symptoms scores as well as depressive scores. In all models the three trauma variables of interest and covariates were modeled in a two block process. In the first block, the three trauma variables were specified with the forced entry method. For the Cox models, in the second block the covariates age (continuous), gender, ethnicity, rural or urban, family history and dagga use (all binary) were specified with a backward selection method based on likelihood ratios with probabilities for entry and removal set at 0.05 and 0.1 respectively. For the multiple linear regression models, in the second block the covariates age (continuous), gender, ethnicity, rural or urban, family history and dagga use (all binary) were specified with a stepwise selection method. The final models were reported, which included the three trauma variables as well as any covariates which met model selection criteria. Thus the effects of the other trauma variables were adjusted for, as well as those covariates which significantly affected the model fit. Those with missing values for any variable were excluded from the analysis, thus n=48 were included in the analysis.
3. Results

3.1. Patient characteristics

Fifty-four individuals were enrolled in the study with an average age of 25 years and 10 months. The sample was predominantly male (70%), of Zulu ethnicity (85%) and of single/separated marital status (85%). Thirty-eight percent had a positive psychiatric history, 35% used cannabis regularly and HIV-seropositivity was detected in 22% of those who had been tested during their admission. A significant proportion had either witnessed (49%) or personally experienced (45%) serious physical assault in the past. Twenty-two percent of the sample had witnessed someone being killed, while 44% of the female participants had previously been sexually assaulted. Thirty-nine percent of the whole sample reported significant past experiences of racism and discrimination.

3.2. Clinical features of FEP

Mean duration of untreated psychosis (DUP) was 35.08 weeks (median 6 weeks; S.D. 62.01; range: 1-260 weeks), while the mean age of onset of psychosis (AO) was 24.64 years (S.D. 7.6; range: 15-47 years). The mean PANSS positive score was 15.8 (S.D. 6.5; range: 7-32), mean PANSS negative score 13.15 (S.D. 5.7; range: 7-30) and mean PANSS general score 24.9 (S.D. 9.5; range 16-56). The mean CDSS depression score was 6.08 (S.D. 4.83; range: 0-21). Table 1. shows these results in detail.
Table 1.
Sample characteristics (n=54)

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<td>Other</td>
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<tr>
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<th>S.D.</th>
<th>Median</th>
<th>Min–Max</th>
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<td>Age (years)</td>
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<td>8.1</td>
<td>25.0</td>
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</tr>
<tr>
<td>Age of onset (years)</td>
<td>24.7</td>
<td>7.6</td>
<td>22.0</td>
<td>15-47</td>
</tr>
<tr>
<td>Duration of untreated psychosis (weeks)</td>
<td>35.1</td>
<td>62.0</td>
<td>6.0</td>
<td>1-260</td>
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<tr>
<td>Positive symptom score (PANSS)</td>
<td>15.8</td>
<td>6.5</td>
<td>13.5</td>
<td>7-32</td>
</tr>
<tr>
<td>Negative symptom score (PANSS)</td>
<td>13.15</td>
<td>5.7</td>
<td>12.0</td>
<td>7-30</td>
</tr>
<tr>
<td>General psychopathology score (PANSS)</td>
<td>24.9</td>
<td>9.5</td>
<td>21</td>
<td>16-56</td>
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<tr>
<td>Depressive symptom score (CDSS)</td>
<td>6.1</td>
<td>4.8</td>
<td>5.0</td>
<td>0-21</td>
</tr>
</tbody>
</table>

S.D.: standard deviation
3.3. Trauma variables associated with onset of FEP

Previous traumatic experiences were associated with a number of clinical features of the first episode that previously have been associated with better outcome. Sexual assault was significantly associated with total positive symptoms (p=0.028). Those who had been sexually assaulted scored on average nearly 5 points higher (on the PANSS positive symptoms scale) than those who had not been sexually assaulted, after controlling for other traumatic experiences and age. Sexual assault was also significantly associated with higher total negative symptoms scores (p=0.035), with a trend towards association with higher depressive symptoms (p=0.092). Witnessing a violent act (49%) was significantly associated with higher total positive symptoms scores (p=0.002). Personal significant experiences of racism and discrimination (39%) were significantly associated with higher depressive symptoms (p=0.042) after controlling for other traumatic experiences.
Table 2. Final Cox regression models for DUP, AO and trauma exposures.

### Duration of Untreated Psychosis

<table>
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<tr>
<th>Step 4</th>
<th>Variable</th>
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<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>HR</th>
<th>95.0% CI for HR</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Upper</td>
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<tr>
<td></td>
<td>Sexual assault</td>
<td>.037</td>
<td>.437</td>
<td>0.007</td>
<td>1</td>
<td>.933</td>
<td>1.037</td>
<td>.440</td>
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<td>Witnessed violent act</td>
<td>.184</td>
<td>.328</td>
<td>0.314</td>
<td>1</td>
<td>.575</td>
<td>1.202</td>
<td>.632</td>
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<td></td>
<td>Racial discrimination</td>
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<td>.359</td>
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<td>.414</td>
<td>1.340</td>
<td>.663</td>
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<tr>
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<td>.954</td>
<td>.914</td>
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<td>Ethnicity (black vs. other)</td>
<td>1.892</td>
<td>.530</td>
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<td>.000*</td>
<td>6.634</td>
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<td>Urban vs. Rural</td>
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<td>7.921</td>
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### Age of Onset

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<td></td>
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<td></td>
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<td>.308</td>
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*P≤0.05
Table 3.
Final multiple regression models for symptoms and trauma exposures.

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<th>Mode</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>t</th>
<th>Sig.</th>
<th>95% Confidence Interval for B</th>
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<td>(Constant)</td>
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4. Discussion

In this study we sought to investigate associations between previous exposure to serious traumatic events and features of FEP that have been shown to have prognostic value – namely duration of untreated psychosis (DUP), age of onset (AO) and levels of positive and negative psychotic symptoms as well as general and affective symptoms at onset. As these latter features have been shown to correlate well with short- and long-term outcome, it is important to clarify the possible impact that individual risk factors may have on these specific clinical features. This is particularly important we argue, in a developing country context where exposure to traumatic events is common (Doolan et al., 2007).

4.1. Trauma, discrimination and clinical presentation of FEP

In keeping with the literature on trauma and FEP, we found an association between exposure to serious traumatic incidents and a number of clinical features of the first episode that previously have been associated with better outcome. Both the witnessing of a seriously violent act and a history of sexual assault were associated with high positive symptoms, supporting Krabbendam’s (2008) argument that the risk-increasing effect of trauma (for manifesting significant positive symptoms) is related to interpersonal events in particular. While childhood sexual abuse appears to have the greatest effect size (Bebbington et al., 2004), it may be that it is the interpersonal nature of the trauma that is key in predicting positive symptoms. For example, Lataster and colleagues (2006) showed a dose response association between victimisation through
childhood bullying (an interpersonal trauma) and non-clinical positive psychotic symptoms in adolescence.

In our study, sexual assault was also associated with high depressive symptoms and, while we did not record when traumatic experiences occurred, we would speculate that those individuals who did report sexual trauma included some whose experiences were in childhood and some whose experiences were later on. Without information on the timing of the sexual assault we cannot relate our result specifically to the hypothesis regarding early sexual abuse and initiation onto the “affective pathway” (Myin-Germys and Van Os, 2007) to psychosis. However we believe that, in a context where sexual abuse and assault is so common, our results are useful in suggesting a link between this form of highly interpersonal trauma and positive and affective symptoms of FEP (symptoms that previously have been associated with a better outcome.) More difficult to explain is the association we found between a history of sexual assault and negative symptoms at onset; especially since this finding is contrary to most previous studies (Read et al., 2005; Üçok and Bikmaz, 2007).

The experience or perception of discrimination based on ethnic, racial and non-racial grounds has been associated with an increased risk for general mental disorders (Gee et al., 2007; Moomal et al., 2009) and for psychotic disorders in particular (Karlsen et al., 2005; Veling et al., 2007). It has also been associated with the emergence of delusional ideation in non-clinical general populations (Janssen et al., 2003). Myin-Germys and Van Os (2008) suggest that repeated experiences of discrimination and resulting ‘social
defeat’ (Cantor-Graae and Selten, 2005) may be responsible for the increased risk of psychosis noted in migrant and ethnic minority groups. In our study, the experience of discrimination and racism was associated with depressive symptoms after controlling for covariates including gender. The concept of ‘social defeat’ is common to the literature relating to depressive illness in general (Marrow et al., 1999; Kroes et al., 2007) and thus the manifestation of affective symptoms in FEP supports the hypothesized association between discrimination and social defeat. Furthermore, both actual and perceived experiences of discrimination have been associated with depression per se in immigrants, refugees, ethnic minorities and adolescents (Schulz et al., 2006; Ellis et al., 2008; Bernstein et al., 2009; Coker et al., 2009) with recent research indicating possible neurobiological mechanisms underlying this association (Lewis et al., 2010). It seems reasonable therefore to speculate that the negative effects of discrimination might operate through the “affective pathway” to increase risk for psychotic illness (Myin-Germys and Van Os, 2007).

It seems then that both early and more recent experiences of trauma and stress may contribute to specific symptoms of FEP. Myin-Germys and Van Os describe two possible mechanisms by which both early and later stress and adversity contribute to increased risk for psychosis (Myin-Germys and Van Os, 2008). These are: early behavioural and biological sensitization of the hypothalamic-pituitary-adrenal (HPA) axis as well as dopamine neurons; and gene-environment (GxE) interactions – both likely to influence neurodevelopmental processes. It is likely that both these mechanisms contribute also to the nature of psychotic presentation at first episode. For example, the Met/Met COMT
polymorphism is associated with poorer cognitive flexibility and adaptability to daily stress with resulting significant increases in positive and affective symptoms (Van Winkel et al., 2008). Specifically, Met/Met subjects reported a larger increase in delusional experiences and negative affect in reaction to stress than subjects of the other genotypes. How exactly GxE interactions and mechanisms of HPA and dopamine sensitization contribute to specific clinical presentations of FEP remains unclear. One might speculate that both HPA and dopaminergic sensitization and GxE interactions, occurring in response to both early and later traumas, give rise to functional brain changes. These changes lead to alterations in information processing, cognitive flexibility and adaptability, emotional regulation and self-monitoring that manifest as mainly positive and affective symptoms at first episode. This however remains to be tested in future studies with novel methodologies suited to unraveling the complex pathways between traumatic exposure and specific clinical phenotype.

4.2. Strengths and limitations

Strengths of this study include the fact that data (including timing of onset of psychosis) was obtained through a number of methods including participant and family/caregiver interviews as well as from case notes, thereby enhancing validity. Also clinical ratings were conducted by trained psychiatrists with good inter-rater reliability and using standardized and validated rating instruments. Importantly, the sample was treatment-naïve at the time of assessment. Finally, this study was conducted in South Africa in a predominantly non-Caucasian sample. This means that previous findings relating to
trauma and FEP conducted almost exclusively in ‘first-world’, mainly Caucasian patients are now replicated in an African context.

The relatively small sample size is an obvious limitation of the study and may have weakened the power of the statistical analysis to yield significant results in some cases. In addition, using indicators of poor outcome rather than actual outcome measures means that we are not looking at prediction of outcome, but only at prediction of clinical presentation. While longitudinal outcome measurements would have been desirable, major loss to follow-up (related to the specific socioeconomic context in which this study was conducted) prevented this. Thus, while factors such as longer DUP, early age of onset and negative symptoms have been shown to predict poorer outcome in other studies, we cannot assume that this would necessarily be the case in our study, were we to have conducted longitudinal assessments of outcome. A further limitation is the fact that we did not record when various traumatic experiences occurred. This would have been desirable for a variety of reasons including being able to differentiate between early (childhood) trauma and later (adult) trauma. Furthermore, generalization from our results is limited by the unique social and cultural context in which this study was conducted. Also, ours was an entirely hospital based sample which almost certainly does not to represent all patients in this area. Finally, the high prevalence of HIV-seropositivity (22%) and cannabis use (35%) in our sample may have been confounders although their effect was reduced through exclusion of individuals where a general medical condition was judged to be aetiological of the psychosis, as well as those with a history of substance abuse within the last week.
5. Conclusion

Despite the limitations, our results suggest that experiences of serious trauma and discrimination may predict a clinical presentation of FEP that has been associated with a more favourable prognosis. These findings provide some support for the notion that traumatic experiences may operate through an “affective pathway” to increase risk for psychosis (Myin-Germys and Van Os, 2007). Those patients who reported traumatic experiences were more likely to manifest a symptom cluster comprised of high positive and affective symptoms that is characteristic of the “affective pathway” and which is associated with a better prognosis at baseline. Clearly, replication with larger sample sizes and longitudinal follow-up methods is necessary to clarify whether this sense of modest optimism can be extended to the medium and long-term.
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Van Winkel R, Henquet C, Rosa A, Papiol S, Fananás L, De Hert M et al. Evidence that the COMT (Val158Met) polymorphism moderates sensitivity to stress in


Conflict of interest

All of the authors declare that they have no actual or potential conflicts of interest including any financial, personal or other relationships that could inappropriately influence, or be perceived to influence their work.

Role of the funding source

Funding for this study was provided by National Research Foundation (NRF) Grant. The NRF had no role in study design, data collection, analysis and interpretation, in the writing of the report and in the decision to submit the paper for publication.

Contributors

Jonathan Burns was the principal investigator, conducted the literature review, designed the study, supervised collection of all data, conducted interviews, contributed to data analysis and wrote the draft of the manuscript. Khatija Jhazbhay participated in subject recruitment and the conducting of interviews. Tonya Esterhuizen assisted with study design and managed the statistical analysis. Robin Emsley supervised the study and contributed to study design and final drafting of the manuscript.

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Cannabis use predicts shorter duration of untreated psychosis and lower levels of negative symptoms in first-episode psychosis:

A South African study

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3. ROBIN EMSLEY
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WORD COUNTS:
Abstract – 196
Text Body – 1904
ABSTRACT

Background
Cannabis use/abuse is a common co-morbid problem in patients experiencing a first episode of psychotic illness (FEP). The relationship between the clinical presentation of FEP and cannabis abuse is complex and warrants further investigation, especially within the South African context.

Method
We tested associations between recent/current cannabis use and duration of untreated psychosis (DUP), age of onset (AO), PANSS-rated (Positive and Negative Syndrome Scale) positive, negative and general psychopathology symptoms and depressive symptoms (Calgary Depression Scale for Schizophrenia) in a sample of 54 patients with FEP.

Results
Mean DUP was 34.4 weeks, while mean AO was 24.7 years. Co-morbid cannabis use occurred in 35% of the sample and was significantly associated with shorter DUP (Mann-Whitney U, p=0.026). While not significant, there was also a trend association between cannabis use and lower negative symptom scores (Mann-Whitney U, p=0.051).

Discussion
Current/recent cannabis use was associated with clinical features of psychosis onset that previously have been associated with better outcome. Medium and long-term outcome for cannabis users however, is likely to depend on whether or not cannabis use is ongoing.
KEYWORDS:

First-episode psychosis
Cannabis
Duration of untreated psychosis
Age of onset
Symptoms
Introduction

Cannabis use/abuse is a common co-morbid problem in patients experiencing a first episode of psychotic illness. While cannabis use is associated with worse outcome in schizophrenia\textsuperscript{1-2}, anecdotal clinical observations suggest that a prominent history of recent cannabis abuse in patients presenting with first-episode psychosis (FEP), predicts rapid resolution of acute symptoms. The relationship then between the clinical presentation of FEP and cannabis abuse is complex and warrants further investigation, especially within the South African context where this pattern of co-morbidity is so prevalent.\textsuperscript{3} It is therefore relevant to explore any associations that may exist between recent/current cannabis use/abuse and clinical features of FEP that previously have been shown to have prognostic value (including age of onset (AO), duration of untreated psychosis (DUP), positive, negative, general psychopathology and depressive symptoms). Importantly, while these features may be predictive of outcome, they are not measures of outcome itself – they might better be considered proxies for outcome.

Sugranyes and colleagues\textsuperscript{4} found that cannabis use (irrespective of frequency) was associated with early AO and that AO decreased as frequency of cannabis use increased. Similarly, González-Pinto and colleagues\textsuperscript{5} showed that AO was earlier in cannabis users compared to non-users, was even earlier in cannabis abusers, and earlier still in those with cannabis dependence. Regarding symptoms however, FEP patients with a history of cannabis use have less prominent negative symptoms and a predominance of positive
symptoms.\textsuperscript{1, 6-7} Outcome though is not favourable in patients with co-morbid schizophrenia and cannabis abuse, with evidence indicating more severe and refractory symptoms, poorer treatment-response, higher relapse rates and an overall worse prognosis.\textsuperscript{1-2} A recent study by Baeza and colleagues\textsuperscript{8} may illuminate the issue. At 6 months follow-up, non-cannabis users (NCU) had the worst outcome, while previous cannabis users (PCU) who gave up on commencing treatment had the best outcome. Those cannabis users who were currently using cannabis (CCU) at 6 months had an intermediate outcome. This suggests that in the PCU group, cannabis may have been a major aetiological contributor to psychosis onset – thus, discontinuing cannabis resulted in a favourable outcome. On the other hand the CCU group, who were persisting with cannabis use, remained symptomatic; and their risk of poor long-term outcome is likely to have been high due to their ‘dual diagnosis’ status. Non-cannabis users (NCU) may have had the worst outcome at 6 months because, in the absence of a major environmental precipitant (cannabis), one might postulate that a greater genetic susceptibility existed. This is relevant to our consideration of cannabis as a risk factor for poor prognosis FEP. One might anticipate that FEP patients with a history of recent or current cannabis use would be more likely in the initial presentation to manifest clinical features of psychosis that have been associated with better outcome in previous studies (with the possible exception of early AO.)

**Method**

*Participants*
Over a 12 month period, all consecutive patients admitted with FEP to Town Hill Hospital, KwaZulu-Natal Province, South Africa were considered for possible inclusion in the study. Inclusion criteria were: a clinical DSM-IV-TR diagnosis of Schizophreniform Disorder, Schizophrenia and Schizoaffective Disorder; and confirmation of first-episode status through review of clinical records and consultation with the primary caregiver. Exclusion criteria were: age younger than 16 years or older than 45 years; intellectual disability; confirmed history or EEG evidence of epilepsy; evidence of psychotic illness precipitated by a general medical condition; and clear clinical evidence of substance-intoxication or withdrawal (or a definite history of cannabis use within the last week prior to admission). Those meeting inclusion and exclusion criteria were approached and invited to participate. Each participant provided written informed consent after the study was explained in his/her first language. The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal.

Procedures and instruments

On admission, patients were interviewed by one of two psychiatrists (JKB or KJ) and rated with the Positive and Negative Syndrome Scale (PANSS)\textsuperscript{9} as well as the Calgary Depression Scale for Schizophrenia (CDSS).\textsuperscript{10} Both these investigators had received prior training in the administration of these instruments and inter-rater reliability was satisfactory ($r = 0.88$ and 0.84 respectively). Demographic data was recorded by a research nurse including questions about recent or current use of cannabis. Patients were
scored as positive for cannabis use if they reported use on a minimum of a weekly basis over the last month prior to admission to hospital.

**Definition of clinical features of FEP**

Duration of untreated psychosis (DUP) was defined as the period in weeks between the first appearance of positive psychotic symptoms and the initiation of treatment in hospital. In common with previous studies\textsuperscript{11}, onset of psychosis was defined as the presence for at least a week of one or more of the following positive symptoms: hallucinations; delusions; thought disorder; disorganized or bizarre behaviour with a marked deterioration in function. Age of onset (AO) was calculated as the age at initiation of treatment, less the DUP. Positive, negative and general symptoms were derived from the PANSS positive, negative and general total scores respectively, while depressive symptoms were derived from the CDSS total score.

**Statistical Methods**

Data were analysed using the SPSS version 15.0 (SPSS Inc., Chicago, Illinois) software package and a P value <0.05 was considered statistically significant. Univariate analyses were performed using non-parametric methods due to the non-normal distributions of the dependent variables which were treated as continuous variables. Analysis of variance (ANOVA) methods (Mann-Whitney U) were used with cannabis use dichotomized as the independent variable.
Results

Fifty-four individuals were included in the study with an average age of 25 years and 8 months. The sample was predominantly male (70%), of Zulu ethnicity (85%) and of single/separated marital status (85%) with a mean age of 25 years and 8 months. Cannabis use occurred in 35% of the sample with a slight (but not significant) male gender bias - 37% of males and 28% of females.

In terms of clinical features of the first-episode presentation, the mean duration of untreated psychosis (DUP) was 35.08 weeks (median 6 weeks; S.D. 62.01; range: 1-260 weeks), while the mean age of onset of psychosis (AO) was 24.64 years (S.D. 7.6; range: 15-47 years). The mean PANSS positive score was 15.76 (S.D. 6.52; range: 7-32), mean PANSS negative score 13.15 (S.D. 5.68; range: 7-30) and mean PANSS general score 24.85 (S.D. 9.5; range 16-56). The mean CDSS depression score was 6.08 (S.D. 4.83; range: 0-21).

Table 1
Sample characteristics (n=54)

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Univariate analysis revealed a number of associations between cannabis use and clinical features of FEP. Current or recent cannabis use was significantly associated with shorter DUP (Mann-Whitney U, $p=0.026$). Mean DUP for cannabis users was 21.0 weeks (S.D. 48.66) and for non-users 41.84 weeks (S.D. 67.06). While not significant, there was also a trend association between cannabis use and lower negative symptoms (Mann-Whitney U, $p=0.051$). The mean PANSS negative score for cannabis users was 10.65 (S.D. 3.22) and for non-users 14.03 (S.D. 5.96). There was no association between cannabis use and AO, positive, general psychopathology or depressive symptoms.

Although it would have been desirable to perform multivariate regression analyses (MVR) on the significant variables in the univariate analysis, we decided not to proceed with MVR due to the small sample size and categorical nature of the independent variable. Under these circumstances the results of a MVR would be of questionable validity.
Table 2.
Bivariate analysis for cannabis use

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<th>CANNABIS USERS (n=17)</th>
<th>NON-CANNABIS USERS (n=32)</th>
<th>Significance (MWU)</th>
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<td>Duration of Untreated Psychosis (weeks)</td>
<td>21.18 (48.58)</td>
<td>41.75 (67.12)</td>
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<tr>
<td>Age of onset (years)</td>
<td>22.24 (3.51)</td>
<td>26.47 (8.91)</td>
<td>0.387</td>
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<td>Positive symptoms</td>
<td>11.71 (6.22)</td>
<td>15.50 (8.70)</td>
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<tr>
<td>Negative symptoms</td>
<td>8.59 (4.96)</td>
<td>13.28 (6.82)</td>
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<tr>
<td>General symptoms</td>
<td>14.59 (9.38)</td>
<td>19.84 (14.81)</td>
<td>0.744</td>
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<tr>
<td>Depressive symptoms</td>
<td>6.41 (4.11)</td>
<td>6.32 (5.31)</td>
<td>0.862</td>
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</table>

S.D.: standard deviation
MWU – Mann-Whitney U
*P≤0.05
Discussion

Strengths and limitations of the study

Strengths of this study include: the fact that data was obtained through a number of methods including participant and family/caregiver interviews as well as from case notes, thereby enhancing validity; clinical ratings were conducted by trained psychiatrists with good inter-rater reliability and using standardized and validated rating instruments; and the sample was treatment-naïve at the time of assessment. Finally, to our knowledge, this is the first study of FEP in a predominantly Zulu sample.

The relatively small sample size is an obvious limitation of the study and together with some missing data for certain variables may have weakened the power of the statistical analysis. In view of this limitation, we elected not to do multivariate analysis (MVA) as we could not be confident of the validity of MVA results. The absence of MVA is obviously a further limitation of the study. Although we relied solely upon self-and caregiver reporting to establish cannabis use, we are satisfied that this is a valid method – Koen and colleagues\(^3\) compared urine THC testing with self-report of cannabis use and concluded that determination based solely on history is reliable and that THC testing “appears to be of limited value”. Generalization from our results is limited by several factors (some mentioned above) including the fact that ours was an entirely hospital based sample which is likely not to represent all patients in this area. Also, the high rate of HIV-seropositivity (22%) in our sample may be a confounder. In our view however, the potential to confound the results is minimal, as we excluded from the study
individuals where a general medical condition was clinically judged to be aetiological of the psychosis. The absence of clinically significant symptoms of HIV-AIDS in our sample suggests that HIV seropositivity is a coincident finding with psychotic disorder (rather than aetiological of the psychosis). Finally, it is important to reiterate that while DUP, AO and symptoms at onset may be predictive of outcome, they are not measures of outcome itself – they might better be considered proxies for outcome.

Cannabis and psychosis

The ethnic distribution of our sample was consistent with that of the local population while the prevalence of cannabis use/abuse (35%) approximated that reported in other African studies: 38% in the Gambia\textsuperscript{12} and 35-49% in South Africa\textsuperscript{3, 13}. The slight gender bias in prevalence of cannabis use observed in our study (37% of males and 28% of females) was also similar to that reported by Roos and colleagues.\textsuperscript{13}

In contrast to previous studies\textsuperscript{1, 6, 14, 15}, we found a significant association between cannabis use and shorter DUP and a trend association between the use of cannabis and a relative absence of negative symptoms. Also, unlike these studies, we did not find increased positive symptoms, nor was there any association with AO (a finding that has been reported from both developed and developing countries\textsuperscript{3-5, 12-15}). Clearly then the relationship between cannabis use and onset of FEP is complex.

It is possible that the shorter DUP associated with cannabis use in our sample may relate to the specific context within which this study was conducted. Locally produced cannabis
within the Province of KwaZulu-Natal is well-known for its very high THC concentration and psychogenic potency\textsuperscript{16}; and it is reasonable to speculate that its use may give rise to particularly disruptive symptomatology and behaviour that hastens individuals’ pathway to care – thereby shortening DUP.

The association between cannabis use and low or absent negative symptoms has attracted a number of possible explanations. Compton and colleagues\textsuperscript{1} argue that individuals with negative symptoms are underrepresented because the apathy, amotivation and social withdrawal associated with negative symptoms impede their ability to access cannabis. However, we do not find this explanation convincing, especially within the South African context where cannabis is easily accessible. Rather, we favour the suggestion that cannabis may reduce the negative symptoms of psychosis. This notion has received some support, notably from a study by Peralta and Cuesta\textsuperscript{17} where low levels of cannabis consumption by patients with schizophrenia attenuated negative symptoms, but had no effect on positive symptoms. The clinical finding then of lower negative symptoms in FEP patients who use cannabis may reflect self-medicating behaviour as has been suggested by a number of authors\textsuperscript{17-20}, but questioned by others.\textsuperscript{21} It is important to note however that the high co-morbidity of cannabis use and psychosis cannot be attributed to self-medication alone. In fact there are now a number of large prospective studies\textsuperscript{22-24} that confirm that primary cannabis use increases risk for subsequent psychotic illness by a factor of two.\textsuperscript{25} The role of cannabis as a risk factor for psychosis must be understood in terms of complex gene-environment interactions where exposure to cannabis modifies gene expression in genetically susceptible individuals.\textsuperscript{26}
With reference then to prognostic features of FEP, it appears that cannabis use in our study is associated with clinical features of psychosis onset that previously have been associated with better outcome, namely shorter DUP and a relative absence of negative symptoms. In terms of a gene-environment model of psychosis onset, one might postulate that in non-cannabis users, where the contribution of ‘environment’ is seemingly less, there may be conversely a greater degree of genetic susceptibility (which may be associated with less favourable course and outcome). In the case of cannabis users however, medium and long-term outcome is likely to depend on whether or not cannabis use is ongoing (see discussion on Baeza and colleagues\textsuperscript{8} above), as persistent use is clearly associated with a more continuous illness and a greater predominance of positive symptoms at follow-up.\textsuperscript{27}
References


Causal attributions, pathway to care and clinical features of first-episode psychosis: a South African perspective

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Abstract – 216
Text Body – 3332
ABSTRACT

Background: Causal belief systems and help-seeking practices may impact on pathway to care and features of first-episode psychosis that have prognostic value. This is particularly relevant in South Africa where many people subscribe to traditional belief systems and consult traditional healers.

Aim: To evaluate the relationship between causal attributions and pathway to care and features of first-episode psychosis (FEP) that have prognostic value.

Method: We tested associations between causal attributions and pathway to care and duration of untreated psychosis (DUP), age of onset (AO), PANSS-rated positive, negative and general symptoms and depressive symptoms (Calgary Depression Scale) in a sample of 54 FEP patients.

Results: Spiritual attribution of cause (49% of patients) was associated with long DUP and high positive symptoms; while consultation with a traditional healer (39% of patients) was associated with long DUP, high negative symptoms and low positive symptoms. Only 19% had consulted a psychiatrist. Seventy-nine percent were referred to hospital by family; police were involved in 44% of admissions; and the 81% were admitted involuntarily.

Conclusions: Spiritual attributions of cause and previous consultation with traditional healers may delay entry to psychiatric care and thereby negatively impact on prognosis of FEP. This highlights the importance of mental health education and developing a positive collaborative relationship with traditional healers, especially in low- and middle-income countries (LMICs).
KEYWORDS:
First-episode psychosis
Causal attributions
Traditional healers
Duration of untreated psychosis
Prognosis
INTRODUCTION

Features of first-episode psychosis (FEP) that have been associated with poorer outcome include: long duration of untreated psychosis (DUP); early age of onset (AO); a predominance of negative symptoms; and a relative absence of positive and affective symptoms (Marshall et al., 2005; Emsley et al., 2007). Understanding possible contributory factors to this cluster of clinical features is important as it may facilitate the planning and implementation of effective early interventions. Individual belief systems and help-seeking practices are likely to impact on pathway to care (Razali et al., 1996; Broadbent et al., 2008) and may also be associated with specific clinical features of FEP that have prognostic value (Haley et al., 2003). In low- and middle-income country (LMIC) contexts, where typically large numbers of people subscribe to culturally specified traditional and religious beliefs and practices (Adebowale & Ogunlesi, 1999; Kurihara et al., 2006a), the role of individual causal attributions is likely to be of major importance in relation to the onset and course of mental disorders such as psychoses. For example, help-seeking behaviours that direct individuals to first consult traditional healers within their communities, may lead to delays in the initiation of medical treatment in FEP (Kurihara et al., 2006b). Such behaviour must be understood within a context where very often formal mental health services are not readily available and accessible to the populace, especially within rural communities (WHO, 2004; Saxena et al., 2007). In such contexts, traditional healers perform a vitally important role for individuals in physical, psychological or spiritual distress. They are very often the first port of call for patients and caregivers alike.
While studies in high-income countries (HIC) such as Germany (Angermeyer & Matschinger, 1996) and Australia (Minas et al., 2007) show that both psychotic patients and their relatives tend to attribute their illnesses to biological or natural causes, it appears that their counterparts in LMICs invoke spiritual and traditional explanations more frequently (Adebowale & Ogunlesi, 1999; Kurihara et al., 2006a; Saravanan et al., 2007; Silove et al., 2008). This seems also to be the case in general population surveys of causal attributions (Angermeyer & Matschinger, 1996; Zafar et al., 2008). Studies in LMICs such as Iran (Sharifi et al., 2009), Zambia (Mbewe et al., 2006) and Singapore (Chong et al., 2005) report that approximately a quarter to a third of patients with FEP consult traditional healers prior to making contact with formal mental health services.

It appears that no previous studies have addressed the issue of whether spiritual or traditional causal attributions impact on DUP; and only two studies have reported on whether previous consultation with a traditional healer impacts on DUP. In Singapore, Chong et al (2005) reported that previous consultation with a traditional healer (24% of the sample) had no impact on DUP. However, in Zambia, Mbewe et al (2006) compared patients with long DUP versus those with short DUP and found that a greater proportion of the former group had consulted traditional healers prior to admission compared with the latter group.

In the present study we sought to investigate the relationship between spiritual/traditional attributions of illness causation and/or a history of previous consultation with traditional
healers prior to hospital admission and features of FEP that have prognostic value – namely DUP, age of onset (AO) and levels of positive and negative psychotic symptoms as well as general and affective symptoms at onset. Given the apparently high rates in FEP patients of spiritual/traditional causal attributions and the significant reliance on traditional healers discussed earlier, we believe that this is an important area of investigation, especially within a LMIC context.

METHODS

Participants
The study was conducted at Town Hill Hospital, the main psychiatric referral hospital in the Province of KwaZulu-Natal, South Africa. Over a period of 12 months, all new admissions with a first episode of psychotic illness were considered for possible inclusion in the study. Those meeting DSM-IV-TR criteria for Schizophreniform Disorder, Schizophrenia and Schizoaffective Disorder and for whom first-episode status was confirmed were invited to participate in the study. Written informed consent was obtained in each participant’s first language and permission was obtained to interview a close relative. Exclusion criteria were: age younger than 16 years or older than 45 years; intellectual disability; confirmed history or EEG evidence of epilepsy; evidence of psychotic illness precipitated by a general medical condition; and recent substance abuse (within the last week) or dependence.
Procedures and instruments

The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal. Within 24 hours of admission, patients were interviewed by one of two psychiatrists (JKB or KJ) and rated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) as well as the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990). Both these investigators had received prior training in the administration of these instruments and inter-rater reliability was satisfactory ($r = 0.88$ and 0.84 respectively). Basic demographic data as well as data on causal attributions as well as pathway to care was obtained from interviews with the patient and a close relative of the patient. Data relating to the onset of psychosis was also obtained from interviews with the patient and relatives and from clinical notes.

With regard to the assessment of causal attributions, patients were asked a series of open-ended questions and their responses were recorded in detail with the assistance of a psychiatric nurse fluent in isiZulu, the predominant first language of the majority of participants. For example, a question was, ‘What do you think is the cause of your illness?’ Answers were analysed and categorized into three groups, namely ‘spiritual/traditional’, ‘natural/scientific’ and ‘other’ explanations. The research team (including two Zulu mental health professionals) later met and discussed each case to reach a consensus as to how each patient’s responses should be categorized. Explanations of a medical nature (e.g. “a problem with my brain”), psychological nature (e.g. “too much stress”) or relating to substance use (e.g. “smoking cannabis”) were categorized as ‘natural/scientific.’ Explanations of a religious nature (e.g. “a curse from God”) or
traditional/cultural nature (e.g. “I did not perform a ritual and the ancestors are punishing me” or “I am sick because of bewitchment”) were categorized as ‘spiritual/traditional.’ Other explanations that did not fit into these categories were classified as ‘other’ (e.g. “I don’t know”). With regard to previous consultation with traditional healers, participants were asked ‘Did you consult a traditional healer for this illness before seeking treatment at the clinic or hospital?’ A simple ‘yes’ or ‘no’ answer was recorded and participants grouped accordingly.

**Definitions of outcome variables of interest**

Duration of untreated psychosis (DUP) was defined as the period in weeks between the first appearance of positive psychotic symptoms and the initiation of treatment in hospital. In common with previous studies (Morgan *et al.*, 2006), onset of psychosis was defined as the presence for at least a week of one or more of the following positive symptoms: hallucinations; delusions; thought disorder; disorganized or bizarre behaviour with a marked deterioration in function. Age of onset (AO) was calculated as the age at initiation of treatment, less the DUP. Positive, negative and general symptoms were derived from the PANSS positive, negative and general total scores respectively, while depressive symptoms were derived from the CDSS total score.

**Statistical analysis**

The data were analysed in SPSS version 15.0 (SPSS Inc., Chicago, Illinois). A p value <0.05 was considered as statistically significant. Characteristics of FEP (AO, DUP, CDSS depressive symptoms and positive, negative and general psychopathology PANNS
symptoms) were treated as continuous variables. Univariate analyses were performed using non-parametric methods due to the non-normal distributions of the dependent variables. Analysis of variance (ANOVA) methods (Mann-Whitney U and Kruskal-Wallis) were used for categorized independent variables.

RESULTS

Patient characteristics
The study sample consisted of fifty-four individuals with an average age of 25 years and 9 months (see Table 1). Participants were predominantly male (70%), of Zulu ethnicity (85%) and of single/separated marital status (85%). There was no significant difference in terms of demographics between the study sample and the seven patients who declined the invitation to participate in the study. With regard to causal explanations of the illness, 49% attributed their illness to spiritual/traditional reasons, while 41% attributed it to natural/scientific causes (and 10% to other causes). 38.5% had consulted with a traditional healer for this illness prior to making contact with formal mental health services. By comparison, only 16% had previously consulted with a general practitioner. Interestingly, 79% were referred to mental health services by family members rather than by general practitioners; and the majority of patients (81%) were admitted involuntarily under the Mental Health Care Act (2002). Police involvement in the admission occurred in 44% of cases.
Table 1
Sample characteristics (n=54)

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<td>0-21</td>
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</tbody>
</table>

S.D.: standard deviation

Clinical features of FEP

Mean duration of untreated psychosis (DUP) was 35.08 weeks (median 6 weeks; S.D. 62.01; range: 1-260 weeks), while the mean age of onset of psychosis (AO) was 24.64 years (S.D. 7.6; range: 15-47 years). The mean PANSS positive score was 15.8 (S.D. 6.5;
range: 7-32), mean PANSS negative score 13.15 (S.D. 5.7; range: 7-30) and mean PANSS general score 24.9 (S.D. 9.5; range 16-56). The mean CDSS depression score was 6.08 (S.D. 4.83; range: 0-21).

**Causal attributions and onset of FEP**

Spiritual/traditional attribution of illness causation was significantly associated with long DUP (Kruskal-Wallis, \(p=0.001\)). (See Table 2. for details.) Those who attributed their illness to spiritual/traditional causes (49%) had a mean DUP of 62.24 weeks (S.D. 77.51), while those who invoked natural/scientific causes (41%) had a mean DUP of 12.52 weeks (S.D. 32.01). Removing outliers (due to the skewed distribution of DUP) did not change the significant result (See Figure 1). There was no difference in level of positive symptoms between those with short DUP and those with long DUP (Spearman’s \(r_s=0.007; \ p=0.958\)). Therefore, one cannot attribute the association between spiritual/traditional cause and longer DUP to the possibility of increased religiose, delusional content in those who had been psychotic for a longer period. While not significant, there was also an association between spiritual/traditional attributions and high negative symptoms (Kruskal-Wallis, \(p=0.12\)). Those who attributed their illness to spiritual/traditional causes had a mean PANSS total negative score of 15.08 (S.D. 6.65), while those who invoked natural/scientific causes had a mean PANSS total negative score of 11.57 (S.D. 4.61).
Table 2.
Bivariate analysis for causal attributions.

<table>
<thead>
<tr>
<th></th>
<th>SPIRITUAL/TRADITIONAL ATTRIBUTIONS (n=25)</th>
<th>NATURAL/SCIENTIFIC ATTRIBUTIONS (n=21)</th>
<th>OTHER ATTRIBUTIONS (n=5)</th>
<th>Significance (KW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Untreated Psychosis (weeks)</td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Age of onset (years)</td>
<td>62.24 (77.51)</td>
<td>12.52 (32.01)</td>
<td>7.00 (4.41)</td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>25.76 (8.38)</td>
<td>23.10 (6.49)</td>
<td>26.00 (9.64)</td>
<td>0.595</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>16.72 (7.14)</td>
<td>15.67 (5.73)</td>
<td>11.20 (5.58)</td>
<td>0.118</td>
</tr>
<tr>
<td>General symptoms</td>
<td>15.08 (6.65)</td>
<td>11.57 (4.61)</td>
<td>10.80 (2.95)</td>
<td>0.118</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>27.56 (12.07)</td>
<td>22.48 (5.91)</td>
<td>23.20 (6.98)</td>
<td>0.571</td>
</tr>
<tr>
<td></td>
<td>6.36 (5.63)</td>
<td>6.33 (4.18)</td>
<td>3.25 (2.36)</td>
<td>0.458</td>
</tr>
</tbody>
</table>

S.D.: standard deviation
KW – Kruskal-Wallis

*P≤0.05
Consultation with traditional healers and onset of FEP

Previous consultation with a traditional healer for the current illness was significantly associated with long DUP (Mann-Whitney U, \( p=0.005 \)) and high negative symptoms (Mann-Whitney U, \( p=0.013 \)). (See Table 3. for details.) Those who had consulted a traditional healer (38.5%), had a mean DUP of 65.15 weeks (S.D. 84.69) and a mean PANSS total negative score of 15.55 (S.D. 6.28), while those who had not had a mean DUP of 17.31 weeks (S.D. 33.31) and a mean PANSS total negative score of 11.72 (S.D. 4.95). Removing outliers (due to the skewed distribution of DUP) did not change the significant result (See Figure 2). There was no relationship between rural/urban status and prior consultation with a traditional healer.
Table 3.
Bivariate analysis for consultation with traditional healer.

<table>
<thead>
<tr>
<th></th>
<th>PREVIOUS CONSULTATION WITH TRADITIONAL HEALER (n=20)</th>
<th>NO PREVIOUS CONSULTATION WITH TRADITIONAL HEALER (n=32)</th>
<th>Significance (MWU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Untreated Psychosis (weeks)</td>
<td>65.15 (84.69)</td>
<td>17.31 (33.31)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Age of onset (years)</td>
<td>25.40 (8.22)</td>
<td>24.37 (7.39)</td>
<td>0.603</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>16.30 (6.37)</td>
<td>14.91 (6.52)</td>
<td>0.224</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>15.55 (6.28)</td>
<td>11.72 (4.95)</td>
<td>0.013*</td>
</tr>
<tr>
<td>General symptoms</td>
<td>26.45 (9.50)</td>
<td>23.78 (9.80)</td>
<td>0.220</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>7.00 (4.96)</td>
<td>5.71 (4.78)</td>
<td>0.290</td>
</tr>
</tbody>
</table>

S.D.: standard deviation
MWU – Mann-Whitney U
*P≤0.05
Figure 2.

Boxplot for DUP and previous consultation with a traditional healer

Although initially intending to perform multivariate regression analyses (MVR) on the significant variables in the univariate analysis, we decided against this due to the small sample size and categorical nature of the independent variables, both of which reduced power of the analysis. In view of these limitations, we felt that the results of a MVR would be of questionable validity.
DISCUSSION

In this study we sought to investigate whether individual attributions of illness causation and previous consultation with traditional healers impacted on clinical features of FEP that have been shown to have prognostic value. Specifically, we investigated associations between these cultural beliefs and behaviours and DUP, age of onset and symptoms at onset. In a context where traditional belief systems are widely adhered to and a significant proportion of the population readily consults traditional healers in the community, we deemed it important to explore these relationships.

The general demographics of our sample reflect that of the local population in the region as well as that of the individuals who were invited but declined to participate in the study. Thus we were reassured that our sample was not subject to selection bias. The hospital where the sample was recruited, receives referrals from all over the Province of KwaZulu-Natal – a geographically widespread region with several urban centers and extensive rural populations. Generally, this population is characterized by significant levels of poverty and high unemployment rates, and for many, access to mental health services is difficult and costly.

In terms of causal attributions, approximately half of our subjects invoked spiritual or traditional causes, with natural or scientific causes cited less commonly. This is a slightly lower proportion than that reported from several other LMICs. For example, a study of causal attributions in India, reported that 70% of FEP patients invoked ‘spiritual and
mystical’ causes (Saravanan et al., 2007), while another in Timor Leste reported that 73% of psychotic patients cited ‘supernatural’ causes (Silove et al., 2008). This discrepancy may be attributed to a number of factors including local cultural differences and methodological variations (including differing methods of evaluating causal attributions).

In our study, 38.5% of FEP patients reported consulting a traditional healer for the current illness prior to seeking medical treatment. This compares with rates reported in FEP patients in other LMIC contexts – a third in Zambia (Mbewe et al., 2006), 24% in Singapore (Chong et al., 2005) and 23% in Iran (Sharifi et al., 2009). It is interesting to note that in different clinical populations, this proportion increases. For example, in general psychotic patients in Malaysia (Razali & Yasin, 2008) and in Timor Leste (Silove et al., 2008), 62% and 81% respectively reported consultation with a traditional healer, while in a general psychiatric population in Bali, 87% reported previous consultation (Kurihara et al., 2006b). It is possible that patients with FEP tend to under-report previous consultation with traditional healers owing to a number of factors, including being on average a young population who may be less confident about potentially displeasing medical personnel by admitting to culturally determined behaviours. Certainly within the South African context there is the perception amongst many individuals who subscribe to traditional beliefs and practices that admission of such beliefs and practices would earn the disapproval of the majority of medical personnel. An alternative explanation for this discrepancy may be that at the onset of the illness, patients and their families tend to more readily seek medical attention; whereas later on their more ‘seasoned’ counterparts (who have perhaps become disillusioned with medical services)
tend to seek help from traditional sources. One further possibility is that the generally younger first-onset patients may be more “Westernised” in comparison with older patients who more readily look to traditional sources of help. These explanations are clearly highly speculative, and specific research comparing help-seeking behaviours between new onset and ‘chronic’ psychotic patients is required to clarify the issue.

In terms of testing associations between causal attributions as well as previous consultation with a traditional healer and the clinical features of FEP, we found a convergence between beliefs and behaviours. Specifically, both spiritual/traditional attribution of illness cause and previous consultation with a traditional healer were related to longer DUP and higher negative symptoms. This is not an unexpected finding as longer DUP is a recognized risk factor for more prominent negative symptoms (Black et al., 2001; Larsen et al., 2006). In Singapore, Chong et al (2005) reported that previous consultation with a traditional healer had no impact on DUP, while in Zambia, Mbewe et al (2006) found that a greater proportion of long DUP patients had previously consulted traditional healers than those with short DUP which is similar to our finding. To our knowledge, the present study is the first to find an association between previous consultation with traditional healers and higher negative symptoms and, in the absence of any previous research on the subject, it is the first to report an association between spiritual/traditional causal attributions and long DUP and higher negative symptoms in FEP patients. Replication in other LMIC populations of FEP patients is clearly called for before such associations can be confirmed.
One may speculate on possible reasons for these apparent associations. Mbewe *et al* (2006) found that rural patients with long DUP were more likely to have consulted a traditional healer than urban patients with long DUP (52% versus 38%). However, in our study, there was no relationship between rural status and consultation with a traditional healer, thus rural status cannot explain the association between previous consultation with a traditional healer and long DUP. A more likely explanation is simply that spiritual/traditional attributions of illness causation tend to direct an individual in the first instance to spiritual/traditional forms of healing rather than to medical services. This may lead to delays in seeking formal mental health interventions. Traditional healers are more geographically accessible and more culturally accessible to many citizens, particularly in the largely rural Province of KwaZulu-Natal. There is good evidence that a significant proportion of individuals experiencing mental health problems in this region consult traditional healers as their first port of call (Mkize & Uys, 2004) despite the fact that the services of traditional healers are often more expensive than public health services. Other factors (besides belief systems) leading individuals to traditional healers include financial barriers and societal stigma associated with the use of formal mental health services. In a qualitative study of pathways to care in this region, Mkize and Uys (2004) found that rapid access to mental health services occurred when “the first signs of psychotic features are severe, including aggressive or violent behaviour”. This supports our personal experience where families and communities tend to ignore the less socially disruptive negative symptoms; and only resort to the financially and logistically burdensome option of seeking medical treatment when the symptoms and behaviours of their loved-ones become intrusive and intolerable.
The relatively small sample size is an obvious limitation of the study and together with some missing data for certain variables may have weakened the power of the statistical analysis. Importantly, the small sample size and categorical nature of the independent variables also rendered multivariate regression analysis (MVR) redundant. In addition, using indicators of poor outcome rather than actual outcome measures limits our findings. Generalization from our results is limited by several factors including: the variability that exists in definitions of variables such as DUP; and the unique social and cultural context in which this study was conducted. Also, ours was an entirely hospital based sample which is likely not to represent all patients in this area.

The apparent links between spiritual/traditional attributions of illness causation, as well as primary dependence on traditional healers for treatment, and prognostically poor clinical features of FEP, have important public health implications. A reactionary response from mental health practitioners, where traditional beliefs and help-seeking practices are condemned, is obviously inappropriate and is to be rejected. Individuals and communities have a right to beliefs and practices of their choice and, as stated previously, in many regions traditional healers are the only carers available. Instead, our results serve to reinforce the importance of developing positive collaborative links between traditional and formal health services. Exchange of information, facilitation of referral procedures and the development of mutually respectful relationships between these two social institutions should be a priority in any public health programme within LMICs. Within our own immediate region served by our psychiatric hospital we have commenced a
project aimed at achieving these goals, involving mental health personnel and local traditional healers. We hope that, among others ends, this cooperation will lead to earlier mental health interventions for individuals experiencing their first psychotic episode.

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GENE-ENVIRONMENT INTERACTIONS IN THE ORIGINS OF SCHIZOPHRENIA

This chapter addresses the issue of how the environment acts through GxE interactions to modify risk and alter the clinical presentation and course of schizophrenia. Paper 5, “Reconciling the ‘new epidemiology’ with an evolutionary genetic basis for schizophrenia”, was published in the journal *Medical Hypotheses* in 2009. This paper presents an hypothesis that integrates novel epidemiological discoveries regarding the role of the environment, with data supporting an evolved genetic basis for the disorder.
Reconciling ‘the new epidemiology’ with an evolutionary genetic basis for schizophrenia

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S U M M A R Y
Recent epidemiological findings of variable incidence and prevalence pose a problem for evolutionary genetic analyses of schizophrenia. The author rejects models of psychosis based on balanced polymorphism and develops an alternative evolutionary model incorporating concepts of antagonistic pleiotropy, ‘cliff-edged fitness’ and gene-environment interactions. In essence, genes for psychosis are considered as ‘normal genes’ that play a fundamental role in neurodevelopment. A spectrum of genetic vulnerability exists in the population, which in the context of a toxic social environment is expressed as a continuum of psychosis. Complex bidirectional gene-environment interactions operate throughout neurodevelopment to mediate expression of the disorder. Harmful social conditions lead to epigenetic alterations in the expression of susceptibility genes/alleles. This in turn alters the trajectory of normal brain development resulting in abnormalities of neural connectivity, dysregulation of neurotransmitter and other biochemical systems, and resulting psychotic illness. In this manner, the evolved genetic make-up that defines the unique social cognitive abilities of modern Homo sapiens, also carries with it an inherent genetic vulnerability to harmful features of the social environment. Psychosis therefore, is not just a costly by-product of social brain evolution in modern humans, but is also a consequence of the unhealthy societies we create around us.

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Data versus dogma [1]
Recent systematic reviews of prevalence and incidence data on schizophrenia [2–4] have called into doubt the validity of the highly cited WHO ten-country studies of the 1980’s [5,6]. One of the core findings of the WHO studies was that the prevalence of narrowly defined schizophrenia is constant worldwide at approximately 1%. In recent reviews McGrath and colleagues have reported that the lifetime prevalence of schizophrenia varies geographically from 0.16% to 1.2% (a variation of almost 8-fold) while incidence rates vary considerably in relation to variables such as geographical site, gender, urbanicity and migration status [3,4,7]. McGrath has argued that we should be “slaves to the data” rather than ideologically clinging to old dogma and that the new epidemiology of schizophrenia “is fertile ground for the generation of new hypotheses” [1].

Rationale for an evolutionary hypothesis
One development that stems in part from the dogma of ‘constant prevalence’ is the creative and original introduction in recent years of the Darwinian paradigm into models of psychiatric disorders including psychosis [8–11]. This influential WHO finding has formed a cornerstone of various attempts to develop an evolutionary hypothesis for the origins of schizophrenia. The commonly stated rationale for adopting an evolutionary approach to schizophrenia is the following:
1. There is an equal prevalence of schizophrenia worldwide.
2. Schizophrenia is a maladaptive phenotype in that the disorder is associated with lower fecundity and shorter lifespan.
3. In terms of natural selection, schizophrenia should have ‘died out’ due to its reproductively maladaptive nature.
4. The persistence of the disorder at constant prevalence despite its maladaptive nature suggests the existence of some ‘hidden’ evolutionary advantage that compensates for the visible disadvantages.
5. Thus it is appropriate to adopt an evolutionary view of schizophrenia.

Thus, efforts to date to conceptualise schizophrenia in evolutionary terms rely on the validity of the WHO finding of constant prevalence. In the light of new evidence that suggests variable prevalence and incidence in relation to environmental factors, is the evolutionary approach now redundant (as argued by Adriaens [12])? Does variability spell the end for a Darwinian perspective on schizophrenia? Is there an evolutionary genetic mechanism that could accommodate not just phenotypic variability but also new
Balanced polymorphism models

A number of authors – starting with Julian Huxley and Ernst Mayr in their 1964 Nature paper, ‘Schizophrenia as a genetic morphism’ [13] – have developed evolutionary formulations of schizophrenia. Most hypotheses have adopted a balanced polymorphism model to explain the ‘hidden advantage’ associated with the phenotype. These models suggest that unaffected heterozygote ‘carriers’ of susceptibility genes for schizophrenia possess compensatory traits that balance the disadvantage associated with the homozygous sufferers of the disorder. For example, Kuttner and colleagues [14] suggested that the heterozygous advantage must lie within the realm of psychological functions such as intelligence, social behaviour and language. Others have invoked claims of individual advantage in the social domain [15–17] as well as group selectionist theories where advantage is accrued to the group [18–20].

However, adherents to balanced polymorphism models of schizophrenia fail to appreciate the central fallacy of this approach, that is: Advantages attributed to the heterozygote ‘carriers’ in the psychotic spectrum are invariably described in terms of social, intellectual, creative and cultural abilities. This is in fact irrelevant because the laws of natural selection demand that the heterozygous advantage must be experienced at the level of reproductive fitness to compensate for the reproductive unfitness of the homozygote sufferer. Studies of relative fertility in schizotypal disorder and in first-degree relatives (i.e. ‘carrier’ phenotypes) are contradictory and most fail to demonstrate an advantage [21–23]. For example, the study by Haukka and colleagues [23], which concludes that there is no fertility advantage in siblings of people with schizophrenia, is large enough and has sufficient power to almost rule out balanced polymorphism as a mechanism explaining the survival of schizophrenia in modern humans.

A disadvantageous by-product of human brain evolution

Does the exclusion of a balanced polymorphism model leave us with an alternative genetic mechanism that explains the central paradox of the ‘survival’ of psychosis genes? In their review of evolutionary approaches to schizophrenia, Polimeni and Reiss [20] distinguish between theories advocating “schizophrenia as an evolutionary advantage” and those advocating “schizophrenia as a disadvantageous by-product of human brain evolution.” Hypotheses relying on balanced polymorphism mechanisms clearly fall into the first category. These authors cite Farley [24] and Crow [8,9] as two authors who fall into the second category. Importantly, neither Farley nor Crow invoke specific ‘psychosis genes’ – rather they postulate that normal genes essential to brain development and function also act as vulnerability genes for psychosis, albeit at the end of a spectrum of genetic variation. In the case of Farley, these normal genes play a critical role in sociability while Crow identifies language as the human gain at the cost of a species vulnerability to psychosis.

The possibility that genetic vulnerability to psychosis is due to normal genes (rather than specific mutations, etc.) may offer an explanation for why several decades of genetic research on psychosis has failed to yield even one strong aetiological candidate. Of course many so-called ‘candidates’ have been claimed (such as COMT, NRG, dysbindin, etc.) but none of these stand up to rigorous statistical analysis of large sample genome-wide scans [25]. It is now apparent that samples of 10,000 plus patients are necessary for genome-wide scans that have the power to detect potential vulnerability genes of small effect. Such recent studies [25] have failed to detect any candidates (including those so-called ‘candidates’ claimed in previous studies of much smaller samples.) If then there are ‘no genes for psychosis’ how can a genetic basis for psychosis exist?

Epigenetic interactions

The answer lies in the form of a ‘normal gene’ model. If gene alleles involved in normal brain development and function also, in certain combinations or at certain frequencies, act as vulnerability alleles then one does not have to count on the existence of specific ‘psychosis genes or polymorphisms.’ Furthermore, as Kato and colleagues point out, psychosis may well result from the epigenetic interaction of numerous susceptibility genes of minor effect [26]. These interactions include gene–gene and gene–environment interactions. As these authors state: “The epigenetic research program may provide a new framework for the integration of genetic and environmental interactions in schizophrenia.” Thus, in developing an evolutionary model for the survival of the functional psychoses, it would seem imperative that such a model addresses both the issue of epigenetic interaction of multiple genes and the issue of environmental regulation of gene expression. Certainly in the light of epidemiological evidence that reveals highly variable incidence and prevalence of psychosis in relation to such variables as urbanicity, migration [3–5,27] and income inequality [28], gene–environment interactions must be accounted for in any model of any value.

This begs the question of how significant genes really are in relation to environmental variables. Panksepp and Moskal [29] suggest that schizophrenia “is not actively maintained in the genome” and that certain genes make one vulnerable to “epigenetic and environmental factors that promote schizophrenic phenotypes.” This is close to the model favoured by this author as it is appropriate that the genetic basis of psychosis should best be conceptualized as conferring a vulnerability to disorder rather than a disorder itself. Twin studies of schizophrenia have shown that genes contribute no more than 50% to aetiology, leaving a major role for developmental and environmental factors. However, Panksepp and Moskal [29] give too much weight to non-genetic factors, instead depending on cultural transmission as a means of survival of the psychotic phenotype. They state: “Our fascination with human quirks may have created cultural spandrels for the survival and propagation of individuals who survived less well without such cultural supports” [29]. But the complexity of psychosis lies partly in the fact that it is perpetuated by neither genetics nor sociocultural factors alone but by an interaction of both. This is largely why psychosis manifests as a protean, multidimensional and heterogenous phenomenon rather than a clearly defined and uniform disease. And this is also why the epigenetic approach gives us a useful tool for beginning to unravel the tangled relationship that exists between the genes that create vulnerability and the environmental factors that contribute to expression of disorder. The fact that environment plays a role is not sufficient reason to exclude an evolutionary scenario since one would still expect genes that confer a 50% risk of vulnerability to an ‘unfit’ phenotype to be subject to negative selection and thus removed from the human genome. The enigma remains and a putative mechanism for the survival of these genes is still required. In this author’s view, to attribute both past and present survival of schizophrenic phenotypes to “cultural spandrels” is to avoid this central challenge.

A ‘normal gene’ model

The ‘normal gene’ model proposes that normal genes or alleles that have played an integral role in human brain evolution and
neurodevelopment also act as vulnerability genes or alleles, albeit in certain combinations or at certain frequencies. We know that the genetic basis of psychosis is almost certainly polygenic, that is: multiple genes contribute to the trait. Presumably different numbers or combinations of these genes, interacting with environmental factors, give rise to a range of differing phenotypes – hence the presence of a spectrum in the clinical expression of psychosis. It is also likely that a wide array of genes is implicated, acting via differing intermediate developmental and physiological pathways. This would, in part, account for the marked heterogeneity that is evident in the psychotic phenotype. Now if the same genes that give rise to psychosis are also responsible for some critical and adaptive human trait, such as brain evolution and development, then it is quite clear why these genes (or alleles) should have and continue to defy natural selection and persist in the human genome. In this scenario one could hypothesise that certain numbers or combinations of these genes/alleles are adaptive, but that an excess number results in a maladaptive trait. So for example, smaller numbers of these genes/alleles may code for the normal development of the brain, but additional genes/alleles cause a disruption of normal neurodevelopment, which results in vulnerability to psychosis. One can imagine there being a threshold, above which there is a reduction in fitness. The Malthusian concept of increasing numbers of individuals reaching a threshold, above which fitness falls, thus provides a metaphor for this kind of genetic model. But there is no need to reinvent the wheel since these concepts of increasing fitness, a threshold and then a drop in fitness, are contained within existing evolutionary genetic models termed ‘cliff-edged fitness’ and ‘antagonistic pleiotropy’.

Nesse [30] and Keller [31] have suggested the application of ‘cliff-edged fitness’ and ‘antagonistic pleiotropy’ models respectively in the construction of an evolutionary genetic model of schizophrenia. Hoffman and colleagues have provided another useful perspective derived from their work on computer-simulated models of psychosis [32], Burns [10] has attempted to integrate these ideas into a workable model that follows below. However these concepts first require some explanation.

The British ecologist David Lack addressed the question “Why don’t birds lay more eggs?” in his 1954 book The Natural Regulation of Animal Numbers [33]. The assumption usually made is that a fit individual will have as many offspring as possible, thus ensuring maximum surviving progeny. However, studying starlings and their breeding patterns, Lack demonstrated that these birds have the greatest number of surviving offspring if they lay no more than four or six eggs [34]. The parents are unable to feed larger broods adequately, so that increasing clutch size above a threshold results in decreased overall survival. Lack proposed that a parent’s fitness is maximized by laying an optimal clutch size (rather than maximal clutch size) i.e. that which yields the greatest number of surviving offspring. Lack’s work was advanced by Mountford [35] and more recently, Nesse and Williams [36] have invoked ‘cliff-edged fitness’ functions in a number of other situations. For example, humans have higher levels of uric acid than other primates and this probably helps protect against oxidative tissue damage. However, it also causes gout in those unfortunate individuals whose levels rise above a threshold. Thus a trait is maintained because of its adaptive character, but if expressed above a critical threshold, fitness falls and the result is often damaging to the individual. One can see however, how the maladaptive genotype survives natural selection.

The concept of ‘antagonistic pleiotropy’ was introduced by Rose [37] in relation to life history theory while Charlesworth [38,39] has developed the concept specifically in regard to the evolution of senescence. Antagonistic pleiotropy is a form of balancing selection and with reference to schizophrenia “a small number of susceptibility alleles may be beneficial … while too many may be maladaptive” [31].

Finally, Hoffman and McGlashan [40] have used computerised ‘pruning’ models to simulate the production of psychotic symptoms. These experiments are based on well supported evidence regarding the neurodevelopmental and neuropathological processes operant in schizophrenia. In these models, connected circuits are pruned of the weakest links in a hierarchical manner. These authors summarise their findings thus: “Darwinian pruning of networks to levels just below the ‘psychotogenic threshold’ actually enhanced network performance in detecting linguistic meaning” [32,40]. Further pruning above this threshold resulted in the emergence of “attractor states that intrude into information processing”; this leads to the production of “spurious outputs” which they argue simulate hallucinated voices. Thus there is progressive enhancement in performance up to a threshold, beyond which further pruning results in a steep decline in function and the emergence of pathological phenomena that mimic psychosis.

Having summarised the ideas proposed by Keller, Nesse and Hoffman and colleagues, it is apparent that there is some convergence between these models. Drawing on each of them it is possible to begin to construct a specific model for the evolutionary genetics of psychosis. Importantly, the functional psychoses are considered as a single entity, albeit an entity that encompasses spectra of variation between the schizotypal and aetiological types and between the normal and psychotic ends of a continuum.

Consider the following:

1. Firstly, all humans have at least one susceptibility allele (SA) for psychosis because these alleles have been selected for their pleiotropic contribution to the evolution and development of the brain.
2. There is variation between individuals in the number of SA’s, and the presence of increasing numbers of SA’s enhances reproductive fitness up to a threshold.
3. An increasing number of SA’s corresponds with an increase in the magnitude of the phenotypic trait. In this model the trait is increasing cortical connectivity with associated neural pruning at the histological level and increasingly sophisticated cognition at the behavioural/psychological level.
4. At a certain threshold (or cliff-edge), the presence of increasing numbers of SA’s results in a sharp decrease in the fitness effects of the phenotype. These post-threshold phenotypes constitute the ‘borderline’ – psychotic spectrum (as conceived by Crow [41]). With reference to Hoffman and McGlashan [40], both the borderline and psychotic phenotypes exhibit reduced fitness. Since an increasing number of SA’s corresponds to an increase in synaptic connections (both normal and abnormal) and increased peri-adolescent pruning, the borderline – psychotic brain is characterized by reduced final cortical connectivity (which is consistent with recent research findings [42]).
5. As suggested by Hoffman et al. [32], the at-risk carrier (the borderline) exhibits normal or reduced fitness, thus negating the need for a balanced polymorphism model. Additional SA’s, environmental factors and epigenetic effects convert some of these at-risk individuals to full-blown psychotic disorder.

This model incorporates concepts of ‘cliff-edged’ fitness and ‘antagonistic pleiotropy’ and also accommodates the findings of Hoffman and colleagues. Furthermore it acknowledges the role of environmental and epigenetic effects in the conversion of the at-risk phenotype to the disorder phenotype. Importantly, the genetic basis for psychosis is conceived in terms of a ‘normal gene model’ where alleles critical in the evolution and development of the human brain also act as susceptibility alleles for psychosis. Important also is the concept of a psychotic spectrum where ‘normal’ is continuous with the ‘at-risk’ phenotype depending on the relative genetic dose and individual variation in the level of the threshold.
note is a recent study from the Max-Planck-Institute in Leipzig that showed a significant overlap between genes implicated in the evolution of human-specific cognition and vulnerability genes for schizophrenia [43]. The authors conclude that their results “are consistent with the theory that schizophrenia is a costly by-product of human brain evolution” (see [44]).

What is missing from this model is the obvious ecological fact that the position of the ‘psychotogenic threshold’ is likely to vary between populations depending on variations in the external environment. Returning to Lack and his starlings, there cannot be one fixed ‘optimal clutch size’ or threshold for all populations of starlings. In harsher and more threatening environments, one would anticipate a lower threshold (or smaller ‘optimal clutch size’). Variability in the environment is as important as variability in genetic susceptibility. This brings us back to the core problem addressed in this paper, namely: the variable incidence of schizophrenia in relation to certain environmental phenomena.

**A developmental systems approach to gene-environment interactions**

The problem is the following: If one maintains that the genetic basis for psychosis is integrally associated with the evolved genetic basis for complex normal brain structure and function in humans, then one would assume a constant prevalence and incidence of psychosis worldwide. As stated in the introduction to this paper, recent meta-analyses of both prevalence and incidence of schizophrenia reveal significant variation in relation to variables such as urban versus rural location, migrant status [3,4,7,27] and societal income inequality [28]. Are these findings reconcilable with an evolutionary genetic model of psychosis? The work of several authors suggests that the key to this reconciliation lies in the existence of complex bidirectional gene-environment interactions throughout human neurodevelopment.

Developmental psychologists, David Bjorklund and Anthony Pellegrini, address the problem of gene-environment interactions in the development of human cognition in their book The Origins of Human Nature: evolutionary developmental psychology [45]. They draw on the work of another developmental psychologist, Gilbert Gottlieb, in arguing for a ‘developmental systems approach’ (DSA). In essence this approach revolves around the concept of epigenesis, which is defined by Gottlieb as “the emergence of new structures and functions during the course of development” [46]. Epigenesis refers to the dynamic interaction of biological and environmental factors during development so that the resulting organism represents a unique individual despite species-specific or group-specific genes in common. Experimentally it has been demonstrated that experiential or environmental factors can directly alter the expression of genes during development. According to Bjorklund, Pellegrini and Gottlieb there are a number of levels, both biological and experiential, that interact and modulate each other in a bidirectional manner. Gottlieb states:

“...Activity of these and surrounding cells can turn on or off a particular gene, causing commencement or cessation of genetic activity. Also, self-produced activity or stimulation from external sources can alter the development of sets of cells. From this viewpoint, there are no simple genetic or experiential causes of behaviour; all development is the product of epigenesis, with complex interactions occurring among multiple levels” [45].

Jean-Pierre Changeux, the French neurobiologist and author of Neuronal Man: The Biology of Mind, emphasizes the fact that a relatively small number of genes give rise to the incredibly complex system that is the human cerebral cortex [48]. He writes of an ‘economy’ within the developmental system. Just a few genes can spawn a myriad of complex differentiated cells, which in turn generate unimaginable numbers of neural pathways and networks simply because there are horizontal, vertical and temporal bidirectional interactions between gene, protein, cell and environment. Regulatory genes operate to control and vary the expression and timing of maturation of other genes; certain proteins such as nerve growth factor equally modulate the interaction of cells and the formation of synapses in the developing cortex; and the amazing phenomenon of the neuronal growth cone, discovered by Ramón y Cajal, which ‘navigates visually,’ steering itself (across the developing cortex) by the cells it meets” [48], are all examples of this bidirectional process. Changeux explains how neuronal impulses are detectable in the developing nervous system of the foetus, which originate from perceived environmental stimuli. These impulses contribute epigenetically to synaptic formation and stabilization. He states:

“Impulses travel through the neuronal network even at very early stages of its formation. They begin spontaneously, but are later evoked by the interaction of the newborn with its environment... The evolution of the connective state of each synaptic contact is governed by the overall message of signals received by the cell on which it terminates. In other words, the activity of the postsynaptic cell regulates the stability of the synapse in a retrograde manner” [48].

Thus the development of the synapse, which is the site of major postnatal brain growth, depends not upon information arising centrally but rather from stimuli derived from the peripheral sensory and perceptual systems. The source of these stimuli is the environment as perceived by the perceptual organs. We therefore have clear evidence for epigenetic regulation of neurodevelopment by the environment. Of significance is the fact that nearly 80% of human brain growth occurs after birth — this reflects the growth of axons, dendritic branches and synapses as well as myelin sheaths around the axons — so we are a species readily adapted to maximize on epigenetic control of development. Furthermore, Homo sapiens experiences a prolonged juvenile period relative to non-human primates and hominid ancestors; this extends the period during which there is relative plasticity or flexibility in brain structure and cognitive function. Epigenetic processes operate when neural circuits retain plasticity; later on, once neural material is committed to specialized functions, brain and behavioural flexibility is reduced. This has given rise to the notion of ‘critical periods’ during development, when neural plasticity ‘allows’ for considerable change. Beyond a critical period, flexibility is lost and the potential for change diminished. A good (but tragic) example of this comes from work done with Romanian orphans rescued from the grossly deprived institutions of the dictator Ceaucescu’s regime. O’Connor and colleagues demonstrated that orphans rescued and adopted before the age of 6 months had equivalent mean IQ at 6 years to their British counterparts [49]. However, those orphans who were older at the time of their adoption had significantly lower mean IQ at 6 years than their UK counterparts. Reversal of early deprivation
was possible if the child was still within the critical period; those unfortunates rescued beyond the critical period... interactions (via intermediate endophenotypic processes) to clinical expression of the disorder [52].

In terms of the evolutionary genetic model elaborated in this paper, one can speculate that there exists an evolved spectrum of vulnerability (due to variable numbers of susceptibility alleles across any population) that is common to all societies worldwide. However, social, economic, cultural and political environments vary considerably. Some are more harmful than others. Harmful social conditions lead to epigenetic alterations in the expression of susceptibility genes/alleles. This in turn alters the trajectory of normal brain development resulting in abnormalities of neural connectivity, dysregulation of neurotransmitter and other biochemical systems, and resulting psychotic illness. In this manner, the evolved genetic make-up that defines the unique social cognitive abilities of modern Homo sapiens, also carries with it an inherent genetic vulnerability to harmful features of the social environment. Psychosis therefore, is not just a costly by-product of social brain evolution in modern humans, but is also a consequence of the unhealthy societies we create around us. In this way, like many other ‘socially sensitive’ diseases, psychosis acts as a measure of how well we structure and maintain the societies in which we live.

References


CHAPTER 5
MENTAL DISABILITY, INEQUALITY AND HUMAN RIGHTS

This chapter presents a human rights perspective on the inequities and inequalities that characterize the lives of those with serious mental disorders such as schizophrenia, resulting from psychosocial, political, economic and cultural forces in the environment. This is reported in Paper 6, “Mental health and inequity: a human rights approach to inequality, discrimination and mental disability” published in Health and Human Rights: An International Journal in 2010.
MENTAL HEALTH AND INEQUITY: A HUMAN RIGHTS APPROACH TO INEQUALITY, DISCRIMINATION, AND MENTAL DISABILITY

Jonathan Kenneth Burns

ABSTRACT
Mental disability and mental health care have been neglected in the discourse around health, human rights, and equality. This is perplexing as mental disabilities are pervasive, affecting approximately 8% of the world’s population. Furthermore, the experience of persons with mental disability is one characterized by multiple interlinked levels of inequality and discrimination within society. Efforts directed toward achieving formal equality should not stand alone without similar efforts to achieve substantive equality for persons with mental disabilities. Structural factors such as poverty, inequality, homelessness, and discrimination contribute to risk for mental disability and impact negatively on the course and outcome of such disabilities. A human rights approach to mental disability means affirming the full personhood of those with mental disabilities by respecting their inherent dignity, their individual autonomy and independence, and their freedom to make their own choices. A rights-based approach requires us to examine and transform the language, terminology, and models of mental disability that have previously prevailed, especially within health discourse. Such an approach also requires us to examine the multiple ways in which inequality and discrimination characterize the lives of persons with mental disabilities and to formulate a response based on a human rights framework. In this article, I examine issues of terminology, models of understanding mental disability, and the implications of international treaties such as the United Nations Convention on the Rights of Persons with Disabilities for our response to the inequalities and discrimination that exist within society — both within and outside the health care system. Finally, while acknowledging that health care professionals have a role to play as advocates for equality, non-discrimination, and justice, I argue that it is persons with mental disabilities themselves who have the right to exercise agency in their own lives and who, consequently, should be at the center of advocacy movements and the setting of the advocacy agenda.

INTRODUCTION
On October 3, 2008, The Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act was signed into law in the United States. This legislation introduced parity for mental health coverage for the first time in large group health insurance plans.1 Theoretically, this brought an end to a system in which it was legal for insurers to limit care for mental health and substance abuse conditions and to require patients to pay more out-of-pocket costs than are required for other medical conditions.2 The Act has been hailed as a progressive step toward removing inequities in access to and affordability of mental health care. At a political and public level, this may reassure those who live with serious mental disabilities and those who campaign for equality. The reality, however, is that the significant array of parity provisions at both the state and national
levels constitute a major barrier for service users and clinicians in realizing real equality as an outcome of this legislation. The Act allows health insurers to determine which mental health and substance use conditions they will cover, to define for what conditions coverage is “medically necessary,” and to gain exemption from the law if providing mental health and substance use coverage increases their costs by 2% or more in the first year or by 1% or more in subsequent years. Furthermore, as Richard G. Frank, a health economist at Harvard Medical School, has observed, people with serious mental disabilities such as schizophrenia require many services, including psychosocial and occupational rehabilitation services, which are crucial to their recovery but are not provided for by the Act.3

Thus, legislation may be enacted to reduce or eradicate inequalities in health care, but statutes on their own often introduce only “formal equality” — that is, the law treats all individuals or health conditions alike. This is a superficial and deceptive form of equality, however, as there are many social, economic, and political factors at play that obstruct the translation of a law into the real, individual experience of equality. Formal equality alone gives an illusion that all are equal and that fairness exists, without addressing underlying inequalities in power, access, and socioeconomic and political circumstances.4 In this way, formal equality alone tends to perpetuate discrimination and inequality because it often fails to address real inequality in circumstances. Under a seemingly progressive veneer of respectability, disparities grow unchecked as public advocacy groups relax their activist efforts. Thus, far from bringing about progressive change, the introduction of equality legislation can have reactionary effects, exacerbating existing disparities in health access and care.

Within the human rights framework, it is imperative that we strive to achieve “substantive equality,” defined here as equality of opportunity, within the context of structural inequalities present in society. This means that circumstances that prevent the individual from achieving equality of opportunity must be addressed and that barriers to access and empowerment must be removed. Within health care, substantive equality does not guarantee equality of treatment outcomes, but it does guarantee equality of opportunity in trying to achieve those best outcomes.5 Mental disability and mental health care are surprisingly overlooked within the global discourse on health equality, and mental health has always appeared to be a side issue in both the public and academic health debate.6 There appears to be social distaste for issues pertaining to mental health and disability.

A significant exception to this attitude was the adoption of the United Nations Convention on the Rights of Persons with Disabilities on December 13, 2006.7 The Convention was negotiated during eight sessions of an Ad Hoc Committee of the General Assembly from 2002 to 2006. To date, there have been 140 signatories to the Convention (with 59 ratifications) and 83 signatories to the Optional Protocol (with 37 ratifications). The Convention is intended as a human rights instrument with an explicit social development dimension:

It marks a “paradigm shift” in attitudes and approaches . . . from viewing persons with disabilities as “objects” of charity, medical treatment and social protection towards viewing [them] as “subjects” with rights, who are capable of claiming those rights and making decisions for their lives based on their free and informed consent as well as being active members of society.8

The Convention is broadly inclusive in terms of what is defined as disability, stating that “[p]ersons with disabilities include those who have long-term physical, mental, intellectual or sensory impairments which in interaction with various barriers may hinder their full and effective participation in society on an equal basis with others.”9 Thus, the Convention constitutes a significant global commitment to a human rights framework in which issues of achieving substantive equality and the full and unfettered rights of persons with disabilities are placed at center-stage.

The importance of this Convention (as well as that of other recent regional declarations on mental disability) cannot be underestimated; mental disabilities are pervasive, common, and responsible for a significant proportion of disability, suffering, mortality, and lost productivity in human society. The social and economic “burden” borne by individuals, their families, their communities, and nations due to men-
Mental disability is enormous.\textsuperscript{10} Co-morbidity with physical illness and substance abuse is considerable.\textsuperscript{11} The relationship between mental disability and poverty, income inequality, social dislocation and alienation, and homelessness is well supported by growing evidence.\textsuperscript{12} Mental disability impacts education, social behavior, economic productivity, and cultural norms. Moreover, in the treatment of such conditions as HIV/AIDS and drug-resistant tuberculosis, mental disability is associated with high-risk behavior, poor treatment adherence, and inability to access care. In short, mental disability is a protean phenomenon whose often hidden tentacles extend into multiple areas of human experience and functioning. And yet, in both high-income countries (HICs) and low- and middle-income countries (LMICs) throughout the world, mental health care is a low priority, receiving stunted budgets, inadequate resources, and little attention from government.\textsuperscript{13} Globally, the integration of mental health into primary care is still in its infancy, while the skills, knowledge, and confidence of generalist health practitioners in managing mental disability are pitiful.\textsuperscript{14} In most countries, the level of mental health and substance use education and knowledge within the general public is minimal, if not negligible. Inequalities in mental health service development, provision, and access exist at all levels and in different contexts.\textsuperscript{15}

The care, treatment, rehabilitation, and full integration of persons with mental disabilities is a complex challenge that cannot be met through the narrow confines of a purely biomedical or even public health model. The social, economic, cultural, and political factors that interact with innate and acquired biological processes in the genesis, course, and outcome of mental disabilities cannot be ignored in striving for equality. Efforts to improve global mental health will fail dismally if they are limited to the development of new drugs and therapeutic interventions. Likewise, attaining full human rights for persons with mental disabilities will never be achieved through a reliance on public health system reform alone.

Importantly, a human rights approach to mental disability requires a paradigm shift, as the Convention articulates, away from a public health approach in its conventional sense. A public health approach is inadequate, as it serves to reinforce paternalism and charity in identifying mental disability as a medical issue necessitating a medical “solution.” It views mental disability as a health issue only, requiring a health services response. In contrast, a rights-based approach to mental disability means acknowledging the social, economic, and political forces that result in the disability experienced by people with impairments. It also means ensuring that the principle of participation, as well as leadership by persons with disability in advocacy for substantive equality, is key to any international or domestic efforts to redress the inequalities and discrimination that exist in society. For health professionals involved in efforts to achieve real equality, a clinical role alone is ineffective. Instead, clinical expertise must be complemented by a commitment to an activist agenda in partnership with persons with mental disabilities — an agenda focused on bringing about change to the structural inequalities within social, economic, and political life that prejudice mental health, promote social exclusion, and retard recovery from mental disability.

**TERMINOLOGY AND MODELS OF MENTAL DISABILITY**

The institutionalized medical language of mental disability is, at best, pejorative and situates mental conditions squarely within an individual disease framework. Terms such as “mental disease” and “mental disorder” construct psychological, emotional, and behavioral conditions as innate, biological, pathological states independent of socioeconomic, cultural, and political context. Likewise, the prevailing medical model of mental disability — which defines disability as an individual’s “restriction in the ability to perform tasks” and handicap as “the social disadvantage that could be associated with either impairment and/or disability” — serves to establish a direct causal relationship between individual impairment and disability.\textsuperscript{16} In contrast, the social model of disability, theorized by disabled activist and scholar Michael Oliver, views disability as something imposed upon persons by an oppressive and discriminating social and institutional structure and that is over and above their impairment.\textsuperscript{17}
The concept of “impairment” is not straightforward here. In terms of mental disabilities, impairment cannot be understood as a fixed structural or mechanical “abnormality” or “departure from human normality,” as Lorella Terzi expresses it.19 Innate or acquired genetic or biological factors associated with the origins of serious mental disabilities are not fixed impairments in the sense that blindness and spinal paralysis are. Rather, these factors exist as “vulnerability factors” — rendering the individual susceptible to psychological and physical risks.20 Such is the extent to which innate or acquired vulnerability factors over time to structural environmental forces act in concert with social and environmental factors within society. Structural environmental forces act in concert with innate or acquired vulnerability factors over time to give rise to illness and disability. Complex reciprocal gene-environment interactions throughout neurodevelopment, involving both environmental mediation of gene expression and genetic influence over individual responses to environmental stressors, lie at the heart of most mental disabilities.20

**MULTIPLE LEVELS OF INEQUALITY AND DISCRIMINATION**

A rights-based approach to mental disability needs to be informed by a clear analysis of the multiple levels of inequality and discrimination that exist in relation to individuals with mental disabilities both within and outside the health system. In a sense then, a “situation analysis” is required to illustrate the clear links that exist among social, economic, political, and cultural aspects of the environment and the origin, personal experience, and outcome of mental disabilities. The following discussion details how substantive inequality and discrimination characterize the manifestation and experience of mental disability in society as well as the provision of mental health care. While this analysis is intended to have global relevance, it contains an over-representation of data from the United States. This is not because that nation is alone in experiencing the inequalities cited, but rather, it is a reflection of the fact that significant research has been conducted in this field within the US, while there is a relative paucity of evidence available from other countries.

**Unequal prevalence due to structural inequalities**

In recent years it has become apparent that the prevalence of a number of mental disabilities varies in relation to social and economic disparities within societies. For example, systematic reviews show differences in both the prevalence and incidence of schizophrenia in relation to variables including urban versus rural status, social class, migration, unemployment, homelessness, and income inequality.21 In the case of schizophrenia, social and economic factors mediate expression of the condition in biologically vulnerable individuals.22 Such is the extent to which these factors impact negatively upon both the onset and outcome of schizophrenia that Brendan Kelly has invoked Paul Farmer’s concept of “structural violence” in relation to this illness.23 Kelly argues that social, economic, and political factors such as poverty and income inequality “shape both the landscape of risk for developing [schizophrenia] and the context in which health-care is provided.”24 He maintains that these forces constitute a form of “structural violence” that impacts the development and course of schizophrenic illness. Common mental disabilities such as anxiety, depression, and substance abuse also show an increased prevalence in relation to social class, unemployment, low income, homelessness, poverty, and income inequality.25 This means that individuals, families, and communities that occupy lower social classes, that are experiencing high levels of unemployment, and that are living in poverty also bear the burden of increased risk for mental disability along with all of its associated consequences. With respect to income inequality, it appears that health depends not just on personal income but also on the incomes of others in the society.26 While individual rank within the income distribution is undoubtedly important, it is clear that a large rich–poor gap within
are discriminated against in terms of their access to mental health services and appropriate treatments. Margarita Alegría and colleagues reported that of those who had depressive disorder in the previous year, more African Americans (59%), Latinos (64%), and Asians (69%) received no mental health treatment for depression compared with non-Latino whites (40%), while Daniel Rosen and colleagues found that nearly a quarter of white women (23%) with a mental disability received treatment as opposed to only 9% of African American women. In a sample of patients with schizophrenia living in the community, Richard Van Dorn and colleagues reported that significantly fewer African American patients had received atypical antipsychotics (the preferred therapy) than their white counterparts.

Disparities in access to mental health services also exist with regard to gender. Women of low socioeconomic status have been shown to be at particular disadvantage in accessing mental health care, and there are clear barriers to accessing alcohol and substance abuse services for women compared with men. Furthermore, women diagnosed with borderline personality disorder encounter significant stigma and denial of access to optimal mental health care in comparison with women with other psychiatric diagnoses. There is a significant body of literature exploring the prejudices and discrimination that underlie the apparent gender bias in the diagnosis of this stigmatized "disorder."

Unequal service access due to structural inequalities

Social and economic factors may serve as barriers to accessing mental health services in high-income countries as well as low- and middle-income countries. A community survey in the US (a high-income country), for example, reported that low-income individuals cited financial barriers to accessing care. However, this was not the case in the Netherlands or in Canada, both HICs, where economic disparities and income inequality are lower. Also in the US, a household survey of adolescents found that those of low-income status reported far more structural barriers to accessing mental health services than did their middle- and high-income counterparts. In LMICs, the impact of socioeconomic factors is likely to be greater.

The “treatment gap” (that is, the absolute difference between prevalence and percentage treated) for mental disabilities is significant worldwide and is due to a number of factors, including lack of knowledge about mental disabilities, stigma, lack of service availability, and socioeconomic barriers to accessing available services. An earlier study in Belize, for example, reported that 63% of individuals with schizophrenia, 89% of individuals with affective conditions, and 99% of individuals with anxiety conditions were untreated. The World Health Organization Mental Health Survey conducted in 14 countries found that 76–85% of individuals with serious mental disabilities in LMICs received no treatment, while 35–50% of those in HICs received treatment. Clearly, lack of treatment cannot be attributed solely to socioeconomic barriers to access — other likely reasons have already been mentioned. However, within LMICs like South Africa, it is patently obvious that poverty, disempowerment, and inadequate health education impede access to care. In such countries with high poverty and unemployment rates, those in need often cannot afford medical fees, the medicines prescribed, or the transport to convey them to clinics and hospitals. In such contexts, it is glaringly apparent how social and economic inequities lead to inequalities in access to care.

Unequal service access due to race, ethnicity, and gender

Racial and ethnic minorities in the United States are discriminated against in terms of their access to mental health services and appropriate treatments. Margarita Alegría and colleagues reported that of those who had depressive disorder in the previous year, more African Americans (59%), Latinos (64%), and Asians (69%) received no mental health treatment for depression compared with non-Latino whites (40%), while Daniel Rosen and colleagues found that nearly a quarter of white women (23%) with a mental disability received treatment as opposed to only 9% of African American women. In a sample of patients with schizophrenia living in the community, Richard Van Dorn and colleagues reported that significantly fewer African American patients had received atypical antipsychotics (the preferred therapy) than their white counterparts. Disparities in access to mental health services also exist with regard to gender. Women of low socioeconomic status have been shown to be at particular disadvantage in accessing mental health care, and there are clear barriers to accessing alcohol and substance abuse services for women compared with men. Furthermore, women diagnosed with borderline personality disorder encounter significant stigma and denial of access to optimal mental health care in comparison with women with other psychiatric diagnoses. There is a significant body of literature exploring the prejudices and discrimination that underlie the apparent gender bias in the diagnosis of this stigmatized “disorder.”
that the mentally disabled receive unequal treatment for co-morbid physical disorders in comparison to their mentally well counterparts — meaning that a diagnosis of mental disability increases an individual’s risk of a poor outcome for co-morbid physical illness. Real and perceived discrimination contribute significantly to non-treatment, delays in accessing treatment, treatment non-adherence, and, ultimately, poorer outcomes.

Unequal funding and resource provision for mental versus physical disabilities

Globally, government funding for mental health services is disproportionately low compared with the burden of mental disability. Despite the fact that mental and substance use disabilities account for 12% of the global “burden” of disease, more than two-thirds of the world’s population lives in countries that spend less than 1% of their total public sector health budget on mental health services. Similarly, in many regions of the world, human resources for mental health care are severely limited in comparison with human resources for physical health care. Many countries, in both high-income and low- and middle-income contexts, report serious shortages of psychiatrists, psychologists, psychiatric nurses, and other mental health care professionals. This inequality in funding and service provision, in the face of the major burden of mental disability, represents global discrimination against mental disability and its care at the level of policy makers, health planners, and governments. Discriminating against those with mental disabilities by failing to pay for and provide care is particularly shortsighted as there are many effective and cheap interventions available that can be highly cost-effective in preventing co-morbidity, reducing disability, and returning mentally ill individuals to productive employment and social reintegration.

Unequal funding, resource provision, and protection from abuse across nations

Low- and middle-income countries, which arguably support the bulk of the burden of mental disability, tend to spend less on mental health services than HICs. For example, of the 19 African countries for which data are available, 15 spend less than 1% of their health budgets on mental health. An additional inequality is the fact that it is very often the poorest people in the poorest countries who are required to make out-of-pocket payments for mental health care as their governments have made little or no provision for public funding of mental health services.

Table 1 presents a comparison of the proportion of health budgets spent as well as the main method of funding for mental health among high-, upper middle-, lower middle-, and low-income countries. With respect to human resources, LMICs experience far greater shortages of mental health professionals than HICs. The average number of psychiatrists in HICs, for example, is 10.5 per 100,000 population, as opposed to low-income countries (LICs), where the average number is 0.05 per 100,000. The vast majority of HICs have established community mental health services, but only half of LMICs have this critical resource for mental health care.

Finally, whereas almost all high- and upper middle-income countries have legislated against abuse of the mentally disabled (both within and outside health care facilities), there are a significant number of

<table>
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<tr>
<th>Income Group</th>
<th>Mean percentage of the health budget spent on mental health (%)</th>
<th>Primary method of financing mental health care (% countries)</th>
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<tbody>
<tr>
<td></td>
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<td>Tax-based/Social Insurance</td>
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<tr>
<td>High Income</td>
<td>7.0</td>
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<tr>
<td>Upper Middle Income</td>
<td>3.8</td>
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<td>Lower Middle Income</td>
<td>2.4</td>
<td>78</td>
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<td>Low Income</td>
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lower middle- and low-income countries in which no such legislation has been passed. While it is con-
ceeded that legislation does not necessarily equate to an absence of abuse of the mentally disabled, it is
nevertheless likely that a complete absence of legal protection is associated with more frequent occur-
cences of abuse. Certainly this has been the case in a number of LMICs without adequate mental health
care legislation.46

A human rights approach to inequality and discrimination in relation to mental disability

The UN Convention sets out a framework for a rights-based approach to disability and in doing so
“calls for changes that go beyond quality of care to include both legal and services reforms” and
“demands that we develop policies and take actions to end discrimination in the overall society that has
a direct effect on the health and well-being of the [mentally] disabled.”47 The Convention sets out a
number of guiding principles:

- Respect for inherent dignity, individual autonomy including the freedom to make one’s own
choices, and independence of persons;
- Non-discrimination;
- Full and effective participation and inclusion in society;
- Respect for differences and acceptance of persons with disabilities as part of human diversity
and humanity;
- Equality of opportunity;
- Accessibility;
- Equality between men and women;
- Respect for the evolving capacities of children with disabilities and respect for the right of chil-
dren with disabilities to preserve their identities.48

In addition to these principles, the Convention high-
lights the importance of a number of related rights. These include the following:

- Equal recognition before the law, access to justice, and legislative reform to abolish discrimina-
tion in society;
- Awareness-raising to educate society, combat prejudices, and promote awareness of the capa-
bilities of persons with disabilities;
- The right to life, liberty, and security of person including freedom from degrading treatment, abuse, exploitation, and violence;
- The right to movement, mobility, independent
living, and full inclusion within the community
including full access to and participation in cul-
tural life, recreation, leisure, and sport;
- Freedom of expression and opinion, access to information, and full participation in political
and public life;
- Respect for privacy, for the home and the family,
including the freedom to make decisions related
to marriage and parenthood;
- The right to equal education, work, and employ-
ment including the full accommodation of individual requirements;
- The right to health, habilitation, and rehabilita-
tion;
- The right to an adequate standard of living, suit-
able accommodation, and social protection.49

With respect to mental disability, how does this framework inform our response to the inequities and
discrimination present at multiple levels of society and mental health care? Specifically, if we take these
principles and rights and apply them to the global “situation analysis” presented in the previous section,
what actions are required to transform our societies so that persons with mental disabilities experience
full equality, an end to discrimination, and full rec-
ognition of their personhood? I would propose that
such an action plan at national as well as local levels
include the following components:

1. The development of a strong advocacy movement, led
by persons with mental disabilities. Repeatedly it has
been shown that “user-led” advocacy around
issues of legal reform, services development,
and societal transformation has been most effec-
tive in ending discrimination and stigmatization
and achieving human rights for specific minority
communities.50

2. Legislative reform to abolish discrimination, to outlaw
abuse and exploitation, and to protect personal freedom,
dignity, and autonomy. Civil commitment laws that
deprive individuals of their freedom “must pro-
vide for minimum substantive and procedural protections that protect mentally ill individuals’
fundamental agency.”51 In addition, such laws
should guarantee the rights to counsel, appeal, and review in relation to involuntary commit-
tment as well as redress for violations. As men-
tally disabled persons may not be in a position
to safeguard their personal rights while unwell,
there should be a mechanism for active monitoring and enforcement of such rights. In South Africa, for example, the Mental Health Care Act (2002) legislated for the establishment of independent regional “review boards” that are tasked with Ombuds office functions.52

3. Legislative reform to enforce equality of opportunity, access, and participation in all aspects of life. While health-related legislative reform is important, this must be accompanied by legal measures aimed at rectifying inequalities and discrimination that exist with respect to the mentally disabled in social, economic, and political facets of society. Substantive equality requires attention to the social context that contributes to the origin of mental disabilities as well as to the use of mental health services by individuals.

4. Inclusion of mental disability on the agenda of development programs and targets such as the Millennium Development Goals. At international, national, and regional levels, mental disability rights and “needs” must be included in programs aimed at achieving development targets and alleviating poverty and inequality — especially within LMICs.

5. Mental health and social services reform with equitable funding for resources, infrastructure, and program development. Governments should be pressured to heed growing calls for the scaling up of health and social services relevant to mental disability as well as increased budget allocations for mental health.53 Signatories to the UN Convention and its Optional Protocol must be held accountable in terms of their domestic planning. The establishment of the Committee on the Rights of Persons with Disabilities as a monitoring organ means that citizens of States party to the Convention have a means of reporting local violations of the Convention and obtaining redress.54

6. Removal of barriers to health services access encountered by persons with mental disabilities. Legal reforms such as The Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act are required within most nations to remove financial barriers to accessing services for those with mental disabilities.55 Legislation is also required to enforce equality and outlaw discrimination based on ethnicity, race, gender, and age within health services. Finally, education campaigns and programs on mental disability and the rights of mentally disabled persons should be conducted on an ongoing basis within all health services.

7. Removal of barriers to accessing social, family-related, accommodation, educational, occupational, and recreational opportunities and to full participation for persons with mental disabilities. Legislative reforms, as well as public and institutional education campaigns and programs, should be implemented at national and local levels to remove these barriers to access, to eradicate stigma, and to ensure the full participation of persons with mental disabilities. Suitable accommodation is a fundamental right as enshrined in the Convention, and domestic policies, planning, and legal reform need to be informed by an acknowledgement of this right.

8. Service systems reform to move away from institutional care toward providing treatment, care, rehabilitation, and reintegration within the community. As Alicia Ely Yamin and Eric Rosenthal state, “From a human rights perspective, people are entitled to live in and receive care in the community not because it is more efficient, but because all human beings develop their identities within social contexts, and have rights to work and study, as well as be with family and friends.”56 Furthermore, planning and decision-making power related to care in the community needs to be transferred to “the individuals and communities that the health system is supposed to serve.”57 This means the integration of “users” and family members into both national and local decision-making structures.

CONCLUSION

Mental disability and mental health care have been neglected in the global debate on health, human rights, and equality. Within the mental health field itself, much of the debate has been at a theoretical level, with a focus on stigma concepts and attitudes rather than on acts of discrimination and on strategies to change behavior.58 Graham Thornicroft and Aliya Kassam argue that stigma research in this field is, to some extent, “beside the point” as it tends to have focused on “hypothetical rather than real situations, shorn of emotions and feelings, divorced from context, indirectly rather than directly experienced, and without clear implications for how to intervene
to reduce social rejection.” They call for a shift of focus from stigma to discrimination as this would place the mentally disabled in a position of parity with respect to anti-discrimination legislation and the human rights agenda.

The development of mental health policy and legislation within countries that have not established formal equality for mental disability is indeed a priority, and there are a number of global institutions actively engaged in this task. While highly necessary and laudable, these efforts to achieve formal equality should not stand alone, without similar advocacy focused on the achievement of substantive equality for persons with mental disabilities. Real life factors such as poverty; illiteracy; income inequality; homelessness; war and displacement; discrimination based on ethnicity, race, and gender; social exclusion; stigma; and abuse all impact the mentally ill individual’s ability to access services and realize full personhood within their communities. These factors also play a role in enhancing individual risk for mental disabilities, and so, too, they act to hinder recovery and reintegration into social and occupational life.

A rights-based approach to mental disability means domesticating treaties such as the United Nations Convention on the Rights of Persons with Disabilities. Using the framework of this convention and others like it, it is possible to formulate an active plan of response to the multiple inequalities and discrimination that exist in relation to mental disability within our communities. While health care professionals arguably have a role to play as advocates for equality, non-discrimination, and justice, it is persons with mental disabilities themselves who have the right to exercise agency in their own lives and who, consequently, should be at the center of advocacy movements and the setting of the advocacy agenda. In support of this agenda, health care professionals need to become activists for the social and economic transformation of society into an environment in which those with mental disabilities can experience substantive equality.

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2. With respect to mental health, substance abuse conditions include a spectrum ranging from problematic abuse of alcohol and drugs to addiction to so-called “dual diagnosis” conditions (co-incident substance abuse and mental disability where each compounds the negative impact of the other.)

3. Harvard Medical School (see note 1).


6. For example, mental health is notably absent from the Millennium Development Goals (MDGs). For a critique, see J. J. Miranda and V. Patel, “Achieving the millennium development goals: Does mental health play a role?” PLoS Medicine 2/10 (2005), pp. 962–965. Miranda and Patel have pointed out that even though mental disability impacts, both directly and indirectly, many areas of social and economic life, mental health is completely absent from the MDGs. They provide evidence linking mental health directly to three of the MDGs — the eradication of extreme poverty and hunger, the reduction of child mortality, and the improvement of maternal health. However, if one considers the numerous effects of mental disability on social and economic development at the individual and community levels, then it is apparent that combating mental disabilities and reducing the morbidity associated with mental disabilities must contribute to the realization of almost all of the MDGs. The omission of mental health from the MDG agenda is a good example of the inequality and discrimination that exists within the health and development discourse itself.

7. The UN Enable website was established to report all aspects of the treaty and contains information on the guiding principles, entry into force, signatories, and monitoring of the Convention, as

8. Ibid.


10. Note: the use of the term “burden” here requires clarification. The term is not used in the sense of individuals being “burdensome” or a cause of hardship for others. The term is used to describe the added social and economic responsibilities and costs associated with either living with a mental disability or being in a care-giving role in relation to a person with a mental disability.


12. For a discussion of socioeconomic factors such as poverty and inequality and their effects on mental health, especially in LMICs, see V. Patel and A. Kleinman, “Poverty and common mental disorders in developing countries,” Bulletin of the World Health Organization 81/8 (2003), pp. 609–615.


17. See M. Oliver, Understanding disability: From theory to practice (Basingstoke: Palgrave, 1996), p. 32. According to Oliver, the social model “does not deny the problem of disability but locates it squarely within society.” Disability is “the disadvantage or restriction of activity caused by a contemporary social organization which takes no or little account of people who have . . . impairments and thus excludes them from participation in the mainstream of social activities.”

roots of disability” excludes other important dimensions of disability, such as the role of culture and cultural processes in shaping disabled persons’ position in society. Terzi also questions the validity of the “break-up of the causal link between impairment and disability, and the consequent causality established between society and disability.”

19. Terzi (see note 18).


24. Kelly (see note 23).


33. Ibid.


38. For a review of stigma experienced within the health services by people with mental disability, see D. Lawrence and R. Coghlan, “Health inequalities and the health needs of people with mental illness,” *NSW Public Health Bulletin* 13/7 (2002), pp. 155–158.


40. For discussion of differential care of co-morbid physical illness in those with mental disabilities within HICs, see A. Bahn and C. Forchuk,


42. Shah and Beinecke (see note 41).

43. World Health Organization (2005, see note 41).

44. Shah and Beinecke (see note 41).


46. Mkize (see note 39); and Mental Disability Rights International and Center for Legal and Social Studies (see note 39).


48. UN Enable (see note 7).

49. Ibid.


51. Yamin and Rosenthal (see note 47).


54. UN Enable (see note 7).

55. Harvard Medical School (see note 1).

56. Yamin and Rosenthal (see note 47).

57. Ibid.


59. Ibid.


CHAPTER 6
CONCLUSION

In this concluding chapter I will review the main findings and conclusions of this research, highlighting the key contributions to the field; I will address important limitations and weaknesses of the research; and I will identify the priority areas for future research in this important field.

6.1 MAIN FINDINGS AND CONTRIBUTIONS TO THE FIELD

The central aim of this thesis has been to investigate the role of the environment in contributing to risk and clinical presentation at onset of psychosis. In examining aspects of the environment, I have focused on psychosocial (exposure to trauma, cannabis use), socioeconomic (income inequality) and cultural (causal attributions and pathway to care) issues that are contextually important in South Africa. South African society is characterized by high levels of poverty and inequality, traumatic violence and substance use/abuse. Importantly also, many citizens of this country (especially in KwaZulu-Natal Province) subscribe to culturally-determined belief systems and practices that impact on many aspects of their lives, including their patterns of treatment-seeking behaviour. In my view, the focus on these important environmental issues in this research is therefore justified. In addition, I would argue that any discussion of the role of the environment in relation to psychosis and schizophrenia must incorporate a focus on two directly related issues that are relevant to both research and clinical practice. Firstly, in what could be termed this ‘post-gene age’ in the search for the origins of behavioural and psychiatric
disorders, it is critical that we engage with the burgeoning field of ecogenetics and gene-environment research (Van Os et al, 2008). And secondly, as a mental health researcher and clinician living and working within a middle-income country context, it would be remiss of me not to address the way in which psychosocial, political, economic and cultural forces in the environment contribute directly to the inequities and inequalities that characterize the lives of those with serious mental disorders such as schizophrenia.

The main findings of this thesis that could be considered modest contributions to the field include the following:

**Income Inequality may be a risk factor for psychotic disorders:** Specifically, increasing income inequality measured at the ecological level is associated with increasing treated incidence rates of FEP. Measures of poverty on the other hand do not appear to increase risk and may in fact correlate with lower incidence rates. This distinction between income inequality and poverty is important as it extends the study of socioeconomics and psychosis beyond a simple focus on ‘socioeconomic status’ (a concept that is rather vague and non-specific.)

**A significant proportion of FEP patients in this context have experienced interpersonal trauma and discrimination:** A large number of FEP patients (40-50%) reported experiences of significant trauma and discrimination and, while this is not entirely surprising within the South African context, it highlights the importance of
considering trauma as a contributory factor to aetiology and alerts us to the possibility of co-morbid mood and anxiety disorders (Muller et al, 2004).

**Experiences of trauma and discrimination are associated with positive and affective symptoms at onset of psychosis:** This lends support to the argument that the risk-increasing effect of trauma (for manifesting significant positive symptoms) is related to interpersonal events in particular (Krabbendam, 2008). It also suggests that interpersonal traumas beyond early childhood abuse (such as witnessing a serious violent act and being a victim of discrimination and racism) and extending into later developmental stages (such as adolescence and early adulthood) are also predictive of positive and affective symptoms at onset. Notably, users identify the toxic effects of discrimination as an important factor impacting negatively on onset and course of schizophrenia (Van Zelst, 2008). Finally, the current results lend support to the suggestion that that the negative effects of discrimination might operate through ‘social defeat’ (Cantor-Graae and Selten, 2005) and the “affective pathway” to increase risk for psychotic illness (Myin-Germys and Van Os, 2007).

**Cannabis use is associated with positive prognostic features of FEP, but only if cannabis use is not ongoing after the first episode:** Specifically, patients who used cannabis had a shorter DUP (possibly related to disruptive behaviour related to the high potency of local cannabis) and relatively low negative symptom scores. This symptom cluster suggests a better prognosis, however we know that ongoing co-morbid cannabis use is predictive of a poorer outcome. Our results therefore support the conclusions of
Baeza and colleagues (Baeza et al, 2009) that outcome may be favourable where cannabis use ceases (and one might speculate that cannabis itself was aetiologically significant), but is likely to be poor where use continues as a dual diagnosis. This hypothesis does not contradict the widely accepted evidence for a gene-environment mechanism underlying the role of cannabis as a risk factor. Instead one might speculate that where cannabis use premorbidly has been high and genetic susceptibility relatively low, such individuals presenting with FEP may have a better prognosis. Conversely, one might speculate that non-cannabis users who develop FEP may have a greater genetic susceptibility and therefore a relatively poorer course and outcome can be anticipated. Clearly, ongoing co-morbid cannabis use predicts a still poorer course and outcome.

Many patients with FEP in KwaZulu-Natal adhere to traditional and supernatural beliefs about causation of their illness and many consult traditional healers prior to presenting to medical services: This is an important fact that needs to be acknowledged in clinical and research practice in this context. It bares witness to the diverse nature of this society; and also may indicate a greater reliance on traditional health resources (in part) due to a lack of availability of and access to community-based mental health services in this region. Certainly the current findings highlight the importance of training mental health professionals in South Africa to be culturally sensitive and aware in their practice.
Adherence to traditional and supernatural beliefs and treatment-seeking behaviours may contribute delays in accessing formal psychiatric care and impact negatively on course and outcome: This clearly highlights the need for positive engagement with traditional healers in the community with a view to fostering a collaborative relationship focused on improving pathways to care.

Complex bi-directional gene-environment interactions underlie the onset of FEP and schizophrenia: While this is a widely supported concept, Paper 5 in this thesis represents an attempt to integrate two important areas of research, demonstrating that they are not incompatible. I present an hypothesis whereby a spectrum of evolved genetic vulnerability to psychosis may or may not be expressed at the phenotypic level depending upon individual degrees of exposure to psychosocial, economic and cultural risk factors in the environment.

Multiple inequalities characterize the lives of those with serious mental disorders owing to psychosocial, economic, political and cultural forces in the environment. This reality calls for a human rights response: If such inequalities increase risk for psychotic illness and schizophrenia and impact negatively upon course and outcome, then it is clear that a broader approach is required (beyond the confines of a medical framework) to reduce risk, reduce morbidity and enhance the quality of life of sufferers.
6.2 WEAKNESSES AND LIMITATIONS OF THE FINDINGS

Within each of the data-based papers, specific weaknesses of the methods and limitations of the findings are reported. There are however, a number of more general issues that serve to limit the overall conclusions of the thesis. These include:

Both studies reported were conducted on hospital-based patients with FEP: In terms of estimating the true incidence of FEP, recruitment of a hospital-based (treated) sample alone, by definition, does not allow one to estimate the true incidence. The incidence rates reported therefore in Paper 1 must be regarded as probable under-estimates of the true incidence within the regions studied. Recruitment of hospital-based patients only in the second (prospective) study may also have resulted in selection bias, although it is not clear how this bias may have influenced the results obtained.

Small sample sizes may have led to a loss of power to generate significant results and limit the generalisability of results: This was specifically a significant limitation in the second study where it would have been desirable to have a larger sample in view of the fact that multivariate regression was the preferred method of data analysis.

Specific critiques of methodological decisions: These have been discussed in Papers 1 to 4 and include: the fact that Income Inequality might be considered a rather vague and non-specific concept that undoubtedly subsumes many component factors; the timing of exposure to trauma was not recorded; cannabis use was based on self-report only
(although see evidence of Koen et al, 2007); and no formal instrument was used to
determine cultural beliefs and attributions (although I argue that our method was sound).

Using DUP, AO and symptoms as proxies for outcome is an inferior method of
measuring impact on outcome itself: As discussed extensively in Chapter 1 and within
Papers 2, 3 and 4, our methods in this study allowed only for the investigation of the
impact of environmental factors on clinical features of psychosis onset (that are proxies
for outcome (Harrigan et al, 2003)) – not for the investigation of the impact of
environmental factors on outcome itself. A longitudinal follow-up study of outcome
would naturally be the ideal method for addressing this question (Van Os and Rutten,
2009).

The field of genetics and ecogenetics is evolving so quickly that the gene-
environment mechanisms reported in this thesis are quite likely already outdated:
Since acceptance for publication of Paper 5 in late 2008, the field of psychiatric genetics
has moved on at a rapid pace. Genome-wide association scans (GWAS) are now the
gold-standard (Gejman et al, 2010; Duan et al, 2010), there is significant interest in copy
number variations (CNVs) (Bassett et al, 2010) and methods for GxE study have become
more complex and ingenious (Lataster et al, 2010).

Advocating a human rights framework for addressing inequities may be
strategically sound, but in practice it is very difficult to effect change: While the
message of Paper 6 is sound and is justified by the evidence for numerous inequalities
with respect to those with mental health disabilities, it is arguably a somewhat idealistic plea for transformation of attitudes and practices. For example, health workers are constrained by their ‘medical model’ of training and practice, while politicians and administrators are constrained by ignorance, bureaucratic processes and other priorities. The public generally lack education on mental health matters; and patients themselves are often ignorant of their illnesses, their rights and their prospects for recovery. In middle-income countries such as South Africa, people with serious mental disorders are commonly disempowered and lack a strong advocacy movement. All these factors act as barriers to effecting changes that would enhance the rights and wellbeing of people with mental disabilities.

6.3 MAIN PRIORITIES FOR FUTURE RESEARCH AND PRACTICE

In this final section, I discuss the implications of this research for helping identify priorities for future research and practice in this field:

6.3.1 Priorities for future research on psychosis, schizophrenia and the environment:

- As we move into an era where there is once more increasing recognition of the role of the environment in determining risk and in shaping course and outcome for psychosis, we need to design and conduct sophisticated studies that focus on the impact of the environment on illness onset, course and outcome. Such
research should investigate both risk factors and protective factors. For example, the role of *social capital* needs to be explored in depth, as early studies seem to indicate that living in a community with high social capital both reduces risk and improves outcome for schizophrenia and other mental disorders (Whitely and McKenzie, 2005; Kirkbride et al, 2007; Lofors and Sundquist, 2007).

- Novel designs are required to develop methods of investigating community-level environmental factors (such as social capital and income inequality) at the individual level. Furthermore, it is important in investigating community-level (or ecological) factors to identify the multiple contributory factors that are undoubtedly subsumed within these rather vague and non-specific concepts. For example, social capital incorporates aspects of neighbourhood trust, social connectedness and involvement, social support and network size and shared values (Harpham et al, 2002).

- Good GxE designs are required to unravel the complex contributions of gene and environment to risk for and course of psychotic disorders (Van Os and Rutten, 2009). In developing country contexts such as South Africa, this is a field of research that is rich with genetic diversity and multiple environmental factors such as trauma, poverty, inequality, substance abuse and infectious diseases (e.g. HIV). The opportunities therefore exist for important contributions to this field to emerge within this context.
• It is imperative to address the question of how HIV infection impacts on the epidemiology, course and outcome of psychotic disorders in South Africa. This question is of global importance: for understanding HIV/AIDS itself; for understanding the contribution of neurotropic viruses to brain disorders; and for understanding better the protean manifestations of psychotic illnesses within a context characterized by an HIV pandemic. There is little data from Sub-Saharan Africa contributing to a better understanding of the differences in clinical presentation of psychosis due to HIV infection of the brain and other forms of psychosis such as schizophrenia. The wider literature on HIV psychosis indicates that the presence of prominent affective and cognitive symptoms as well as rapid fluctuations in symptom profile may support this diagnosis (Treisman and Angelino, 2004; De Ronchi et al, 2006; Saunders, 2006). In the current study, although efforts were made to exclude participants with clear HIV/AIDS disease, it is not clear to what extent the high prevalence of HIV seropositivity in the sample (22% of those tested) as well as the presence of antiretroviral treatment may have impacted on the symptom profile of the sample. The small sample size in this study precluded analyses that might have addressed this issue. Future research in larger samples needs to seek answers to this important question and generate important evidence that will help clarify the phenomenology, clinical features and clinical course of psychosis due to HIV infection.

• While the World Health Organisation (WHO) conducted a number of multisite epidemiological studies of schizophrenia within both high and low- and middle-
income countries during the 1970s, 1980s and 1990s (World Health Organization, 1973; Jablensky et al, 1992; Hopper et al, 2007), these studies did not investigate the role of the environment in predicting risk, course and outcome. Huge changes have occurred on the African continent since the WHO studies (with mass urbanization, migration, conflicts and HIV-AIDS) and the conclusions of those studies need to be re-examined in the contemporary period. For example, the WHO finding that course and outcome of schizophrenia is better in ‘developing countries’ (in comparison with ‘developed countries’) has become an axiom in the psychiatric literature, but is a finding subject to extensive criticism and doubt (Cohen et al, 2008; Burns, 2009). We therefore need good community-level epidemiological studies and longitudinal follow-up studies of FEP and schizophrenia in order to better understand the distribution, onset, course and outcome of these common disorders within a context characterized by multiple environmental hazards.

Given the importance of early and effective intervention in FEP and schizophrenia, we need to focus our efforts on carefully defining the various pathways to care of people suffering from these disorders. As the current research has indicated, the pathway to care within low- and middle-income countries (LMICs) such as South Africa is by no means straightforward. Multiple factors specific to LMIC socioeconomic and cultural contexts impact on and shape pathways to care. Poverty, disempowerment, lack of mental health education, lack of access to formal services, language and cultural barriers and a strong reliance
on traditional forms of treatment all contribute to people’s treatment seeking
decisions and behaviours. This means one cannot simply apply models of
treatment seeking that have been derived from high-income countries to LMIC
contexts. Rather, multidisciplinary community-based research studies that
incorporate qualitative and ethnological methods are required to arrive at an
understanding of pathways to care that can then reliably inform the development
of interventions that are contextually relevant and appropriate.

- In view of the fact that many people with first-onset psychosis in this context
consult traditional healers prior to seeking formal medical care, future research
should explore both the healing practices employed by traditional healers in
respect of psychosis and the attitudes of traditional healers to referring such
patients onwards to medical services. In the current FEP study, no participants
had been referred directly by traditional healers to medical services – all were
referred by district hospitals, primary care clinics, general practitioners, family
members or the police services. Further research in this area should focus on
understanding the reasons for non-referral by traditional healers with a view to
planning interventions aimed at improving communication and cooperation
between formal and traditional health sectors.

- Finally, there is a need for the development of a science of adaptation, testing and
dissemination of community-based interventions for serious mental disorders in
South Africa and other LMICs. The building of such a foundation would provide
a solid platform for new generation genetic and other basic science research on serious mental disorders within the LMIC context. This development, I believe, would have great relevance and importance for the global research effort on serious mental disorders.

6.3.2 Priorities for future practice and intervention related to psychosis and schizophrenia.

- The results of this research highlight the importance of working constructively with traditional healers in our communities to develop effective, culturally sensitive methods of investigation and intervention in relation to psychotic and other common mental disorders. Such initiatives have proved successful in KwaZulu-Natal (KZN) in respect of HIV and TB education, detection and care programmes (Colvin et al, 2001; African Press International 2010). In this respect, the author has initiated a programme in the greater Pietermaritzburg region of KZN in which local traditional healers and mental health care professionals at Town Hill (Psychiatric) Hospital meet to discuss respective models of understanding mental illness and treating it. It is hoped that this initiative will develop into a collaboration aimed at: a) building both formal and informal community-based detection and care services for those with mental illness; b) improving pathway to care for those with incipient mental disorders such as FEP; and c) improving the sensitivity of mental health care professionals to important culturally determined beliefs and practices in the community.
Given the high prevalence of experiences of significant trauma in our FEP study cohort, it is essential that we modify our existing practices to include routine assessments of these and other patients with mental disorders for co-morbid psychopathology related to trauma (e.g. PTSD). Untreated co-morbid disorders due to trauma are likely to impact negatively on the course and outcome of psychosis (Seedat et al, 2003). Results from the current research suggest that prognosis (at onset) may in fact be better for those FEP patients who have a history of significant interpersonal trauma (than for those who don’t). Obviously this relatively positive prognosis is contingent upon these individuals receiving timely and appropriate treatment for any co-morbid trauma-related psychopathology.

If the negative effects of cannabis use (on outcome of psychosis) in patients with FEP relate mainly to ongoing use after the first episode, then it is critical that cessation of cannabis use becomes a major goal of treatment of FEP. While it is often difficult (due to structural constraints) to emulate within LMIC contexts the highly sophisticated multidisciplinary FEP treatment programmes that exist in well-resourced high income countries such as Australia, the Netherlands and Britain, it is possible to focus the limited resources that do exist on simple interventions to reduce substance abuse. This is an important consideration at both the level of policy development and planning as well as at the level of service provision.
Finally, enumerating the multiple inequities and inequalities that result in ongoing discrimination against people with mental disorders in our societies, must lead us to an acceptance that an important part of our work as mental health professionals must be advocacy for the human rights of our patients. Furthermore, incorporating a human rights perspective of mental disability will help mental health professionals to move beyond the narrow confines of their medical training and experience. Specifically: It will help focus their efforts on advocacy for the scaling-up of health and other services for the mentally disabled; It will help them engage meaningfully with their patients, empowering them as equal partners in the healing process; And it will help them appreciate the profound influence of the psychological, social, economic, political and cultural environment on the onset, experience and outcome of schizophrenia and other serious mental disorders.
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medication: A study with risperidone long-acting injection. *International Journal of 
Clinical Psychopharmacology* 23(6): 325-331.


Dear Jonathan,

I am pleased to confirm that your paper "Exposure to trauma and the clinical presentation of first-episode psychosis in South Africa" has been accepted for publication in Journal of Psychiatric Research.

Comments from the Editor and Reviewers can be found below.

Thank you for submitting your work to this journal.

With kind regards,

Florian Holsboer
Editor-in-Chief
Journal of Psychiatric Research
Divison of Psychiatry

Prof CP Szabo

5th March 2010

To Whom It May Concern

RE Cannabis use predicts shorter duration of untreated psychosis and lower levels of negative symptoms in first-episode psychosis: A South African study

This serves to confirm that the above mentioned paper, authored by Dr J Burns, has been accepted for publication in the African Journal of Psychiatry.

Christopher P. Szabo
Editor-in-Chief
African Journal of Psychiatry

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4 May 2010

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Dear Dr Burns

Article Reference Number: 4260B

Title: Causal attributions, pathway to care and clinical features of first-episode psychosis: a South African perspective

I am writing to let you know that the revised manuscript of the above article has been accepted for publication in the International Journal of Social Psychiatry.

Your amended manuscript will be forwarded for typesetting and the proofs will be sent to you for checking as soon as they are ready. Please be aware, though, that due to the amount of accepted papers already being held for publication, this may take several months.

Please also return a signed copy of the enclosed Journal Contributor's Publishing Agreement. This should be sent to Andrea Livingstone, the Editorial Assistant.

If you wish your article to be freely available online immediately upon publication (as some funding bodies now require) you can opt for it to be included in SAGE Open on payment of a publication fee. Manuscript submission and refereeing procedure is unchanged, but on acceptance of your article you will be asked to let SAGE know directly if you are choosing SAGE Open. For further information, please visit http://www.sagepub.co.uk/sageopen.sp. Authors wishing to publish their papers under the SAGE Open scheme should contact Richa Diwan (richa.diwan@sagepub.in).

Thank you very much for submitting your findings to this journal.

With best wishes

Yours sincerely

Professor Dinesh Bhugra
Editor
APPENDIX B

ADDITIONAL NOTES
The FEP study context

[Chapter 3 (Paper 2), page 35] The catchment area for the FEP study was not well described and further information on this important area is provided. The study was conducted at a 250-bed psychiatric hospital in the KwaZulu-Natal Midlands. This institution is the major psychiatric hospital in the region and its catchment area therefore includes a large proportion of the province, including the cities of Durban and Pietermaritzburg as well as large semi-rural and rural regions to the west and south. The catchment population is estimated to be approximately 5 million people. Due to a requirement in mental health legislation, individuals with mental disorders requiring hospital admission have to be treated for a minimum of 72 hours in general district hospitals before being referred to the psychiatric institution. Mental health professionals are generally not available at district hospitals, especially in rural regions. In addition to district hospital services, primary health care clinics exist in most areas, where basic mental health care can be accessed. Due to the shortages of psychiatric facilities and mental health professionals in the wider region, individuals in the community with mental health problems only tend to gain admission to the psychiatric hospital if they are actively psychotic and behaviourally disruptive. All of these hospital and community-based services are free for indigent people, while a small payment is made for those with income. Nevertheless, costs associated with transporting ill relatives to hospital are a barrier to access for a significant proportion of the population (although ambulance and police services often transport patients to hospital, even great distances.)

It is possible that the specific context in which this study was conducted may have resulted in selection bias of the sample. Since the sample was hospital-based, it is true
that one is sampling from a population of patients who tend to be more socially disruptive (and who may have more acute positive symptomatology.) This is a further possible limitation of this study.

**The impact of urbanicity on FEP**

[Chapter 2 (Paper 1), page 332] The analysis of treated incidence of psychosis and measures of poverty and inequality included urban versus rural status as a covariate. The effect of urbanicity was not presented or discussed in the paper. In fact urbanicity did not have an effect on treated incidence in this sample (Pearson’s correlation 0.557; Sig (2-tailed) 0.194). This is surprising considering the known increase in incidence associated with urbanicity in developed country studies.

[Chapter 3 (Paper 2), page 41] In Table 2, the final Cox regression model for DUP and trauma exposures is presented. In this model, longer DUP is significantly associated with rural status ($p=0.05$). Mean DUP in rural participants was 46.3 weeks (SD 77.5; range 2-260), while in urban participants it was 28.8 weeks (SD 51.7; range 1-208). A likely explanation is the following: in KwaZulu-Natal, rural communities tend to be far less affluent than their urban counterparts. In fact, most rural regions in the province are characterized by significant poverty. In addition, mental health services are less available and accessible in rural areas – psychiatric services are largely concentrated in urban centers. There are thus a number of barriers to accessing treatment for rural residents – financial constraints, unavailability and cost of transport and removal from psychiatric services. It is not surprising then that patients coming from rural regions should experience a longer period without formal treatment than their urban counterparts. This finding highlights in a very clear manner how
poverty contributes indirectly to poorer mental health outcomes – as we know, delayed treatment in FEP correlates with poorer course and outcome.

**The Gini coefficient**

[Chapter 2 (Paper 1), page 334] In Paper 1, the Gini coefficient was referred to erroneously as the ‘GINI coefficient’, implying that this is an acronym. In fact ‘Gini’ is the surname of the statistician who described it.

**Gender difference in the FEP sample**

[Chapter 3 (Papers 2, 3 and 4)] The FEP sample in this study had a clear predominance of male participants – 38 males (70%) and 16 females (30%). This sex difference was not discussed in this chapter. It is important to clarify whether this difference reflected the true underlying sex difference in psychosis in this population or whether it was an artifact of sampling from a hospital population. The male preponderance of this study sample reflects the sex difference in hospital admissions of patients with FEP. In fact, an almost 2:1 ratio of male: female exists in all admissions of patients with psychotic disorders to this hospital (and to other psychiatric hospitals in the province.) This is unlikely to reflect an actual male: female difference in prevalence and incidence of psychosis in the general population, but unfortunately we do not have local epidemiological data to confirm this assumption. Since access to psychiatric hospitals is limited by a host of factors including poverty, geographical separation of large rural communities from urban-centered services and a shortage of psychiatric beds within institutions, patients with psychotic disorders tend only to gain admission to psychiatric hospitals when their symptoms are socially disruptive. Cannabis use may play a role here as use is much higher in men than
women and may contribute to more disruptive symptomatology, thereby leading to the preponderance of men gaining admission. Another possible factor may be that referral of women to hospital is not socially sanctioned as it is for men – since clearly defined domestic roles for women exist almost universally within this context, and their absence from the home tends to be discouraged.

**Measurement of previous trauma and experiences of discrimination/racism**

[Chapter 3 (Paper 2), page 35] Some elaboration is required on the methods used in recording data on previous exposure to serious trauma and experiences of racism and discrimination. This is important as a variety of formal instruments exist for eliciting data on previous trauma (e.g. the trauma exposure items from the Composite International Diagnostic Interview - CIDI). Other instruments commonly used in this literature include: The Childhood Trauma Questionnaire (CTQ) (Bernstein et al, 2003); The Davidson Trauma Scale (DTS) (Davidson et al, 1991); The Life Events Checklist (LEC) (Gray et al, 2004); and the Childhood Experience of Care and Abuse (CECA) (Bifulco et al, 1994).

In this study, no formal instrument was used as validation of instruments is a perennial problem in LAMIC contexts. Study participants were asked a number of structured questions with options of a ‘yes’/’no’ answer. Regarding witnessing a serious violent act, 2 questions were asked and an affirmative response to either resulted in the participant’s response being recorded as ‘yes.’ (These questions were: “Have you ever witnessed someone being beaten up?” and “Have you ever witnessed someone being killed?”) Regarding sexual assault, participants were asked “Have you ever been sexually assaulted?” For experiences of racism and discrimination,
participants were asked two questions and an affirmative response to either resulted in the participant’s response being recorded as ‘yes.’ (These questions were: “Have you ever personally experienced racism against yourself?” and “Have you ever felt discriminated against?”) Notably, in all cases except for one, participants’ responses for these two questions were the same (i.e. ‘yes and ‘yes’ or ‘no’ and ‘no’.)

There are some limitations to this method of eliciting information about previous trauma. Firstly, it is possible that participants’ responses may have been influenced by the presence of psychotic symptoms. For example, it is conceivable that an affirmative response to any of these questions may have been motivated by persecutory delusions rather than by recall of true events. However, this risk of false positive responses is likely to be a factor in any research on trauma performed in individuals with psychotic disorders – regardless of whether a formal instrument is used or an informal method such as in this study. A strategy that could be employed to reduce this risk of false positive responses in this population is to control the analysis for level of positive symptoms. In this study, the small sample size precluded such an analysis being performed reliably.

**Local literature on explanatory systems for psychosis and the role of traditional healers**

[Chapter 3 (Paper 4)] The literature review in Paper 4 on causal attributions and the use of traditional healing services by patients was perhaps a little narrow and did not draw much on local literature. In part this is because local literature tends to be general rather than specific; and citation of literature in journal articles needs to be specific and selective. It is important though to demonstrate the breadth of local
Sorsdahl and colleagues (Sorsdahl et al, 2009) reported from a national survey of common mental disorders that a minority of those with a DSM-IV diagnosis consulted traditional healers (only 9%), with the majority of these being older, of black ethnicity, unemployed, having lower education and being more likely to have a diagnosis of anxiety disorder or substance abuse. With respect to psychotic disorders, Temmingh and Oosthuizen (2008) found in a Cape Town sample that only 5.6% of patients with either FEP or multi-episode psychosis consulted traditional healers at some point in their pathway to care. This is far lower than the 39% reported in the current FEP sample (Paper 4), the 71% reported by Ensink and Robertson (1999) in an African sample in Cape Town, and the 84% reported by Koen and colleagues (Koen et al, 2003) in a large Xhosa schizophrenia sample. Notably, all three of these latter studies were conducted in either Xhosa (Koen and colleagues; Ensink and Robertson) or predominantly Zulu (Burns and colleagues) patients – this may explain the higher proportion in comparison with the two former studies (Sorsdahl and colleagues; Temmingh and Oosthuizen) which were likely to have been more multicultural samples.

In relation to causal attributions of symptoms of a psychological, emotional or psychopathological nature, a number of authors have researched and described the common explanatory categories recognised within traditional African healing systems in South Africa. These authors concur in their findings that the major categories include both causes of a natural/environmental nature and causes of a
spiritual/metaphysical nature. Traditional healers recognize hereditary causes, substances of abuse, stress and psychological conflict as well as a variety of supernatural causes (Ensink and Robertson, 1996; Mufamadi, 2001; Mzimkulu and Simbayi, 2006). Supernatural causes include: possession by ancestral spirits; possession by evil spirits; bewitchment; and failure to follow the counsel of ancestors. Furthermore, traditional healers differentiate between illnesses which signify a calling to training as a traditional healer (ukuthwasa) and illnesses which signify possession (amafufunyana) or simply ‘madness’ (ukuphambana) (Zabow, 2007). Niehaus and colleagues (Niehaus et al, 2004) reported that Xhosa patients with schizophrenia themselves recognize and accept traditional healers’ diagnoses of both ukuthwasa and amafufunyana. In a sample of 247 adults with schizophrenia, 53% reported a previous diagnosis of amafufunyana, while 4.5% reported a previous diagnosis of ukuthwasa. Interestingly, the latter patients were more likely to have a family history of either schizophrenia or any psychiatric disorder – the authors suggest that the “identification of cases as amafufunyana and ukuthwasa may correlate with a distinction between sporadic and familial cases of schizophrenia.”

Finally, the issue of collaboration between formal medical services and traditional healers is topical in South Africa. Since 1994, the South African Government has worked actively to promote the registration and recognition of traditional healers. It has also included in its health policies an exhortation to develop collaborative partnerships between formal health services and traditional healers (Peltzer, 2009). The national mental health policy was approved in 1997 and urges collaboration between mental health services and traditional healers who form an important community resource (Department of Health, 1997). Regrettably, the government has
failed in terms of dissemination and implementation of this policy (Draper et al., 2009). The norms and standards published for a primary health care package also specifically states “Staff respect and where appropriate seek collaborative association with local traditional healers” (Department of Health, 2000). Several projects aimed at developing a cooperative relationship between these two important sectors have already commenced (South African Depression and Anxiety Group, 2010; and see discussion of a local project of the author’s on page 133 of this thesis); and their successes to date give hope that such cooperation is possible and not just a pipe-dream.

Genetic contribution to aetiology of schizophrenia

[Chapter 4 (Paper 5)] In this paper, a statement was made that “Twin studies of schizophrenia have shown that genes contribute no more than 50% to aetiology, leaving a major role for developmental and environmental factors” (page 354). This statement is erroneous and misleading. One cannot in fact attribute portions of causality to genes as complex gene-environment interactions underlie the origins of this disorder (as discussed in Paper 5). A more accurate statement would be the following: “Recent studies indicate that heritability (the proportion of variance that can be attributed to genetic factors) in schizophrenia is in the region of 80% (Sullivan, 2005; Wray and Visscher, 2010).”