Geographical variation in incidence of first episode psychosis by place at birth vs place at onset and relationship to the social environment in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS)

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I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree, MD, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

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The following publications are offered in support of this thesis (please see Appendix I):


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Summary

Examination of spatial variation is an important line of epidemiological research that can help improve our understanding of the aetiology of psychosis. Geographical variation by place at birth would implicate factors operating during gestation and early childhood, while variation by place at onset would implicate later factors that precipitate the onset of psychosis. Further, there is a dearth of literature on the associations between the social environment and risk for psychosis within rural settings. This thesis sought to examine the relationship between the environment and incidence of first episode psychosis using data from the Cavan-Monaghan first episode psychosis study (CAMFEPS) accrued during the 12-year period 1995-2007. First, geographical variation in incidence of first episode psychosis by place at onset vs place at birth was investigated using Bayesian methods. Second, both ecological analyses and multilevel modelling were applied to investigate associations between incidence of psychosis by place at onset and socio-environmental risk factors of material deprivation, social fragmentation and urban-rural classification across electoral divisions. Finally, a matched case-control design was used to investigate the relationship between socioeconomic status at birth and risk for first episode psychosis. There was no evidence for geographical variation by place at onset; conversely, the geographical distribution of incidence of all psychoses and the diagnostic subcategories by place at birth appeared to follow a non-random distribution for men but not women. For the relationship between socio-environmental risk factors and place at onset, the primary finding was an association between more deprived social contexts and higher rates of psychotic disorder, after adjustment
for age and sex [all psychoses: incidence rate ratio (IRR) = 1.12 (95% CI 1.03-1.23)]. In the socioeconomic status at birth and incidence of first episode psychosis study, while neither the distribution nor the ordinal scale of parental social class differed between cases and controls, logistic regression revealed both parental social class III and increasing level of rurality to be associated (p ≤ 0.05) with reduced risk for affective psychosis. There was a prominent relationship (p < 0.001) between lower parental social class and older age at first presentation [mean age at first presentation for all psychoses: social class I, 22.8; social class IV, 44.3]. These findings support an association between adverse socio-environmental factors and increase in risk for psychosis by both place at onset and place at birth within an essentially rural environment. This study suggests that poorer social environments, rather than urbanicity per se, may be relevant to the incidence of psychosis, though such exposures may have greater impact in more urban settings. The substantive finding in relation to age at first presentation may indicate that a gradient of socioeconomic position is influential on delay in presentation to mental health services.
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<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIMS</td>
<td>Abnormal involuntary movement scale</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain derived neutrophic factor</td>
</tr>
<tr>
<td>CAMFEPS</td>
<td>Cavan-Monaghan first episode psychosis study</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CNE</td>
<td>Condensed Neurological Examination</td>
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<tr>
<td>CNV</td>
<td>Copy number variation</td>
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<tr>
<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DALYs</td>
<td>Disability-adjusted life years</td>
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<td>DAOA</td>
<td>D-amino acid oxidase activator</td>
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<tr>
<td>DISC1</td>
<td>Disrupted in schizophrenia1</td>
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<tr>
<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<td>DTI</td>
<td>Diffusion tensor imaging</td>
</tr>
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<td>DUP</td>
<td>Duration of untreated psychosis</td>
</tr>
<tr>
<td>Dysbindin</td>
<td>Dystrobrevin binding protein 1</td>
</tr>
<tr>
<td>ECA</td>
<td>Epidemiologic catchment area</td>
</tr>
<tr>
<td>ED</td>
<td>Electoral division</td>
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<tr>
<td>EXIT</td>
<td>Executive Interview</td>
</tr>
<tr>
<td>FA</td>
<td>Fractional anisotropy</td>
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<tr>
<td>GP</td>
<td>General practitioner</td>
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<tr>
<td>GRIN2B</td>
<td>Glutamate receptor subunit 2B</td>
</tr>
<tr>
<td>GWAS</td>
<td>Genome-wide association studies</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>IRR</td>
<td>Incidence rate ratio</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>ISC</td>
<td>International Schizophrenia Consortium</td>
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<tr>
<td>LRT</td>
<td>Likelihood ratio test</td>
</tr>
<tr>
<td>MDD</td>
<td>Major depressive disorder</td>
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<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MSP</td>
<td>Multiple scan probability</td>
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<td>NES</td>
<td>Neurological Evaluation Scale</td>
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<td>NMDA</td>
<td>N-methyl-D-aspartic acid</td>
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<td>NRG1</td>
<td>Neuregulin 1</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
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<tr>
<td>PCP</td>
<td>Phencyclidine</td>
</tr>
<tr>
<td>PGC</td>
<td>Psychiatric Genomics Consortium</td>
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<td>PNOS</td>
<td>Psychotic disorder not otherwise specified</td>
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<tr>
<td>RR</td>
<td>Rate ratio</td>
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<tr>
<td>SAHRU</td>
<td>Small Area Health Research Unit</td>
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<td>SCID</td>
<td>Structured Clinical Interview for DSM axis 1 disorders</td>
</tr>
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<td>SERF</td>
<td>Socio-environmental risk factor</td>
</tr>
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<td>SFI</td>
<td>Social fragmentation index</td>
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<tr>
<td>SIR</td>
<td>Standardised Incidence rate</td>
</tr>
<tr>
<td>SMR</td>
<td>Standardised mortality ratio</td>
</tr>
<tr>
<td>SNP</td>
<td>Single nucleotide polymorphism</td>
</tr>
<tr>
<td>SUMD</td>
<td>Scale to assess unawareness of mental disorder</td>
</tr>
<tr>
<td>TBI</td>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>URC</td>
<td>Urban-rural classification</td>
</tr>
<tr>
<td>VBM</td>
<td>Voxel-based morphometry</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>ZIP</td>
<td>Zero inflated Poisson</td>
</tr>
<tr>
<td>δ-ALA</td>
<td>δ–aminolevulinic acid</td>
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Chapter 1
History and epidemiology

1.0 History of the concept of psychosis

Mental illness has a long history that can be traced back to early Egyptian writings, ancient Greece and the Old Testament (Johnstone & Lawrie, 2010). However, the term psychosis is relatively new. It was introduced in the first half of the 19th century in Germany by Canstatt (1841) (Bürgy, 2008) and Feuchtersleben (1845) (Beer, 1996). Feuchtersleben viewed psychosis as a disease of the personality that is to be differentiated from neurosis and considered it to be an interaction between mental and physical processes (Beer, 1996; Bürgy, 2008). This was around the same time when Greisinger defined mental illness as a disease of the brain (Bürgy, 2008). For the rest of the 19th century the term psychosis became widely used, with various authors such as Flemming and Mobius debating its origin (Bürgy, 2008). However, it was Kraepelin (1856-1926) who provided a comprehensive classification system in which psychotic disorders are subdivided into dementia praecox and manic-depressive psychosis (Jablensky, 2010). Kraepelin described dementia praecox as a 'series of states, the common characteristic of which is a peculiar destruction of the internal connections of the psychic personality' (Kraepelin, 1919). Initially, Kraepelin regarded dementia praecox and manic-depressive psychosis as distinct disorders, with the former showing progressive clinical deterioration with poor outcome, ‘the terminal state’, while manic-depressive psychosis had a fluctuating course with dull remission between episodes. However, in successive editions of his textbook of psychiatry, Lehrbuch der
Psychiatrie, Kraepelin appears to have had some doubts about his original classification system. For example, he acknowledged that ‘the possibility cannot in the present state of our knowledge be disputed, that a certain number of cases of dementia praecox attain to complete and permanent recovery’ (Craddock & Owen, 2010). Nonetheless, Kraepelin’s original view, the so called Kraepelinian dichotomy, remains at the heart of current debate in academic psychiatry (Craddock & Owen, 2010). As Kraepelin predicted, the name dementia praecox did not survive and was replaced by ‘schizophrenia’, a term that was coined by Bleuler in 1911 (Bleuler, 1951). Bleuler viewed schizophrenia as a group of disorders with (a) fundamental symptoms, including autism, thought disorder, affective incongruence and ambivalence, and (b) accessory symptoms, including delusions and hallucinations (Bleuler, 1951).

In the ensuing decades of the 20th century our understanding of the concept of psychosis was enhanced by the contribution of notable authors such as Kasanin, who introduced the term schizoaffective disorder in 1932 (Kasanin, 1994), and those of the Heidelberg school of psychiatry, including Jaspers and subsequently Schneider, who laid the foundations of the psychopathology of schizophrenia and introduced first rank symptoms, including audible thoughts, delusional perception, and thought withdrawal (Jablensky, 2010; Janzarik, 1998). Other notable attempts at classifying schizophrenia include the work of Leonhard, who classified schizophrenia into systematic, unsystematic and cycloid psychosis, and Crow’s classification of type I (positive) and type II (negative) schizophrenia (Jablensky, 2010).
Contemporaneous classification systems rely heavily on the work of Kraepelin and Schneider’s first rank symptoms. Of these, there are two important classification systems: 1) the World Health Organization’s International Classification of Diseases, now in its tenth edition (ICD-10) and the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, now in its fifth edition (DSM-V). Historically, there were significant differences between the two systems in the diagnosis of schizophrenia, as the US adopted a broader definition based on Bleuler’s fundamental symptoms. However, from the 1970s onwards there has been greater convergence between the two systems with the use of operationalised diagnostic criteria. In ICD-10, the term ‘psychotic’ is described as the ‘presence of hallucinations, delusions, or a limited number of severe abnormalities of behaviour, such as gross excitement and overactivity, marked psychomotor retardation, and catatonic behaviour’ (World Health Organization, 1992). In DSM-V, psychotic disorders are grouped under ‘schizophrenia spectrum and other psychotic disorders’ that are defined by one or more of five domains that include: delusions, hallucinations, grossly disorganised motor behaviour, disorganised speech, and negative symptoms (American Psychiatric Association, 2013).

As we are now at points of inflection regarding these classification systems, with the recent publication of DSM-V and the anticipated publication of ICD-11, several issues remain debated by researchers in the field, such as the classical question of the validity of categories vs dimensions that can be traced back to Kraepelin (Fischer & Carpenter, 2009), the inclusion of cognitive impairment as a diagnostic criterion for schizophrenia (Barch & Keefe, 2010) and whether at-risk mental state should be included as a diagnostic class (Carpenter, 2009).
Nonetheless, in DSM-V the core criteria for diagnosing psychotic disorders were retained with only modest changes, including the elimination of subtypes of schizophrenia, clarification of the relationship between schizophrenia and catatonia, and the addition of new psychopathological dimensions (American Psychiatric Association, 2013; Tandon et al., 2013).

In the present study, diagnoses are based on the DSM-IV classification system (American Psychiatric Association, 1994), which provides operational criteria defining each disorder based on symptoms and loss of function. Psychotic disorders ascertained in CAMFEPs include: schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, bipolar I disorder, major depressive disorder with psychotic features, psychotic disorder due to a general medical condition, mania due to a general medical condition, substance-induced psychotic disorder, substance-induced mania and psychotic disorder not otherwise specified.

1.1 Epidemiology

1.1.1 Introduction

Psychotic disorders have a large, adverse effect on patients, families and communities. For example, in the World Health Report 2001 on mental health, schizophrenia and bipolar disorder ranked 8th and 9th, respectively, as leading causes of disability-adjusted life years (DALYs) among the 15-44 age group (World Health Organization, 2001). Epidemiology is the study of the distribution and determinants of disease in the population. Therefore, it is one of the first lines of inquiry when examining the burden of any disorder, including psychotic illness. While many aspects of the epidemiology of psychosis are yet to be
understood, such as identifying risk factors, there is a wealth of literature on the distribution of disorders such as schizophrenia. This section will focus on the descriptive epidemiology of various psychotic disorders, with a particular emphasis on schizophrenia and bipolar disorder.

1.1.2 Epidemiology of schizophrenia

1.1.2.1 Case definition

DSM-IV defines the essential features of schizophrenia (criterion A) as the presence of two or more of the following symptoms: delusions, hallucinations, thought disorder, grossly disorganised or catatonic behaviour and negative symptoms; these must be accompanied by social or occupational dysfunction (criterion B), a six-month duration of illness, including at least one month of symptoms (criterion C), and exclusion of other disorders (criteria D, E & F) (American Psychiatric Association, 1994).

1.1.2.2 Prevalence and incidence

The lifetime prevalence of schizophrenia is estimated to be just below 1% (Stilo & Murray, 2010). Using DSM-IV criteria in a general population survey from Finland, Perälä and colleagues estimated the lifetime prevalence of schizophrenia to be 0.87% (95% CI 0.68-1.11) (Perälä et al., 2007). A systematic review of diverse studies from 46 countries reported a lifetime prevalence of 0.4% (Saha et al., 2005). Similarly, a recent systematic review of 65 studies that were conducted from 1990-2013 reported a slightly higher lifetime prevalence of 0.48% (Simeone et al., 2015). McGrath et al. examined the incidence rate of schizophrenia in a systematic review of studies involving diverse modes of case ascertainment and varying stringencies of diagnosis, which showed the median
incidence of schizophrenia world-wide to be 15.2 (95% CI 7.7-43.0) per 100,000 (McGrath et al., 2004). A recent meta-analytic review of the incidence of schizophrenia over a sixty-year period in England has reported a pooled estimate of 15.2 (95% CI 11.9–19.5) per 100,000 person-years (Kirkbride et al., 2012a). The annual incidence of schizophrenia in the Irish counties of Cavan and Monaghan, as determined in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS) that is the source of the cases studies here, is 7.0/100,000 of population age >15 (Baldwin et al., 2005).

An important line of epidemiological investigation is whether rates of schizophrenia vary across international, national and regional geographical and temporal domains. While there is clear evidence of variation in incidence of schizophrenia by place, which will be discussed separately, the picture is less clear when it comes to secular trends. For example, the aforementioned systematic review by McGrath et al. reported lower incidence rates in more recent studies compared to older studies (McGrath et al., 2004), while in the UK a study by Boydell et al. reported increasing incidence, with a doubling in rate of schizophrenia in South-East London over a three decade period (1965-1997) (Boydell et al., 2003). However, a systematic review and meta-analysis by Kirkbride et al. found the incidence of schizophrenia and other psychoses to be stable in England over a sixty-year year period (1950-2009) (Kirkbride et al., 2012a). In the present study area of Cavan-Monaghan, Waddington and Youssef examined morbid risk for schizophrenia over a 50-year period and found evidence for a decline in rate of schizophrenia during the last three decades of the study period (1920-1969), with this decline being more prominent in women (Waddington & Youssef, 1994).
1.1.2.3 Sex differences

Evidence from three meta-analyses indicates that risk for schizophrenia, by
diverse modes of case ascertainment and varying stringencies of diagnosis, is
higher in men than in women (Aleman et al., 2003; Kirkbride et al., 2012a,
McGrath et al., 2004). This finding has also been reported in CAMFEPS, with a
substantially higher incidence in men than in women (relative risk (RR) = 4.16
[95% CI 1.93-8.97]) (Baldwin et al., 2005). Proposed explanations for such
findings include (i) that increasing stringency of diagnostic criteria leads to a
lower number of women receiving a diagnosis of schizophrenia, (ii) that the
incidence of schizophrenia in women is declining, and (iii) that variations in
environmental influences on the incidence of schizophrenia, such as the urban
birth effect that is obviated in the rural region of CAMFEPS, may be more
marked in women (Baldwin et al., 2005).

1.1.2.4 Age at onset

Men appear to develop schizophrenia earlier than women, with peak incidence at
20-24 compared to 29-32 years, respectively (Stilo & Murray, 2010). A meta-
analysis by Eranti et al. has estimated an earlier onset of schizophrenia in men
by 1.5 years (Eranti et al., 2013). In CAMFEPS, mean age at first presentation
for men was 28.5 (range 17-77) and for women 33.6 (range 16-53) (Baldwin et
al., 2005); this somewhat older age at first presentation in CAMFEPS is likely
explained by the elimination of an arbitrary upper age limit that has been
imposed in the majority of epidemiological studies of schizophrenia (Baldwin et
al., 2005).
1.1.2.5 Mortality

There is a wealth of literature indicating that people with schizophrenia experience reduced life expectancy, due to not only suicide but also natural causes, than do the general population. For example, a systematic review by Saha and colleagues of 37 studies from 25 countries has found evidence for considerably elevated mortality in patients with schizophrenia, with an estimated pooled standardised mortality ratio (SMR) of 2.58 (95% CI 2.18-2.43); suicide was a leading cause of death, with a median SMR of 12.86 (Saha et al., 2007). In this review there was no difference in mortality between men and women. A more recent meta-analytic review has estimated relative risk for mortality in those diagnosed with psychosis to be 2.54 (95% CI 2.35–2.75) (Walker et al., 2015). While suicide remains the leading cause of mortality in patients with schizophrenia, natural causes such as cardiovascular disease (CVD) also contribute to this excess mortality (Ringen et al., 2014). Proposed aetiological mechanisms for the increased cardiovascular mortality in patients with schizophrenia include increased prevalence of tobacco and substance misuse, physical inactivity, role of antipsychotic medications and a possible shared pathophysiology between schizophrenia and CVD (Ringen et al., 2014).

1.1.3 Epidemiology of schizophreniform disorder

1.1.3.1 Case definition

DSM-IV diagnostic criteria for schizophreniform disorder are similar to those for schizophrenia, with two main differences: 1) a shorter duration of illness (at least 1 month but less than 6 months) and 2) impaired occupational or social functioning is not required (American Psychiatric Association, 1994).
1.1.3.2 Prevalence and incidence

Less is known about the prevalence and incidence of schizophreniform disorder. In a general population study from Finland, lifetime prevalence was found to be 0.07% (Perälä et al., 2007). DSM-IV estimates the incidence of schizophreniform disorder in the US and other developed countries to be approximately five times less than that of schizophrenia, with a markedly higher incidence in developing countries (American Psychiatric Association, 1994).

1.1.4 Epidemiology of bipolar disorder

1.1.4.1 Case definition

According to DSM-IV, the presence of at least one manic episode is required for the diagnosis of bipolar I disorder, whereas bipolar II is characterised by major depressive episodes and at least one hypomanic episode (American Psychiatric Association, 1994).

1.1.4.2 Prevalence and incidence

The lifetime prevalence of bipolar disorder is generally considered to be around 1%. However, estimates of prevalence and incidence of bipolar disorder tend to show variations that may be explained in part by difference in methodologies and case definitions; for example, whether bipolar II disorder is or is not included. Waraich and colleagues conducted a systematic review of general population studies of bipolar I disorder and found a pooled prevalence estimate of 0.82% (95% CI, 0.56-1.10) (Waraich et al., 2004). Recent epidemiological surveys have shown lower rates. For example, in the aforementioned general population study from Finland, the lifetime prevalence of bipolar I disorder was estimated to be 0.24% (95% CI 0.16-0.37) (Perälä et al., 2007). Furthermore, a more recent
international mental health survey that used the same methodology across 11 countries established a pooled lifetime prevalence of 0.6% for bipolar I and 0.4% for bipolar II disorder (Merikangas et al., 2011). As this is a population-based study with a large sample size (61,398), it is probably more reflective of the true prevalence of bipolar disorder. Incidence studies of bipolar disorder have demonstrated variation across sites even in studies that have used identical methodological approach. For example, a large multicentre study in the UK has estimated the pooled incidence of bipolar disorder to be 4.0 per 100,000 with an incidence range that varied from 1.7 per 100,000 in Bristol to 6.2 per 100,000 in London (Lloyd et al., 2005). In Cavan-Monaghan, the counties in which CAMFEPS operates, the annual incidence rate for bipolar I disorder was 5.2 per 100,000 (Baldwin et al., 2005).

1.1.4.3 Age at onset

Epidemiological studies have shown bipolar I disorder to have a slightly earlier age at onset compared to bipolar II. For example, in the world mental health survey initiative, the mean age at onset for bipolar I was 18.4 whereas for bipolar II this was 20 (Merikangas et al., 2011). Furthermore, a large study from six international sites has estimated a median age at onset of 24.3 for bipolar I and 30.1 for bipolar II, with an earlier age at onset in men (Baldessarini et al., 2010). Additionally, some epidemiological studies suggest three subgroups of bipolar disorder, i.e. early, intermediate and late in terms of age at onset of illness (Leboyer et al., 2005). Earlier age at onset of bipolar disorder has been found to be associated with a more severe clinical form, poorer outcome and more comorbidities (Baldessarini et al., 2012; Leboyer et al., 2005; Schulze et al., 2002; Schürhoff et al., 2000; Suominen et al., 2007). Moreover, patients with
early onset bipolar disorder are more likely to have a family history of the illness, suggesting a greater genetic contribution in this subgroup of patients (Baldessarini et al., 2012; Leboyer et al., 2005). These findings have led to a considerable debate as to whether putative subgroups of bipolar disorder constitute distinct clinical syndromes, with some authors having suggested the addition of age at onset as a course specifier in DSM-V (Colom & Vieta, 2009). In Cavan-Monaghan the mean age at first presentation for bipolar disorder was 34.8 years, with the rate being indistinguishable between men and women (Baldwin et al., 2005).

1.1.4.4 Sex distribution

The majority of studies, including the present study region, indicate bipolar disorder to occur at similar rates across the sexes (Baldwin et al., 2005; Bardenstein & McGlashan, 1990; Diflorio & Jones, 2010).

1.1.4.5 Mortality

Similar to schizophrenia, accumulating evidence indicates increased mortality from natural and unnatural causes in patients with bipolar disorder compared to the general population. For example, in a large case register study from Denmark, Høyer and colleagues examined the mortality of patients with affective disorders, including bipolar disorder, and found excess mortality in all diagnostic subgroups, with suicide being the leading cause of death (Høyer et al., 2000). These findings were replicated in another case register study from Sweden (Osby et al., 2001). More recently, a large case register study from Sweden has reported a two-fold increase in all-cause mortality in patients with bipolar disorder compared to the general population (Crump et al., 2013). This study showed that
several chronic diseases contributed to increased mortality in patients with bipolar disorder including cardiovascular disease, diabetes, and chronic obstructive airway disease.

1.1.5 Epidemiology of schizoaffective disorder

1.1.5.1 Case definition

The concept of schizoaffective disorder has long attracted considerable debate within academic circles in relation to the validity of the construct and whether it should be primarily considered as a mood or a psychotic disorder (Jäger et al., 2011; Malhi et al., 2008). In DSM-IV, schizoaffective disorder is included in the section of schizophrenia and other psychotic disorders. Schizoaffective disorder is defined by DSM-IV as a period of uninterrupted illness in which psychotic symptoms are present simultaneously with features of a depressive episode, a manic episode, or a mixed episode (criterion A) (American Psychiatric Association, 1994). Moreover, delusions and hallucinations have to be present for at least two weeks in the absence of prominent affective symptoms (criterion B) (American Psychiatric Association, 1994).

1.1.5.2 Prevalence and incidence

Little is known about the exact prevalence and incidence of schizoaffective disorder. Lifetime prevalence estimates range between 0.1% in rural Ireland (Scully et al., 2004) to 0.32% in Finland (Perälä et al., 2007). Incidence was 2.0 per 100,000 in Cavan-Monaghan (Baldwin et al., 2005).

1.1.5.3 Sex distribution

Some studies suggest that schizoaffective disorder may be more prevalent in women than in men, particularly among married women (Bardenstein &
McGlashan, 1990; Malhi et al., 2008), and that women may develop schizoaffective disorder later than men (Malhi et al., 2008). In Cavan-Monaghan the rate of schizoaffective disorder was indistinguishable between men and women (Baldwin et al., 2005).

1.1.6 Epidemiology of major depressive disorder with psychotic features

1.1.6.1 Case definition

Major depressive disorder with psychotic features is defined by DSM-IV as the presence of either delusions or hallucinations, often mood-congruent but sometimes mood-incongruent, during an episode that satisfies the criteria for major depression, including depressed mood, loss of interest, sleep disturbance and loss of energy (American Psychiatric Association, 1994).

1.1.6.2 Prevalence and incidence

The literature on major depressive disorder generally reports on the full spectrum of the disorder, with relatively few studies examining major depressive disorder with psychotic features. One such study by Johnson and colleagues, using data from the Epidemiologic Catchment Area (ECA) study in the USA, reported a lifetime prevalence of 0.6% (Johnson et al., 1991). Another study, which employed telephone interviews of a large European general population sample, has estimated the prevalence of major depressive disorder with psychotic features to be 0.4% (95% CI 0.35-0.54) (Ohayon & Schatzberg, 2002). In the general population study from Finland the lifetime prevalence of major depressive disorder with psychotic features was found to be 0.35% (Perälä et al., 2007). First episode psychosis studies have provided data on the incidence of major depressive disorder with psychotic features. For example, a study from the
UK has reported an incidence of 6.02 (95% CI 4.87-7.17) per 100,000 (Reay et al., 2010). Similarly, in Cavan-Monaghan the annual incidence of major depressive disorder with psychotic features was 6.4 per 100,000 (Baldwin et al., 2005).

1.1.6.3 Sex distribution
Epidemiological studies on the sex distribution of major depressive disorder with psychotic features have shown varied results: in the study by Johnson et al. major depressive disorder with psychotic features was more prevalent in women (Johnson et al., 1991); however, in the general population study from Finland and in Cavan-Monaghan rates were indistinguishable between men and women (Baldwin et al., 2005; Perälä et al., 2007).

1.1.6.4 Age at onset
Age at onset of major depressive disorder with psychotic features appears to show a wide range, from early adulthood through to later years in life. In the study by Johnson and colleagues mean age at onset of major depressive disorder with psychotic features was 42.0 (Johnson et al., 1991), while in Cavan-Monaghan mean age at first presentation was 45.6 (range 16-81) (Baldwin et al., 2005). In contrast to bipolar disorder, there is limited evidence to suggest that later age at onset of major depressive disorder with psychotic features is associated with more severe clinical features than is the case for those developing the illness earlier in life (Gournellis et al., 2011).
1.1.7 Epidemiology of delusional disorder

1.1.7.1 Case definition

DSM-IV requires the presence of non-bizarre delusions for a period of at least one month for the diagnosis of the delusional disorder (criterion A) (American Psychiatric Association, 1994). Furthermore, the symptoms should not satisfy criterion A for schizophrenia (criterion B).

1.1.7.2 Prevalence and incidence

Delusional disorder is another illness whose prevalence and incidence is poorly understood. DSM-IV gives an estimate of the population prevalence of delusional disorder to be approximately 0.03% (American Psychiatric Association, 1994). Kendler reviewed 17 studies on delusional disorder and estimated a prevalence range of 0.02 to 0.03%, with an annual incidence of first admissions between 1 to 3 per 100,000 (Kendler, 1982). In Cavan-Monaghan, the annual incidence of delusional disorder was 1.5 per 100,000 (Baldwin et al., 2005).

1.1.7.3 Age at onset

Delusional disorder shows a wide range of age at onset, with the disease mainly occurring in middle to late adulthood (Kendler, 1982). The estimated mean age is 48.8 (17-72) years for men and 44.9 (29-78) years for women (Manschreck & Khan, 2006). In CAMFEPS, mean age at first presentation for men was 36.4 (range 22-52) and for women 43.3 (range 17-68).

1.1.7.4 Sex distribution

Women may be more likely to develop delusional disorder than men (de Portugal et al., 2010; Manschreck & Khan, 2006), with a recent study having estimated a male to female ratio of 1.6:1 (de Portugal et al., 2010). Moreover, the
same study reported sex differences in clinical and psychopathological characteristics, such as greater severity of positive and negative psychotic symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) in men (de Portugal et al., 2010).

### 1.1.8 Conclusion

Epidemiological studies have improved our understanding of the prevalence and incidence of schizophrenia and to some extent of other psychotic disorders. The use of standardised diagnostic criteria and assessment methods has allowed for greater comparability across studies and may explain why more recent studies report lower rates than do earlier counterparts.
Chapter 2

Neurobiology and genetics of psychosis

2.0 Neurobiology of psychosis

2.1 Neuroimaging

2.1.1 Schizophrenia

2.1.1.1 Structural neuroimaging

The first neuroimaging study to report brain abnormalities in schizophrenia was carried out by Johnstone and colleagues in the UK in 1976 (Johnstone et al., 1976). Using computed tomography (CT), the authors reported significantly increased ventricular size in patients with chronic schizophrenia compared to matched controls. This study paved the way for neuroimaging in schizophrenia, with subsequent studies using CT and magnetic resonance imaging (MRI) techniques. Several studies, including a meta-analysis, have documented structural abnormalities in several brain regions in patients with schizophrenia that include: enlarged lateral and third ventricles; temporal lobe abnormalities that include medial temporal lobe structures (hippocampus and parahippocampal gyrus), and neocortical temporal lobe structures (superior temporal gyrus); frontal lobe abnormalities that include the prefrontal cortex and orbitofrontal cortex; other brain regions involved include the basal ganglia, corpus callosum, cavum septum pellucidum, cerebellum and thalamus (Shenton et al., 2010).

An important consideration when discussing neuroimaging findings is the issue of timing; at what stage in the course of illness do such changes occur? This question has been addressed by studies that examined first episode patients and
by longitudinal investigations. For example, Cahn and colleagues reported significant reduction in grey matter volume and increase in lateral ventricle volume in patients with schizophrenia during the first episode of illness (Cahn et al., 2002). Furthermore, a meta-analysis of 52 cross-sectional and 16 longitudinal studies of first-episode schizophrenia has established a significant increase in ventricular volume and reductions in whole brain and hippocampal volume in patients with first episode schizophrenia compared to healthy controls (Steen et al., 2006). Additionally, Hulshoff and Kahn reviewed 11 longitudinal neuroimaging studies and found evidence for progressive brain tissue reduction, twice that in healthy controls, and increases in volume of the lateral ventricles in patients with chronic schizophrenia (Hulshoff & Kahn, 2008). Progressive brain tissue loss was more pronounced in the frontal and temporal brain regions. Moreover, a more recent meta-analysis of voxel-based morphometry (VBM) studies has found evidence for structural brain changes in high-risk individuals, at the first psychotic episode and in chronic schizophrenia (Chan et al., 2011). Together, these studies provide strong evidence for structural brain changes in schizophrenia that are present as early as the prodromal phase, with modest evidence of progression during the course of the disease.

2.1.1.2 Functional neuroimaging

Integrating functional neuroimaging with neuropsychological activation paradigms has enabled investigation of deficits in different brain regions in response to specific tasks, as well as studying connectivity between regions (Gur & Gur, 2010). Studies have documented that patients with schizophrenia have significant deficits in several domains such as executive function, memory and learning (Gur & Gur, 2010; Minzenberg et al., 2009; Ruiz et al., 2013). These
studies have also identified potential brain areas that may be responsible for neuropsychological symptoms of schizophrenia. For example, a meta-analysis by Minzenberg and colleagues has linked executive dysfunction in patients with schizophrenia to reduced activity in the dorsolateral prefrontal cortex, anterior cingulate cortex, and the mediodorsal nucleus of the thalamus (Minzenberg et al., 2009). Research has also shown that working memory impairment in schizophrenia is related to altered connectivity in the prefrontal cortex, anterior cingulate, basal ganglia, medial temporal, inferior frontal and bilateral posterior parietal regions (Meda et al., 2009).

2.1.1.3 Diffusion tensor imaging

The development of diffusion tensor imaging (DTI) has allowed for examination of the involvement of white matter in schizophrenia. Positive findings from DTI studies include ‘decreased fractional anisotropy (FA), along with increased diffusivity within prefrontal and temporal lobes, as well as abnormalities within the fibre bundles connecting these regions’ (Kubicki et al., 2007). There is evidence from meta-analytic review that disruption in white matter connectivity is present in the early course of schizophrenia and may be compounded by the use of cannabis (Cookey et al., 2014).

2.1.2 Bipolar disorder

While brain volume appears to be normal in patients with bipolar disorder, structural neuroimaging studies have identified brain abnormalities in patients with bipolar disorder such as decreased volume in subregions of the prefrontal cortex and enlargement of the striatum and amygdala (Strakowski et al., 2005).
Furthermore, functional neuroimaging studies have implicated prefrontal subregions in patients with bipolar disorder (Strakowski et al., 2005).

2.2 Pathobiology

2.2.1 Dopamine hypothesis

Central to the pathophysiology of schizophrenia is the dopamine hypothesis. Dopamine was first implicated in schizophrenia by the work of Carlsson and Lindqvist in 1963, who, using animal models, demonstrated that the mechanism of action of antipsychotic drugs involved blockade of dopamine receptors (Carlsson & Lindqvist, 1963). This was supported by subsequent evidence relating the potency of antipsychotic drugs to their affinity to block dopamine receptors of the D2 subtype (Seeman et al., 1976). Further evidence was provided by studies that showed psychostimulant drugs such as amphetamine, which enhance the activity of dopamine, lead to worsening of psychotic symptoms in patients with schizophrenia (Lieberman et al., 1987). This evidence has led to what Howes and Kapur describe as version 1 of the dopamine hypothesis (Howes & Kapur, 2009). However, evidence from further studies showed that dopaminergic activity was not elevated in all regions of the brain. This, combined with the observation that an efficacious antipsychotic drug such as clozapine has weak affinity for D2 receptors, led to ‘reconceptualization’ of the dopamine hypothesis by Davis and colleagues in 1991 (Davis et al., 1991). The authors hypothesised that dopamine dysfunction in schizophrenia comprised high dopaminergic activity in the mesolimbic system with low dopamine activity in the prefrontal cortex.
More recently, Howes and Kapur reviewed evidence from several domains, including neurochemical imaging, genetic and animal studies, to refine the dopamine hypothesis (Howes & Kapur, 2009). These authors provide a framework in which multiple genetic and environmental risk factors converge in a ‘final common pathway’ that leads to the development of psychosis through increased presynaptic dopaminergic activity in subcortical brain areas that may be accompanied by reduced presynaptic dopaminergic activity in cortical regions (Howes & Kapur, 2009). As our understanding of the pathophysiology of schizophrenia evolves, the dopamine hypothesis continues to witness further refinements. A recent review by Howes et al. has emphasised the role of presynaptic striatal dopamine dysfunction in the aetiology of schizophrenia and that evidence for dopaminergic dysfunction extends to the prodromal phase of the illness (Howes et al., 2017).

2.2.2 Glutamate hypothesis

Early evidence for the glutamate hypothesis can be traced back to the work of Luby and colleagues, who, over 50 years ago, observed that administrating the N-methyl-D-aspartic acid (NMDA) receptor antagonist phencyclidine (PCP) induced symptoms of schizophrenia in both patients with schizophrenia and healthy volunteers (Luby et al., 1959). Moreover, subjects who abused PCP displayed symptoms similar to those seen in patients with schizophrenia. Further evidence for the role of glutamate in schizophrenia came from the observation that the structural analogue of PCP, the anaesthetic agent ketamine, exacerbated psychotic symptoms in patients with schizophrenia (Lahti et al., 1995). It was also shown that administration of ketamine to healthy volunteers induced thought disorder that was similar to that seen in patients with
schizophrenia (Adler et al., 1999). Moreover, evidence from post-mortem studies has demonstrated low expression of glutamate receptors in brain of patients with schizophrenia; Kantrowitz and Javitt discuss the evidence and propose an alternative model in which NMDA receptor dysfunction or dysregulation is the ‘final common pathway for schizophrenia’ (Kantrowitz & Javitt, 2010). In addition to schizophrenia, there is limited evidence implicating the glutamatergic system in the pathophysiology of mood disorders (Krystal et al., 2002).

2.2.3 Serotonin and noradrenaline

Both the serotonergic and noradrenergic systems of the monoamine pathway have been implicated in the pathophysiology of bipolar disorder and unipolar depression. This is based on several lines of evidence such as the mechanism of action of antidepressants and mood stabilisers, functional imaging, genetic and animal model studies (Berton & Nestler, 2006; Bremner et al., 2003; Manji et al., 2003).

2.3 Neuropsychological abnormalities

Several studies, including meta-analyses, have documented a wide range of neuropsychological impairments in patients with schizophrenia. These range from generalised cognitive decline to specific deficits in attention, memory, learning, executive function and processing speed (Dickinson, et al., 2007; Fioravanti et al., 2005; Heinrichs & Zakzanis, 1998; Henry & Crawford, 2005; Johnson-Selfridge & Zalewski, 2001; Laws, 1999; Saykin et al., 1991). However, neuropsychological abnormalities are not universally present in all patients, with some studies reporting patients with schizophrenia who are ‘neuropsychologically normal’ (Palmer et al., 1997). These findings have
contributed to a considerable debate regarding the extent to which cognitive impairment is a core feature of schizophrenia, with some researchers suggesting that cognitive impairment should be included in the diagnostic criteria for schizophrenia classification systems (Keefe & Fenton, 2007). However, recent studies comparing neuropsychological performance in patients with schizophrenia, schizoaffective disorder, psychotic bipolar disorder and major depressive disorder with psychotic features have demonstrated that differences in neuropsychological performance between schizophrenia and other psychotic disorders are quantitative and not qualitative (Reichenberg et al., 2009; Zanelli et al., 2010). These findings are supported by a recent meta-analysis of cognitive impairment in affective psychosis that has shown cognitive deficits in affective psychosis were comparable to those reported in patients with schizophrenia (Bora et al., 2010).

2.4 Neuropathology

Findings from neuroimaging studies of structural brain changes in schizophrenia, such as loss of brain volume and ventricular enlargement, have been corroborated by post-mortem studies; further, at a microscopic level several neuropathological findings have been reported, including absence of gliosis, cytoarchitectural abnormalities such as reduced size of cortical and hippocampal neurons, and fewer neurons in dorsal thalamus (Harrison, 1999).

2.5. Genetics

2.5.1 Genetics of schizophrenia

Understanding the genetic epidemiology of schizophrenia is crucial for unravelling the underlying mechanisms that lead to this complex disorder. Early
evidence of a role for genetic factors in the aetiology of schizophrenia came from family, twin and adoption studies (Gejman et al., 2011). Family studies showed substantial aggregation of schizophrenia, with an estimated risk in a first-degree relative of a patient with schizophrenia to be approximately 10-fold greater than that in a relative of an unrelated control (Kendler & Diehl, 1993). Further evidence on genetic influence in schizophrenia came from twin studies; a meta-analysis of 12 twin studies established a point estimate of the heritability of schizophrenia to be 81% (95% CI; 73-90) (Sullivan et al., 2003). Adoption studies allow for examination of genetic risk independent of environmental influence (Gejman et al., 2011). Such studies have demonstrated increased risk for schizophrenia amongst offspring of patients with schizophrenia regardless of the rearing environment and whether the onset of illness in the parent was before or after adoption (Gejman et al., 2011).

2.5.1.1 Molecular genetic studies

The next wave of genetic studies of schizophrenia employed two main strategies, namely linkage and association.

2.5.1.1.1 Linkage studies

Linkage studies aim to identify genetic alleles that segregate with the disease in multiply affected families (Zammit et al., 2003). While linkage studies have so far failed to identify genes of major effect, significant evidence was found for linkage in several chromosomal regions (Zammit et al., 2003). For example, Badner and Gershon used the multiple scan probability (MSP) techniques to meta-analyse genome scan studies of schizophrenia and bipolar disorder; they found significant evidence for linkage on chromosome 8p, 13q and 22q for
schizophrenia (Badner & Gershon, 2002). In another meta-analysis by Lewis et al. in which a rank-based genome scan was used, the strongest evidence for linkage was found on chromosome 2q (Lewis et al., 2003). This finding was confirmed more recently in another meta-analysis by the same group (Ng et al., 2009). However, some caveats limit our ability to interpret findings from linkage studies: findings are not replicable across studies and implicate a broad range of chromosomal regions (Zammit et al., 2003).

2.5.1.1.2 Association studies

Association studies use case-control design to identify alleles that are more common in cases than controls. Historically, association studies consisted of targeting candidate genes. However, advances in genotyping technologies have allowed for comprehensive examination of the human genome in what is known as genome-wide association studies (GWAS) (Bertram, 2008). GWAS are based on linkage disequilibrium, 'a non-random association of alleles at different loci', and is applied via single nucleotide polymorphism (SNP) arrays that probe common variation across the genome (Duan et al., 2010). Realising the need for greater sample sizes to achieve statistical power in association studies, multiple researchers from across the world collaborated to establish consortia for GWAS, such as the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) (Bergen & Petryshen, 2012). This consortium has yielded significant results, such as the initial identification of 7 susceptibility loci for schizophrenia that achieved genomewide significance, including 1p21.3, 2q33.2, 8p23.2, 8q21.3, and 10q24.23-q24.33 (Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011). More recently, the PGC conducted a meta-analysis that identified 13 new risk loci for schizophrenia,

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(Ripke et al., 2013). A subsequent large GWAS by the PGC, which included 36,989 cases and 113,075 controls, has identified 108 schizophrenia-associated risk loci, 83 of which have not been previously reported (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In this study, several of the identified loci were in genes that are aetiologically relevant to hypotheses of schizophrenia and its treatment, including \textit{DRD2}, \textit{GRIN2A}, \textit{GRM3}, \textit{SRR} and \textit{GRIA1}.

2.5.1.2 Chromosomal abnormalities

Several studies have reported associations between chromosomal abnormalities and schizophrenia. The most significant finding relates to chromosome 22q11. Murphy and colleagues studied fifty adults with 22q11 deletions (velo-cardio-facial syndrome) and found significantly increased risk for schizophrenia, with 24\% of subjects fulfilling DSM-IV criteria for schizophrenia (Murphy et al., 1999). Other important findings in chromosomal abnormalities include chromosome 1q42. Blackwood and colleagues studied an extended family in Scotland with a balanced chromosomal translocation (1; 11) (q42; q14.3) and found significant association with schizophrenia, bipolar disorder and recurrent depression (Blackwood et al., 2001). Furthermore, using data from the same family, the study group was able to identify the gene \textit{DISC1} in chromosome 1 as disrupted by chromosomal translocation (Millar et al., 2000).

2.5.1.3 Copy number variants

A recent development in schizophrenia genetics is the study of copy number variations (CNVs), which are defined as ‘chromosomal segments where DNA has been deleted or duplicated’ (Cichon et al., 2009). Using genome scanning
techniques, studies have identified deletions and duplications in CNVs in several regions, such as 1q21, 15q11.215q13.3, that, though rare, are associated with prominently increased risk for schizophrenia (St Clair, 2009). This risk, however, is not specific to schizophrenia, as these mutations are also associated with increased risk for other disorders, including bipolar disorder, autism and learning difficulties (St Clair, 2009). The overall evidence points towards involvement of multiple, rare CNVs of large effect in the aetiology of schizophrenia (Bassett et al, 2010). A more recent study by the PGC that included 21,094 cases and 20,227 controls has identified CNVs in 8 loci, including 1q21.1, 2p16.3 (NRXN1), 3q29, 15q13.3, 7q11.2, distal 16p11.2, proximal 16p11.2 and 22q11.2 (CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium, 2017).

2.5.1.4 Polygenic model

Using the international schizophrenia consortium (ISC) dataset, Purcell and colleagues (Purcell et al., 2009) examined the polygenic hypothesis of schizophrenia (Gottesman & Shields, 1967) by assessing whether several common variants of small effect could explain a large proportion of variation in disease risk. By generating an aggregate risk score for each individual, based on defined sets of common variants of small effect, the study found that aggregate scores for subjects with schizophrenia were significantly higher than for controls (Purcell et al., 2009). The ISC concluded that the polygenic model contributed to one third of variation in liability to schizophrenia.
2.5.2 Genetics of bipolar disorder

2.5.2.1 Early evidence

Similar to schizophrenia, early evidence for genetic involvement in bipolar disorder came from family, twin and adoption studies. For example, family studies have shown that first-degree relatives of patients with bipolar disorder are at increased risk of developing the disorder. The odds ratio is estimated to be around seven times that of the general population (CI% 5-10) (Craddock & Jones, 1999). Furthermore, family studies have also demonstrated that first degree relatives of bipolar probands are at increased risk for unipolar depression (Craddock & Jones, 1999). Pooled data from twin studies point towards a concordance rate of 50% in monozygotic twins (Craddock & Jones, 1999). Moreover, adoption studies have found significantly increased risk for affective disorders in biological parents of patients with bipolar disorder (Craddock & Jones, 1999).

2.5.2.2 Molecular genetic studies

2.5.2.2.1 Linkage studies

Linkage studies of bipolar disorder have shown some inconsistent findings. For example, Badner and Gershon conducted a meta-analysis of genome scan studies and identified susceptibility loci on chromosomes 13q and 22q (Badner & Gershon, 2002). However, another meta-analysis failed to detect genome-wide significance (Segurado et al., 2003). In a combined analysis of 11 genome-wide scan studies, McQueen and colleagues identified susceptibility loci on chromosomes 6q and 8q as meeting genome-wide significance (McQueen et al., 2005). Other regions identified by genome-wide scans include 10q25, 10p12, 16q24, 16p13, and 16p12 (Cheng et al., 2006). Again, our ability to interpret
findings from linkage studies is hampered by the lack of reproducibility of findings and the modest effect sizes of those associations identified.

2.5.2.2.2 Association studies

Several susceptibility loci for bipolar disorder have been identified by GWAS. These include ANK3 on chromosome 10q21, CACNA1C on chromosome 12p13, ODZ4 and TRANK1 (Ferreira et al., 2008; Mühleisen et al., 2014; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011).

2.5.2.3 Candidate genes

Unlike schizophrenia, studies of candidate genes for bipolar disorder have shown inconsistent findings that failed to identify replicable susceptibility genes (Craddock et al., 2005; Craddock & Sklar, 2013). Nonetheless, some functional candidate genes have been studied, with some evidence for association between bipolar disorder and brain derived neutrophic factor (BDNF), D-amino acid oxidase activator (DAOA), and the NMDA glutamate receptor subunit 2B (GRIN2B) (Barnett & Smoller, 2009; Craddock et al., 2005).

2.5.3 Overlap between schizophrenia and bipolar disorder

Genetic studies of schizophrenia and bipolar disorder have provided evidence for considerable overlap between the two disorders. This manifests in shared susceptibility loci and mutations as CNVs. Further evidence has come from the aforementioned ISC study in which polygenic contribution to risk for schizophrenia was found to be shared with bipolar disorder (Purcell et al., 2009). Moreover, the PGC GWAS studies have also identified loci that confer risk to both bipolar disorder and schizophrenia (Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011).
2.6 Gene-environment interaction

Traditionally, the aetiology of psychosis has been viewed in terms of the nature vs nurture dichotomy, with genetic researchers focusing solely on genetic causes while epidemiologists considered primarily environmental factors (van Os et al., 2008). In recent years there has been a significant shift in research, with increasing attention being paid towards understanding interactions between genetic and environmental factors as a pathway that leads to psychosis.

There are several models by which gene-environment relationships can influence risk for psychosis, such as correlation; for example, parental influence on risk for schizophrenia may be through the child-rearing environment, but there is also independent risk via genetic heritability (van Os et al., 2008). An alternative model is that of synergism, in which the effects of environmental factors are dependent on genetic liability and vice versa (van Os & Sham, 2003). This model would explain why certain people are more (or less) vulnerable to some environmental risk factors. There is some evidence supporting this model from epidemiological studies that have measured genetic risk indirectly (van Os & Sham, 2003). For example, a study by Tienari and colleagues has found that adoptees with high-genetic risk for psychosis were more likely to develop a psychotic disorder if they were reared in a dysfunctional environment, when compared to those at low genetic risk (Tienari et al., 2004); similar evidence for gene-environment interactions has been reported for obstetric complications such as foetal hypoxia (T.D. Cannon et al., 2002). Additionally, epidemiological studies that have used ‘proneness to psychosis’ as a measure of genetic risk have also established evidence for gene-environment interaction; for example, Henquet and colleagues found the relationship between cannabis use and
psychosis to be stronger among subjects who were predisposed to psychosis (Henquet et al., 2005). However, studies that have measured genetic risk directly have so far showed mixed results; for example, examining the relationship between the COMT gene and cannabis in increasing risk for psychosis have yielded both positive and negative findings (Caspi et al., 2005; Zammit et al., 2011). This highlights the complex nature of gene-environment relationships and the methodological challenges in examining their interplay in research settings.
Chapter 3

Geographical variation in rates of psychosis

3.1 Introduction

Examination of spatial variation is an important line of epidemiological research that can help improve our understanding of the aetiology of psychosis (March et al., 2008). Geographical variation by place at birth would implicate factors operating during gestation and early childhood, while variation by place at onset would implicate later factors that precipitate the onset of psychosis (Youssef et al., 1999). Over the past century, several researchers have investigated geographical variation in rate of psychosis and its relationship to the social environment. In this chapter I will review the literature concerning geographical variation.

3.2 International variation

3.2.1 Schizophrenia

The bulk of our knowledge of international variation in rates of psychotic disorders comes from studies of schizophrenia. These can be subdivided into prevalence and incidence studies.

3.2.1.1 Prevalence studies

In a review of 30 prevalence studies of schizophrenia from across the world, Torrey reported wide variations in prevalence of schizophrenia, amounting to an over 50-fold difference between the highest reported rate (1700 per 100,000 in Northern Sweden) to the lowest reported rate (30 per 100,000 in the Amish...
community in the USA) (Torrey, 1987). While Torrey concluded that ‘there may be significant differences among population groups’, he urged caution in interpreting these findings due to methodological differences between studies (Torrey, 1987).

A systematic review of 188 prevalence studies of schizophrenia from 46 countries found the prevalence of schizophrenia in ‘least developed’ countries to be significantly lower than both ‘emerging’ and ‘developed’ countries (Saha et al., 2005). A more recent study by the WHO, the world mental health survey that included nationally representative samples from 52 countries, has also established wide variation in the lifetime prevalence of schizophrenia ranging from 0.07% in Vietnam to 5.10% in Swaziland (Nuevo et al., 2012).

3.2.1.2 Incidence studies

An influential study that examined international variation in rates of schizophrenia is the WHO ten-country study. In this large multi-centre study of 1379 patients, which used uniform methodology and standard assessment instruments, significant variations in incidence of ‘broadly’ defined schizophrenia were found across centres, with a range between 15 and 42 per 100,000. However, the incidence of ‘narrowly’ defined schizophrenia [class S+ of CATEGO, a computer-based diagnostic system derived from the Present State Examination] showed less variation, with a range between 7 to 14 per 100,000, which was not statistically significant (Jablensky et al., 1992). This study has led to a considerable academic debate as to whether the findings are evidence for or against spatial variation of schizophrenia (McGrath, 2006). More recently, a systematic review of 158 incidence studies of schizophrenia has estimated
variance in rates between sites of between 7.7 to 43.0 per 100,000 (10%-90% quantile) (McGrath et al., 2004), thus confirming wide variation in rates of schizophrenia across different countries.

3.2.2 Bipolar disorder
As discussed in the previous chapter, comparability of cross-national studies of bipolar disorder is limited due to differences in methodology and the definition of bipolar disorder adopted. Nonetheless, there is some evidence to suggest cross-country variation in rates of bipolar disorder. For example, the world mental health survey initiative, a population-based study of 11 countries that used identical methodology, has established variations in the lifetime prevalence of bipolar disorder, with the lowest rate reported in India (0.1%) and the highest in the US (4.4%) (Merikangas et al., 2011).

3.3 Within-country variation
In addition to variations between countries, differences in rates of psychosis within countries by place at onset have been reported. In the above mentioned review by Torrey, he noted within country variation in prevalence of schizophrenia in several countries such as the then Yugoslavia (Croatia), Japan, Sweden and the USA (Torrey, 1987). In a more recent, large population-based 3-centre study in the UK, the incidence of both non-affective and affective psychoses, including bipolar disorder, was found to be higher in South East London compared with Nottingham and Bristol (Kirkbride et al., 2006).

In Ireland, there is a long history of reports of elevated rates of psychosis in some parts of the country. In 1911, Dawson found that rates of psychosis in some counties such as Waterford and Kilkenny were considerably higher than in
the rest of the country (Dawson, 1911). He concluded that ‘it appears, then, that in Ireland insanity tends to prevail in the agricultural counties, and has a close relation - if special conditions be disregarded - to pauperism’. In the second half of the 20th century, the West of Ireland attracted attention as a possible high pocket of psychosis. This was demonstrated in first admission data studies such as that by Walsh and Walsh (Walsh & Walsh, 1970). However, it has been suggested such findings may be a result of a methodological error that resulted in exaggerated admission rates (Ninuallain et al., 1987). In a widely cited study, Torrey and colleagues estimated the prevalence of schizophrenia in a small area of county Roscommon to be around 12.6 per 1000 (Torrey et al., 1984). However, a subsequent study of incidence of schizophrenia in three Irish counties, including Roscommon, failed to replicate those findings (Ninuallain et al., 1987). As such it can be concluded that claims of high-density pockets of psychosis in Ireland have not been supported by methodologically robust studies (Youssef et al., 1999).

There is paucity of research in relation to within country variation of rates of psychosis by place at birth other than those studies that examined urban-rural variations. One such study found significant regional variations in rates of schizophrenia and other non-affective psychoses, but not for affective psychoses, by place at birth in Finland (Perälä et al., 2008).

3.4 Urban/rural variations

3.4.1 Urbanicity at onset of psychosis

One of the most consistent findings in psychiatric epidemiology is the differential in rates of psychosis between urban and rural areas. In the Netherlands, Peen &
Dekker found strong correlation between admissions rates for schizophrenia and degree of urbanisation (Peen & Dekker, 1997). In the UK, the incidence of schizophrenia in Camberwell, London, was higher than in rural Scotland (Allardyce et al., 2001). In a large cohort study of first admissions in Denmark, Schelin et al. found higher rates of schizophrenia with increasing urbanisation (Schelin et al., 2000). In Ireland, comparison of incidence data from the present study (CAMFEPS) with findings from an urban study that used identical methodology revealed that the incidence of schizophrenia in males in Dublin was almost twice that of rural males, with a less prominent pattern evident for females; conversely, the incidence of affective psychosis was higher in rural compared to urban areas for both men and women (Kelly et al., 2010). In a systematic review of incidence studies in schizophrenia, McGrath and colleagues found higher rates of schizophrenia in urban vs urban-rural mixed areas (McGrath et al., 2004). van Os and colleagues demonstrated that the urban-rural gradient extends beyond psychotic disorders to community level psychotic symptoms (van Os et al., 2001).

3.4.2 Urbanicity at birth/upbringing and psychosis

Findings of higher rates of schizophrenia and non-affective psychoses in urban setting by place at onset have raised concerns about the possibility of social drift of patients after the onset of their symptoms to urban areas, i.e. reverse causation. Large population-based case register studies have attempted to address the issue of timing of exposure by examining place at birth and upbringing; using a national case register in Sweden, Lewis and colleagues established urban upbringing to be associated with risk for schizophrenia in males (Lewis et al., 1992); similarly, in a large population-based birth cohort
study from Denmark, those born in the capital city had a higher risk for schizophrenia (relative risk 2.40, 95% CI 2.13-2.70) compared to those born in rural areas (Mortensen et al., 1999). In another population-based cohort study, the same investigators demonstrated that urbanicity during upbringing was associated with risk for schizophrenia in a dose-response relationship (Pedersen & Mortensen, 2001a). In this study, mutual adjustment of urbanicity at birth and upbringing rendered the effect of urbanicity at birth to be non-significant. This finding suggests that the effect of urbanicity at birth is explained by urbanicity at upbringing (Pedersen & Mortensen, 2001a). In contrast, in Finland, a study of birth cohorts (1950-1969) showed risk for schizophrenia to be higher in those born in a rural environment in the oldest cohort (1950-54), but such risk was higher in urban areas in the youngest cohort (1964-9) (Haukka et al., 2001). In a more recent study by the same investigators, being born in a rural area was found to be associated with having a diagnosis of any psychotic disorder but not for individual diagnostic categories (Perälä et al., 2008). A meta-analytic review of the association between urbanicity at birth and upbringing and the risk of schizophrenia provided a pooled odds ratio of 2.37 (95% CI 2.01-2.81) (Vassos et al., 2012).

While the body of research on the relationship between urbanicity at birth and risk for psychosis comes from developed countries, the literature from developing countries is sparse. One such study from Uganda has found urban birth to be associated with lifetime symptoms of psychosis (Lundberg et al., 2009); the authors of this study suggest that the urban factor may be universally present and not limited to developed countries.
In summary, with the exception of studies from Finland, several studies have found a significant relationship between urbanicity at birth and upbringing and risk for psychosis in adult life. This may accord with the neurodevelopmental model of schizophrenia.

3.4.3 Methodological considerations

An important line of enquiry into the relationship between urbanicity and psychosis is to establish whether this is a true association or a result of a methodological artefact. Several methodological issues have been examined in a recent literature review, including chance, bias and confounding (Kelly et al., 2010). In this review, the authors describe the possibility of chance findings as a potential explanation for the relationship between urbanicity and psychosis as extremely low (Kelly et al., 2010). Different forms of bias are considered but do not appear to explain this relationship. With regard to confounding, several factors that are associated with risk for psychosis could mediate the relationship between urbanicity and psychosis. These include age, sex, season of birth, obstetric complications, family history, cannabis use, immigrant status, level of education and differential uptake of services in urban and rural areas (Kelly et al., 2010; March et al., 2008).

Advances in statistical methods have allowed for examination of such confounders in multilevel analyses. For instance, Harrison et al. studied a large birth cohort in Sweden and found the association between urban birth and schizophrenia to remain significant after adjusting for obstetric complications and maternal educational level (Harrison et al., 2003). Lewis et al. found urban upbringing to be independently associated with the development of
schizophrenia after adjusting for family history, parental divorce and family finances (Lewis et al., 1992); similarly, in a large population-based Danish cohort, Pedersen and Mortensen showed the effect of urbanicity to remain after adjusting for family history (Pedersen & Mortensen, 2001b). These findings, however, do not rule out a potential role for genetic risk in contributing to the relationship between urbanicity and psychosis. For example, van Os et al. found a positive interaction between urbanicity and familial liability in increasing risk for schizophrenia (van Os et al., 2003). Krabbendam and van Os argue that the effect of the urban environment is conditional on genetic risk factors (Krabbendam & van Os, 2005).

In a large population-based cohort study from Sweden, the association between urbanicity during upbringing and risk for non-affective psychosis remained after adjusting for individual-level characteristics, including family history and being foreign-born (Zammit et al., 2010). However, risk for non-affective psychosis was attenuated on adjusting for area-level social fragmentation. This mirrors the findings of a study by Allardyce and colleagues in which the relationship between urbanicity and schizophrenia appears to be explained by area-level characteristics of fragmentation and deprivation (Allardyce et al., 2005). These studies suggest that the effect of urbanicity may be mediated by contextual rather than individual-level characteristics. Potential mechanisms that may explain the relationship between urbanicity and psychosis will be discussed next.

3.4.4 Aetiology

Having established the validity of the relationship between urbanicity and non-affective psychosis, I now turn to the question of causality. In his paper
‘environment and disease’, Hill proposes several criteria for establishing any causal relationship, including strength of the association, consistency, temporal association, dose-response relationship, plausibility and coherence (Hill, 1965). From the above discussion there is evidence, including a meta-analysis, that the relationship between urbanicity and schizophrenia meets several of those criteria and could be described as a causal relationship. What has been lacking so far is the plausible mechanism through which urbanicity exerts its influence to result in a severe mental illness like schizophrenia. Over the years several mechanisms have been examined. For example, Pedersen and colleagues found that the level of traffic, benzene and carbon monoxide at the residence at birth are associated with the development of schizophrenia (Pedersen et al., 2004). However, it has been argued that the biological plausibility of this relationship is not immediately clear (Kelly et al., 2010). The possibility of biological mechanisms such as infective agents and vitamin D mediating the relationship between urbanicity and psychosis has been explored but there is insufficient evidence to support these hypotheses (Kelly et al., 2010).

A recent novel study has shed some light into the possible role of social factors in the relationship between urbanicity and psychosis. Lederbogen and colleagues used functional magnetic resonance imaging to study neural social stress processing in healthy volunteers (Lederbogen et al., 2011); they found urban upbringing to be associated with differential activation in the perigenual anterior cingulated cortex, a brain region that is ‘implicated in processing chronic social stressors such as social defeat’. On the other hand, current city living was found to be associated with increased amygdala activity (Lederbogen et al., 2011). More recently, the same investigators published findings of a functional
neuroimaging study on a sample of 110 healthy volunteers that showed a
negative correlation between early-life urbanicity and grey matter volume in the
right dorsolateral prefrontal cortex (DLPFC), an area that is known to be sensitive
to stress (Haddad et al., 2015). However, the sample size of these studies is
small. Other limitations include the cross-sectional design of these studies that
precludes assessing the direction of causality and samples that may not be
representative of the general population (Lederbogen et al., 2011). Nonetheless,
if these findings are true, taken together with the above mentioned studies that
showed the relationship between urbanicity and non-affective psychosis is
attenuated after adjusting for area-level socio-environmental risk factors
(Allardyce et al., 2005; Zammit et al., 2010), these findings offer a plausible
mechanism by which the effect of urbanicity during upbringing is mediated by
social stress that operates in the hypothalamic-pituitary-adrenal axis to cause
schizophrenia. It has to be emphasised that such a model is hypothetical and
further research is needed to validate these findings.

3.5 Small area variation
Small area variation in rates of psychosis by place at onset was highlighted by
the pioneering study by Faris and Denham in 1939. Using first admission data
from Chicago, they noted the distribution of schizophrenia to follow the ecological
structure of the city, with concentration in inner city areas and reduction in the
peripheries. Conversely, manic-depressive psychosis (i.e. bipolar disorder)
appeared to follow a random distribution (Faris & Dunham, 1939). Three decades
later, another study by Levy and Rowitz examined the ecological distribution of
mental disorders in Chicago; this study confirmed the findings of Faris and
Denham for all admissions for schizophrenia but not for first admissions (Levy &
Spatial variation in rates of schizophrenia has also been found in several European cities such as Bristol (Hare, 1956), Nottingham (Giggs & Cooper, 1987) and Mannheim (Maylath et al., 1989). While earlier ecological studies may have suffered methodological limitations, such as reliance on hospital admission data, findings of small area variation in rates of psychosis by place at onset were confirmed by more recent methodologically robust studies that used standardised assessment instruments. For example, in a large epidemiological study in South East London, variation was reported for incidence of broad, non-affective psychoses but not for affective psychoses (Kirkbride et al., 2007a).

The body of research on small area variation comes from urban centres. Literature on small area variation within rural areas is sparse. Further, the majority of studies on small areas use onset data, therefore raising the possibility of drift or reverse causation. Notable exceptions are studies from the present study region. These studies, within essentially a rural environment, have indicated small area variation in the prevalence of schizophrenia by both place at onset and birth (Scully et al., 2004; Youssef et al., 1991, 1999). No such variation was found for bipolar disorder (Scully et al., 2004).

3.6 Conclusion
As can be seen from the above review, there is a substantial body of evidence indicating geographical variation in both incidence and prevalence of schizophrenia at national, regional, and small-area levels. The strongest association is between urbanicity and schizophrenia, with an estimated rate of double that for rural areas (Krabbendam & van Os, 2005). With studies
demonstrating that the timing of exposure to urbanicity clearly predates the onset of illness, it is reasonable to conclude that the relationship between urbanicity is causal and not a result of drift of patients to urban areas after the onset of illness. The picture for affective psychoses is less clear, with less consistent findings in the literature. Differences in spatial patterns of affective and non-affective psychoses lend support to the hypothesis that they may be distinct disease processes. Furthermore, evidence of geographical variation in rates of schizophrenia and non-affective psychoses points towards a possible role of environmental factors in the aetiology of those disorders. Some of those factors have been briefly mentioned in relation to urbanicity and will be discussed in detail in the next chapter.
Chapter 4

Environment and psychosis

4.1 Introduction

The substantial geographical variation in rates of psychosis discussed in the previous chapter indicates an important role for environmental factors in the aetiology of psychosis. However, this area of research is relatively understudied; as described in an editorial in *Nature*, ‘too little fundamental research is devoted to environmental factors’ (‘A decade for psychiatric disorders’, 2010). This paucity of research may be explained in part by the various methodological challenges inherent to studying environmental factors, such as difficulties in defining exposure, confounding, reverse causality and the lack of a theoretical framework that would explain any associations found between environment and psychosis (European Network of Schizophrenia Networks for the Study of Gene-Environment Interactions., 2008; van Os et al., 2008). Notwithstanding these caveats, several environmental factors have been implicated in the causation of psychosis. These will be discussed below.

4.2 Obstetric complications

Several studies have provided evidence for a relationship between obstetric complications and schizophrenia. For example, a case-control study by O’Callaghan and colleagues found patients with schizophrenia were significantly more likely to have experienced at least one obstetric complication compared to controls (O’Callaghan et al., 1992). In this study there was a marked sex effect, as male subjects were more vulnerable to obstetric complications. A meta-
analysis of eight population-based studies identified three groups of complications to be significantly associated with schizophrenia: 1) pregnancy complications (e.g. preeclampsia and bleeding), 2) abnormal foetal growth and development (e.g. congenital malformations and low birth weight) and 3) complications of delivery (e.g. asphyxia and uterine atony) (M. Cannon et al., 2002). Finding positive association between obstetric complications and risk for schizophrenia provides support to the neurodevelopmental hypothesis.

4.3 Maternal infection

Maternal infection is considered a plausible risk factor for schizophrenia, as there is evidence from the medical literature documenting a relationship between infective agents during pregnancy and a range of congenital brain disorders (Brown & Patterson, 2011). Several infective agents have been implicated in relation to schizophrenia, including rubella, influenza and toxoplasmosis (Brown, 2006). Early evidence for association between maternal infection and schizophrenia came from a Finnish birth cohort study of the 1957 influenza pandemic (Mednick et al., 1988). The main methodological limitation of such an ecological approach is the possibility of misclassification of exposure, as being born during or immediately after an epidemic does not necessarily confirm individual exposure (Brown & Patterson, 2011). Further, a meta-analysis of studies of the 1957 pandemic described the evidence as ‘insufficient’ (Selten et al., 2010).

Subsequent research used a methodologically robust approach by measuring biomarkers in individual pregnancies to confirm exposure (Brown & Derkits, 2010). Brown and Derkits reviewed birth cohort studies that used this approach
and found evidence for a seven-fold increase in risk for schizophrenia following exposure to influenza during the first trimester of pregnancy (Brown & Derkits, 2010). Additionally, in utero exposure to elevated maternal antibodies of Toxoplasma gondii immunoglobulin G was associated with increased risk for schizophrenia (Brown, 2006). In a separate study, exposure to rubella in the first trimester was also found to be associated with a more than five-fold increase in risk for non-affective psychosis (Brown et al., 2000a). In summary, there is a strong body of evidence supporting increased risk for schizophrenia in subjects whose mothers are exposed to infection during pregnancy. With regard to the mechanism(s) through which maternal infection increases risk for schizophrenia, one of the leading hypotheses relates to the role of maternal cytokines that are released in response to infectious insults (Brown & Derkits, 2010). Other potential mechanisms such as hyperthermia and foetal hypoxia have also been considered (Brown & Derkits, 2010).

4.4 Dietary factors

Similar to the evidence linking maternal infection to schizophrenia, early evidence supporting a relationship between prenatal malnutrition and schizophrenia came from ecological research. In a study of the Dutch Hunger Winter of 1944-1945, Susser and Lin found exposure to severe food deprivation during the first trimester of pregnancy to be associated with hospitalised schizophrenia for women but not for men (Susser & Lin, 1992). Similarly, an increase in risk for schizophrenia was reported in those exposed to the Chinese famine of 1959-1961 (St Clair et al., 2005). Moreover, ecological research has implicated a potential role for specific micronutrients such as Vitamin D in risk for schizophrenia (McGrath et al., 2011). However, evidence supporting a role for
Vitamin D in the aetiology of schizophrenia from analytical epidemiology is lacking; a large case-control study from Denmark found both low and high neonatal concentrations of Vitamin D to be associated with increased risk for schizophrenia (McGrath et al., 2010). Other micronutrients that have been implicated in the aetiology of schizophrenia include homocysteine and iron; using a case-control design, Brown and colleagues found elevated levels of homocysteine in the third trimester to be associated with increased risk for schizophrenia (Brown et al., 2007). The same study group found low maternal hemoglobin levels, indicative of iron deficiency, to be associated with an almost four-fold increase in risk for schizophrenia in a dose-response relationship (Insel et al., 2008).

4.5 Traumatic brain injury

Traumatic brain injury (TBI) is known to be associated with a range of psychiatric disorders, including depression, generalised anxiety disorder and post-traumatic stress disorder (Bryant et al., 2010). However, the relationship between TBI and psychosis is less clear, with previous reviews of the literature being inconclusive (David & Prince, 2005; Hesdorffer et al., 2009). More recently, Molloy and colleagues conducted a systematic review and meta-analysis of 9 studies and found an association between TBI and schizophrenia with a pooled odds ratio of 1.68 (95% CI 1.17-2.32) (Molloy et al., 2011); such risk was higher among subjects with a family history of schizophrenia, suggesting a possible gene-environment interaction (Molloy et al., 2011).
4.6 Advanced paternal age

Malaspina and colleagues examined a large population-based Israeli birth cohort and reported an association between advanced paternal age and risk for schizophrenia (Malaspina et al., 2001), and this finding was replicated in other studies; a meta-analysis of 12 studies reported association between advanced paternal age (≥30) and risk for schizophrenia (Miller et al., 2011). A striking finding in this meta-analysis was the association between younger paternal age (<25) and risk for schizophrenia in men but not women. The finding in relation to advanced paternal age is biologically plausible, as this may be related to mutations. However, the mechanism through which younger paternal age influences schizophrenia risk is not immediately clear.

4.7 Season of birth

An often-replicated finding in psychiatric epidemiology is the season of birth effect on risk for schizophrenia. This was confirmed in a meta-analysis of eight studies from the Northern Hemisphere (Davies et al., 2003); in this study a small increase in risk for schizophrenia was found in subjects born during winter/spring months in the Northern Hemisphere (OR 1.07, CI% 1.05-1.08) (Davies et al., 2003). Seasonality of birth appears to be limited to the Northern Hemisphere, as the findings of a meta-analysis from the Southern Hemisphere were negative (McGrath & Welham, 1999). Moreover, there is some evidence that excess winter birth is confined to those without a family history of mental illness, indicating a possible greater role for environmental factors (O’Callaghan et al., 1991). Suggested environmental factors that may contribute to excess winter births in patients with schizophrenia include Vitamin D and viral infections (Davies et al., 2003).
4.8 Lead exposure

Two studies from the USA established an association between lead exposure, measured by determining levels of δ–aminolevulinic acid (δ-ALA), in the prenatal period and risk for schizophrenia in adulthood (Opler et al., 2004, 2008). A plausible biological mechanism that may explain the relationship between lead exposure and psychosis is antagonism of the N-methyl-D-aspartate (NMDA) receptor, which is implicated in the pathophysiology of schizophrenia (Guilarte, 2004).

4.9 The social environment and psychosis

4.9.1 Introduction

One of the most hotly contested topics in psychiatric epidemiology is the role of socio-environmental risk factors (SERFs) in the aetiology of psychosis (van Os & McGuffin, 2003). It is worthwhile placing this in historical context. One of the first studies to implicate a role for social factors in the onset of psychosis is the study by Faris and Denham in the 1930s (Faris & Dunham, 1939). Using first-admission data from psychiatric hospitals over a 12-year period, higher rates of schizophrenia were found in inner city areas characterised by extreme social disorganisation and residential mobility; conversely, rates of manic-depressive psychoses appeared to follow a random distribution. Faris and Dunham hypothesised that social isolation played a causal role in the aetiology of schizophrenia. Despite the positive correlations found by Faris and Dunham, their hypothesis and ecological research of SERFs were relatively neglected for the most part of the 20th century. Notable exceptions to this are studies from Bristol (Hare, 1956), Nottingham (Dauncey et al., 1993; Giggs & Cooper, 1987) and Mannheim (Maylath et al., 1989). Research in this field focused on
individual-level SERFs as exemplified by dominance of the social drift hypothesis. Another factor that played a role in the decline of ecological research is concern about ecological fallacy; the incorrect use of aggregate data as substitutes for individual-level variables (for example, using a neighbourhood deprivation index as a proxy measure for individual socioeconomic status). However, it has been argued that a distinction should be made between ecological fallacy and ecological perspective, that is, ‘analysis of the effects of the social and physical environment on the health of individuals and populations’ (McIntyre & Ellaway, 2003).

In recent years, several factors contributed to renewed interest in the role of the social environment in the aetiology of psychosis: (1) advances in statistical methods in the form of multilevel modelling have allowed for delineation of individual-level and neighbourhood–level attributes (Allardyce & Boydell, 2006); (2) a growing body of evidence supporting variation in incidence of schizophrenia by place; and (3) convergence of ‘old dichotomies’ towards an integrated, biopsychosocial model that leads to the development of psychosis (Allardyce & Boydell, 2006; Morgan et al., 2007c).

A key issue in studying the relationship between the social environment and psychosis is identifying a unit of analysis from the various layers of societal organisation (individual, family, and neighbourhood). In this review, studies are organised around the classical two levels most commonly studied: (1) area-based (contextual) characteristics, such as deprivation, social fragmentation and social capital; and (2) individual–level (compositional) factors, such as ethnicity, social class, social adversity and cannabis use.
4.9.2 Neighbourhood-level characteristics and onset of psychosis

4.9.2.1 Social fragmentation/disorganisation

Researchers have used aggregates of census-derived variables as single measurements (e.g. residential mobility) and/ or composite measures (e.g. social fragmentation index) to assess the relationship between neighbourhood-level social fragmentation and rates of psychosis. For example, in Maastricht van Os and colleagues reported an association between variance in incidence of schizophrenia and the neighbourhood-level factor of the proportion of single and the proportion of divorced people, independent of individual-level factors (van Os et al., 2000). Similarly, in the USA Silver and colleagues used data from the ECA study to examine the relationship between neighbourhood characteristics and prevalence of mental illness (Silver et al., 2002); residential mobility was associated with higher rates of schizophrenia, major depression and substance abuse disorder. This neighbourhood-level effect remained after adjusting for individual-level characteristics. In Scotland, social fragmentation was associated with first admission rates for psychosis in a dose-response relationship, independent of deprivation and urban/rural status (Allardyce et al., 2005).

There are also some negative results: another study from Maastricht reported no association between treated incidence of schizophrenia and neighbourhood-level measures of residential instability on adjusting for individual-level characteristics (Drukker et al., 2006). Moreover, in a large population-based study from Sweden, most of the variance in rates for non-affective psychosis was explained by individual-level characteristics (Zammit et al., 2010). However, area-level social fragmentation appeared to explain the excess of rates of non-affective psychosis in urban areas. Thus, it has been argued that neighbourhood-level variables may
be responsible for the differential in rates of psychosis between urban and rural environments (Allardyce et al., 2005; Zammit et al., 2010). This mirrors earlier findings from Italy whereby neighbourhood effects were present in urban but not rural regions of the study (Thornicroft et al., 1993). In summary, over the past two decades evidence from several ecological studies suggests that social fragmentation is as an important contextual candidate in the onset of non-affective psychosis. This, it has been argued, takes us back ‘full circle’ to Faris and Dunham (Morgan, 2007a). Furthermore, the effect of social fragmentation appears to be more marked in urban settings. However, these findings are subject to inherent limitations of ecological studies, such as their cross-sectional design precluding determination of the direction of causality for any associations and resultant inability to exclude some role for social drift.

4.9.2.2 Deprivation

Several ecological studies have demonstrated an association between neighbourhood-level deprivation and rates of psychosis. For example, Harrison and colleagues reported an association between admission rates for schizophrenia and aggregates of census variables of material deprivation, including overcrowding and unemployment (Harrison et al., 1995). This finding was replicated in studies that used composite measures of material deprivation, such as the Townsend (Townsend et al., 1988) and Carstairs (Carstairs & Morris, 1991) indices (Allardyce et al., 2005; Boardman et al., 1997). However, while a study by Croudace et al. found a strong relationship between social deprivation, measured by the mental health need index, and incidence of psychosis, this relationship was non-linear (Croudace et al., 2000). One of the main methodological shortcomings of these studies is their sole reliance on aggregate-
level data, without adjusting for individual-level deprivation. More recent studies that examined both individual and neighbourhood-level deprivation have shown attenuation of neighbourhood-level deprivation on adjusting for individual-level variables (Silver et al., 2002; van Os et al., 2000).

4.9.2.3 Social Capital

Social capital is becoming increasingly recognised as an important neighbourhood-level factor. Social capital was defined by Putnam (Putnam, 1993) as consisting of five principal characteristics:

3. Local civic identity: sense of belonging and solidarity, and of equality with other members of the community
4. Reciprocity and norms of cooperation: a sense of obligation to help others, along with confidence that such assistance will be returned.
5. Trust in the community.

Research on the association between social capital and mental illness is in its infancy. A systematic review of the relationship between mental illness and both individual and ecological-level social capital found no evidence for relationships between them (De Silva et al., 2005). The authors attributed this to the diverse methods and outcome measures used in different studies (De Silva et al., 2005). Even less is known about the association between area-level social capital and psychotic disorders. One of the few studies that have examined the relationship between neighbourhood-level social capital and incidence of psychosis reported this to be non-linear (Kirkbride et al., 2008b). Kawachi and Burkman suggest
three potential mechanisms through which social capital could influence individual health: first, by influencing health-related behaviours; second, by influencing access to services; and finally by affecting psychosocial processes (Kawachi & Berkman, 2000). However, despite the strong theoretical basis, evidence for an association between ecological social capital and psychosis is yet to emerge.

4.9.2.4 Ethnic density

One of the often overlooked findings from the study of Faris and Denham (Faris & Dunham, 1939) is the inverse proportionality between admission rate for schizophrenia for any given ethnic group and size of the group living in that area. The authors conclude: “it is apparent that the schizophrenic rate is significantly higher for those races residing in areas not primarily populated by their own group”. Four decades later, this finding was replicated by Rabkin in a study of the relationship between hospital admission rates and ethnic density in health areas in New York; higher hospitalisation rates for black, white and Puerto Rican residents were reported in areas where they represented minority group (Rabkin, 1979). In the UK, a study by Boydell and colleagues reported an inverse dose-response relationship between the incidence of schizophrenia and the proportion of the non-white minority living in their neighbourhood in London (Boydell et al., 2001). Similarly, another study from London reported an effect of ethnic density on risk for schizophrenia (Kirkbride et al., 2007b). A study from the Netherlands also reported a higher incidence of psychotic disorders among immigrants in low-density neighbourhoods, i.e. where they comprised a small proportion of the population (Veling et al., 2008). More recently, a meta-analysis of eight studies has found elevated incidence of psychosis in low ethnic density areas (Bosqui et
A possible mechanism that may explain the effect of ethnic density is the role of discrimination. In a study by Veling and colleagues from the Netherlands, incidence of psychosis was found to be associated with perceived discrimination among ethnic minorities (Veling et al., 2007). Further support for a possible role of adverse social experiences in mediating the role of ethnic density comes from another study by the same investigators in the Netherlands; negative ethnic identity (negative identification with one’s ethnic group) was associated with increased risk for schizophrenia (Veling et al., 2010).

4.9.3 Neighbourhood-level characteristics by place at birth

One of the main challenges for neighbourhood research is the difficulty in disentangling cause from effect. Therefore, it could be argued that increased rates of psychosis in socially deprived neighbourhoods are a result of social drift of patients to those areas after the onset of their symptoms (the causation vs selection debate). Ideally, studies examining the relationship between neighbourhood social environment and rates of psychosis should be able to capture both the timing and duration of such exposure. In reality this is methodologically difficult. Thus far, only few studies have attempted to overcome this methodological limitation by examining the relationship between neighbourhood-level SERFs by place at birth and psychosis risk later in life: using the Camberwell case register, Castle and colleagues found subjects who develop schizophrenia were more likely than controls to have been born into socially deprived neighbourhoods (Castle et al., 1993); similarly, in a matched case-control study in Nottingham, area–level deprivation at birth was associated with increased risk for developing schizophrenia in later life (Harrison et al., 2001). More recently, a large population-based birth cohort study that used
multilevel analysis reported higher rates of schizophrenia among subjects who were born in poorer residential areas after adjusting for individual-level variables, including socioeconomic status, sex and age of the father at the subject’s birth (Werner et al., 2007). These studies indicate the relationship with neighbourhood-level deprivation is not necessarily due to social drift and add weight to the social causation hypothesis.

4.9.4 Aetiological considerations

Despite the accumulating evidence suggesting a role for the neighbourhood social environment in the aetiology of schizophrenia, the mechanisms that explain this association remain unknown. A potential unifying mechanism that may explain the role of both ethnic density and social fragmentation in risk for schizophrenia is the hypothesis of social defeat. Selten and Cantor-Graae proposed that long-term exposure to social defeat/’outsider status’ increases risk for schizophrenia (Selten & Cantor-Graae, 2005). The authors offer a biological explanation for the role of social defeat through sensitisation of the mesolimbic dopamine system (Selten & Cantor-Graae, 2005). This hypothesis is in agreement with the concept of behavioural sensitisation proposed by van Winkel and colleagues (van Winkel et al., 2008); in this model the postulated underlying mechanism is that repeated exposure to severe psychosocial stress increases the biological and behavioural response to subsequent exposure to a similar event, even if subsequent exposure is not as severe (van Winkel et al., 2008). The authors hypothesised a neurobiological substrate ‘involving the dysregulation of the hypothalamic-pituitary-adrenal axis, contributing to a hypothesised final common pathway of dopamine sensitisation in mesolimbic areas and increased stress-induced striatal dopamine release’ (van Winkel et al., 2008).
These models are extended further by Morgan and colleagues who proposed a ‘sociodevelopmental pathway to psychosis’, in which social adversity interacts with genetic liability and impacts on the dopaminergic system and stress sensitivity to ultimately lead to the development of psychosis that becomes evident in the event of further stress (Morgan et al., 2010). While the authors acknowledge that this model is speculative and is only supported by limited evidence, it provides a conceptual framework that can be tested by further research.

4.9.5 Individual-level SERFs

4.9.5.1 Migration and ethnicity

4.9.5.1.1 Early US studies

There is a rich literature on the relationship between migration and psychosis. For example, in his study of ‘lunacy’ in Massachusetts in 1855, Edward Jarvis noted that ‘The result of this lunatic inquiry reveal the great number of foreigners among our insane; and this is more remarkably seen in the public institutions appropriated to the guardianship and the care of those afflicted with this malady’ (Jarvis, 1971). In the 20th century, one of the earliest studies to report excess rates of psychosis among immigrants was conducted by Ødegaard (Ødegaard, 1932). He examined first admissions of Norwegian immigrants in the state of Minnesota, USA, and rates were compared to those of native residents of Minnesota and rates of admissions in Norway; in this detailed analysis, Norwegian immigrants were found to have higher rates than the two comparator populations, hence Ødegaard proposed selective migration as a potential explanation for his findings. Subsequent large studies by Malzberg also showed higher rates of dementia praecox (i.e. schizophrenia) among foreign-born
residents of New York State compared to the native population (Malzberg, 1955, 1964). However, attention to the relationship between migration and psychosis only began in earnest with the UK studies of African-Caribbean immigrants.

4.9.5.1.2 UK migrant studies

In the second half of the 20th century, the literature on the relationship between migration and psychosis derived mainly from studies of African-Caribbean immigrants living in the UK. One of the first studies was conducted by Hemsi in the boroughs of Camberwell and Lambeth (Hemsi, 1967). This study found excess rates of schizophrenia and affective disorders among West Indian immigrants. Over the next four decades several studies have consistently shown higher rates of schizophrenia among African-Caribbeans (Bebbington et al., 1981; Bhugra et al., 1997; Harrison et al., 1988; Wessely et al., 1991). While earlier studies had several limitations, including lack of adequate information on the denominator population and reliance on hospital register diagnoses as opposed to using standardised diagnostic instruments, the findings of excess rates persisted even with more methodologically robust studies that used the 1991 census, the first in the UK to contain data on the ethnic structure of the general population (Fearon & Morgan, 2006). Further evidence has come from a recent large multi-centre study that confirmed elevated rates of schizophrenia and manic psychosis among African-Caribbeans living in the UK (Fearon et al., 2006).

4.9.5.1.3 Other migrant studies

Higher rates of psychosis among immigrants were also found in other European countries: in the Netherlands, Selten and colleagues found the incidence of
schizophrenia in the Surinamese and Antillean immigrants to be three- to four-fold higher than in the general population (Selten et al., 1997). In Sweden, a large population-based study, using national hospital discharge data as an outcome measure, reported elevated rates of schizophrenia and other psychoses among first- and second-generation immigrants from different ethnic backgrounds (Hjern et al., 2004). In a meta-analysis of 18 schizophrenia incidence studies of migrant groups between 1977 and 2003, Cantor-Graae and Selten estimated the relative risk for development of schizophrenia among first-generation immigrants to be 2.7%, with a higher risk of 4.5% for second-generation immigrants (Cantor-Graae & Selten, 2005). The highest risk was observed for migrants from countries where the majority of the population is of a black skin colour. In summary, epidemiological research from the past century has consistently shown high rates of psychosis among immigrants. Several hypotheses have been proposed for such findings. These will be considered below.

4.9.5.1.4 Aetiological explanations

The Afro-Caribbean studies came at the time of dominance of the ‘social drift’ hypothesis. Therefore, sociological explanations were ignored for the most part and the focus of research was on biological pathways including selective migration, obstetric complications and increased genetic susceptibility. However, so far, research has failed to find any significant support for such biological hypotheses. For example, in a novel study by Selten and colleagues (Selten et al., 2002), the authors examined the selective migration hypothesis by assessing the rate of schizophrenia among Surinamese immigrants to the Netherlands while including the resident population of Surinam in the denominator for the
Surinamese-born relative risk; this was still found to be higher than among those born in the Netherlands. The role of obstetric complications was examined by Hutchinson and colleagues, who found African-Caribbean psychotic patients were less likely to experience pregnancy and birth complications compared to their white counterparts (Hutchinson et al., 1997).

By the turn of the 21st century, it has become increasingly clear that biological mechanisms could not solely account for the differential rate of psychoses among immigrants. This, together with revival in interest in the role of the social environment, has led to a shift of focus towards the role of SERFs. In a matched case-control study of 100 patients and the same number of controls, Mallett and colleagues examined the role of individual-level SERFs across Afro-Caribbean, Asian and white populations in the UK (Mallett et al., 2002) and found unemployment to be associated with casesness, the risk being highest among the Afro-Caribbean group; another important risk factor was separation from both parents before the age of 17. The authors of the study acknowledge the small sample size as a limitation to their study. Moreover, it is difficult to interpret unemployment in a causal pathway, as this indeed maybe a consequence of schizophrenia. Two other studies from the UK reported associations between risk for psychosis and individual-level SERFs, including separation from a parent during childhood, living alone, being single, and limited social networks (Morgan, et al., 2007b, 2008). In the aforementioned Swedish study (Hjern et al., 2004), when socio-economic indicators at the household level were controlled for, the risk ratios for schizophrenia and other psychoses were considerably reduced among immigrant groups. This reduction was more marked in the non-European immigrants. However, risk ratios for Finnish, Eastern and Southern European
immigrants remained elevated. The reason for this finding is not immediately clear but it indicates that other unknown factors may contribute to risk for psychosis in European migrant groups.

To conclude, there is a strong body of evidence indicating increased rates of schizophrenia and to some extent other psychoses among migrant groups. This appears to be valid and not a result of methodological artefacts. While available data do not implicate a single factor in explaining the increased rate of psychosis among migrants, there is limited evidence that social adversity plays an important role in this relationship (Morgan et al., 2010).

4.9.5.2 Socio-economic position

There is a wealth of literature on the relationship between socio-economic position and psychosis. In 1855, Edward Jarvis stated that ‘there is a manifestly larger ratio of the insane among the poor, and especially among those who are paupers, than among the independent and more prosperous classes’ (Jarvis, 1971). In Ireland, in 1911 Dawson observed that the geographical distribution of insanity in Ireland highly corresponded with rates of pauperism (Dawson, 1911). Over the next century, several studies have reported higher rates of schizophrenia among lower social classes; Hollingshead and Redlich examined a large sample of psychiatric patients in New Haven, Connecticut, and found an excess of schizophrenia among lower social class (Hollingshead & Redlich, 1958). This finding was replicated by Hare in Bristol (Hare, 1955). To determine whether the relationship between schizophrenia and social class is due to ‘social drift’, Goldberg and Morrison examined the social class of fathers of patients with
schizophrenia and found this to be comparable with the general population
(Goldberg & Morrison, 1963). This lent support to the drift hypothesis.

However, subsequent studies that examined parental social class showed mixed
results. In Nottingham, Harrison and colleagues found an inverse association
between parental social class and risk for schizophrenia in adult life (Harrison et
al., 2001). Conversely, a study from Dublin found no link between schizophrenia
and social class at birth (Mulvany et al., 2001). One study even found higher
social class at birth to be associated with increased risk for schizophrenia
(Mäkikyrö et al., 1997). More recently, this issue has been re-visited in a number
of population-based cohorts. In Denmark, Byrne and colleagues found risk for
schizophrenia to be associated not only with paternal lower income and
unemployment but also with parental higher education (Byrne et al., 2004). In a
large population-based study of childhood adversity in Sweden, the unclassified
socioeconomic group was the only group to be associated with increased risk for
schizophrenia (Wicks et al., 2005). However, after adjusting for potential
confounders such as paternal age this effect was no longer evident. Another
large population-based cohort from Israel found a modest increase in risk for
schizophrenia among those whose fathers were in the lowest social class after
adjusting for advanced paternal age (Corcoran et al., 2009). More recently, a
systematic review of 14 studies has concluded that there is not enough evidence
to support a relationship between social class at birth and psychosis (Kwok,
2014). All in all, evidence from population-based studies indicates that any
relationship between socio-economic position and schizophrenia may not simply
be a result of social drift, but the evidence is not conclusive.
4.9.5.3 Childhood abuse

There are mixed reports in the literature on the relationship between childhood abuse (either sexual or physical) and risk for psychotic disorders. For example, in a case register study in Australia, rates of schizophrenia among victims of child sexual abuse were no different to the general population (Spataro et al., 2004). In contrast, in the United Kingdom, Bebbington and colleagues showed that reported child sexual abuse was associated with psychosis in adulthood (Bebbington et al., 2004). In a large population-based study in the Netherlands, Janssen and colleagues found reported childhood sexual abuse to predict the development of positive psychotic symptoms (Janssen et al., 2004). Studies of childhood abuse, however, are subject to several methodological limitations, such as recall bias and the difficulty in measuring abuse. A systemic review of the literature was inconclusive and cited methodological problems (Bendall et al., 2008).

4.9.5.4 Adult adversity

There is some evidence that psychosocial stress in adulthood is associated with the onset of psychosis. Using data from the Camberwell collaborative psychosis study, Bebbington and colleagues found subjects with psychosis had an excess rate of life events preceding the onset of psychosis in comparison with the general population (Bebbington et al., 1993). Further analysis of these data showed the relationship between life events and psychosis was still evident after adjusting for clinical and sociodemographic variables (Bebbington et al., 1996). However, the retrospective nature of these studies limits our ability to interpret their findings.
4.9.5.5 Cannabis misuse

The role of cannabis misuse in the aetiology of psychosis has attracted considerable research interest over the past two decades. While there is little doubt that higher rates of cannabis use are found in patients with psychosis, what has been less clear is the nature of this relationship. In other words, is cannabis use a cause or a consequence of psychosis? One of the first studies that showed a temporal relationship between cannabis use and psychosis is the Swedish conscripts study, which demonstrated a strong relationship between heavy cannabis use and risk for schizophrenia in a dose-response manner (Andréasson et al., 1987). In this large cohort study of 45,570 Swedish conscripts, subjects who self-reported heavy cannabis use at conscription were at higher risk for developing schizophrenia at follow-up. Criticisms of this study centred on the possibility that the results may be explained by confounding factors. However, a re-analysis by Zammit et al. showed that the relationship between cannabis use and schizophrenia was reduced but remained evident after adjusting for several potential confounders such as low IQ, poor social integration, disturbed behaviour, and city upbringing (Zammit et al., 2002). Furthermore, Arseneault and colleagues reviewed five population-based cohort studies, including the Swedish conscripts study, and found a temporal association between cannabis use and development of schizophrenia (Arseneault et al., 2004). They estimated cannabis use to confer ‘an overall two-fold increase in the relative risk for later schizophrenia’. Similarly, Moore et al. conducted a systematic review of the literature and found elevated risk for ‘any psychotic outcome’ in those who ever used cannabis (pooled adjusted odds ratio 1.41, 95 CI% 1.20-1.65) (Moore et al., 2007). In a meta-analysis, Semple et al.
suggested that cannabis use increases the risk of developing ‘schizophrenia or schizophrenia-like psychotic illness’ by almost three-fold (Semple et al., 2005).

4.10 Conclusion

In this chapter, several environmental factors have been examined with regard to their contribution to the development of psychotic disorders. Some of these factors are supported by meta-analytical studies, such as those concerning migration, obstetric complications, season of birth, cannabis use and traumatic brain injury. There is also a growing body of evidence to support a role for socioenvironmental factors in the aetiology of psychosis, including neighbourhood effects of ethnic density and social fragmentation. We have limited understanding of the mechanisms through which environmental factors influence risk for psychosis. Nonetheless, there are emerging hypotheses that integrate biopsychosocial mechanisms and provide promising conceptual frameworks for further research.
Chapter 5

Aims and Methods

5.1 Aims

This thesis aims to examine the relationship between the environment and incidence of first episode psychosis using data from CAMFEPS accrued during the 12-year period 1995-2007. CAMFEPS aims to capture ‘all’ incident cases of first episode psychosis in a geographically defined area in rural Ireland. Several factors operate to help achieve this aim of high capture, including: Firstly, the strict catchment area policy relating to public mental health services in Ireland; patients presenting to hospitals in catchment areas other than their residence are transferred back to their catchment area service as soon as possible. Second, Cavan-Monaghan Mental Health Service enjoys close links with primary care; this allows for detection and ease of tracing of cases with first episode psychosis. Finally, the study protocol includes identification of all admissions from the catchment area to the two main private psychiatric hospitals in Ireland and to the Central Mental Hospital, which provides the national forensic service. Together, these factors make the CAMFEPS dataset to be of unusual epidemiological completeness.

Specific aims of the present study include:

1. Assessment of geographical variation in incidence of first episode psychosis by place at onset vs place at birth.

2. Examination of the relationship between socio-environmental risk factors at the neighbourhood level and incidence of psychosis by place at onset.
3. Examination of the relationship between socio-environmental risk factors at the neighbourhood level and incidence of psychosis by place at birth.

5.1.1 Geographical variation

The first aim of this study is to examine geographical variation beyond the traditional urban/rural divide. In the past, studies of geographical variation have focused on urban/rural differences and small area variation within urban centres. The few studies that have examined geographical variation within rural areas have primarily used prevalence data, due to the small size of these areas and therefore low numbers of incident cases. The inception sample from CAMFEPS is sufficient to allow such examination for ‘all psychoses’ and across broad diagnostic categories using incidence data. Further, the demographics of the study area allow examination of geographical variation in relation to temporal aspects of the illness: geographical variation by place at birth would implicate factors operating during gestation and early childhood, while variation by place at onset would implicate factors precipitating the onset of psychosis.

5.1.2 The social environment and onset of psychosis

The second aim of this study is to assess, for the first time, the contribution of socio-environmental risk factors at the neighbourhood-level to the onset of psychosis within a rural setting. The ethnic homogeneity of the study area during the study period, together with the predominantly rural nature of Cavan-Monaghan, allows for examination and possible elucidation of socio-environmental risk factors in the essential absence of migration and urbanicity that have so far been a particular focus of epidemiological studies on the relationship between the social environment and psychosis.
5.1.3 The social environment by place at birth and incidence of psychosis

The third aim of this study is to investigate the relationship between socio-environmental risk factors by place at birth and risk for psychosis later in life. This will allow examination of putative risk factors operating during pregnancy and childhood. Further, such investigation informs on the direction of causality for found associations, a potential challenge for studies proximal to the onset of psychosis.

5.2 Study area

5.2.1 Geography

Cavan and Monaghan are two contiguous rural counties in the province of Ulster in the North East of the Republic of Ireland (Fig. 1). The two counties cover an area of 3225 square kilometres, with a landscape that consists of numerous lakes and elongated hills and ridges of glacial origin known as drumlins. The region consists of remote areas, villages and small towns, with an absence of any major urban areas. Electoral divisions (EDs) constitute the smallest administrative sub-regions below county level for which census population data are available. The study region contains a total of 155 EDs, having a population mean per ED of 697 in 2002 (Fig. 2).

5.2.2 Population

According to the 2002 census, which is the closest to the midpoint of the present study (1995-2007), the total population of County Cavan was 56,546 [29,015 males and 27,531 females]; the population of County Monaghan was 52,593 [26,806 males and 25,787 females] (Central Statistics Office, 2003). This signalled a 2.5% increase in County Monaghan and a 6.8% increase in County Cavan from the 1996 census, in comparison with an 8.0% increase in the total
population of Ireland. The region is characterised by low level of residential mobility, with 93% of the population of County Cavan and 94% of the population of County Monaghan residing at the same address as one year previously according to the 2002 census. This compares to 91% for the country as a whole (Central Statistics Office, 2003). These are substantially ethnically homogeneous counties, with the great majority of the population being white Irish (89.6% in Monaghan, 89.4% in Cavan) (Central Statistics Office, 2007). Moreover, a substantial proportion of the population of Cavan and Monaghan were born in Ireland: 87% of the population of County Monaghan born in Ireland, 10% born in the UK, 90% of the population of County Cavan were born in Ireland, 7% born in the UK (Central Statistics Office, 2003). This facilitates accrual of data in relation to place at birth.

5.2.3 Socioeconomic indicators

While historically Cavan-Monaghan was an overwhelmingly agriculture-based economy, more recent statistics reveal a picture of diverse socioeconomic groups. The Central Statistics Office divides socio-economic groups into 10 categories including employers and managers (socioeconomic group A), higher and lower professional workers (socio-economic groups B &C) non-manual, and manual skilled workers (socio-economic groups D & E), semi-skilled and unskilled workers (socio-economic groups F & G), own account workers (socio-economic group H), farmers (socio-economic group I), agricultural workers (socio-economic group J), and all other gainfully occupied and unknown (socio-economic group Z) (Central Statistics Office, 2003). In 2002, skilled workers (socio-economic groups D & E) represented 26% of socio-economic groups in Cavan-Monaghan while farmers and agricultural workers represented 16% and
14% in Cavan and Monaghan respectively (Central Statistics Office, 2003). Further, 82% households in Cavan-Monaghan own at least one car and over 80% of the houses are owner-occupied (Central Statistics Office, 2003).

5.2.4 Mental health service provision

The study is based within Cavan-Monaghan Mental Health Service that serves the two counties, with the exception of a very small number of EDs located in the North-West (panhandle) of County Cavan that are (for more effective provision of care) served by Sligo/Leitrim Mental Health Services.

Cavan-Monaghan Mental Health Service operates a community-based model comprising two community mental health teams, including home-based treatment teams, a specialist service for the elderly and a community rehabilitation team. The service has been recently re-organised with the amalgamation of the two admission units into a single unit in Cavan General Hospital with the appointment of an inpatient consultant. Central to the delivery of health services in this model is the use of home-based treatment as an alternative to hospital admission (McCauley et al., 2003). In addition to home-based care, Cavan-Monaghan Mental Health Service provides multi-centre outpatient clinics, day centre and day hospital services. The service puts strong emphasis on maintaining close links with general practitioners (GPs) who comprise the main source of referrals. For example, one of the community mental health teams had pioneered (in an Irish context) a GP consultation-liaison model in which a consultant psychiatrist meets on-site on a regular basis with GPs to give advice and discuss clinical problems (Wright & Russell, 2007).
Fig. 1 Map of the Republic of Ireland with the counties of Cavan and Monaghan outlined.
Fig. 2 Map of Cavan-Monaghan Electoral Divisions with population density, 2002. Source: DG Pringle, Department of Geography, National University of Ireland, Maynooth.
5.3 Methods

5.3.1 Ethical approval

The CAMFEPS study protocol was approved by the Research Ethics Committees of (initially) the North Eastern Health Board and (subsequent to reorganisation) the Health Service Executive Dublin North East Area, St. Patrick’s Hospital, St. John of God Hospital and the Central Mental Hospital, to include (a) cases giving informed consent to formal assessment and (b) obtaining diagnostic/demographic information from case notes/treating teams for cases declining formal assessment and entering these data into an anonymised dataset.

5.3.2 Study cohort

Cases were participants in the first 12 years of CAMFEPS (1995-2007). This is a prospective study of ‘all’ incident cases presenting with a first episode of any of the 12 DSM-IV psychotic disorders, including a first manic episode, in Cavan-Monaghan since 1995 and has previously been described in detail (Baldwin et al., 2005; Kingston et al., 2013; Owoeye et al., 2013). In outline, the study involves the following ascertainment procedures: cases identified from (a) all treatment teams in the catchment areas, (b) cases from the catchment areas who present privately to St. Patrick’s Hospital or St. John of God Hospital, Dublin, which together account for >95% of all national private psychiatric admissions, and (c) cases from the catchment areas having forensic admission to the Central Mental Hospital, Dublin. The primary criterion for entry to the study is a first lifetime episode of any psychotic illness at age 16 or above, with no upper age cut-off. DSM-IV diagnosis is made at inception, together with psychopathological and cognitive assessments, with repeat DSM-IV diagnosis
made at 6 months; there are no exclusion criteria other than a previously treated episode of psychosis or psychosis occurring with a prior, overriding diagnosis of gross neurodegenerative disease.

Accrual of cases, assessment and diagnosis was conducted by a Clinical Research Fellow/Registrar who is embedded in Cavan-Monaghan Mental Health Service and based in St. Davnet’s hospital, Monaghan (see Kingston et al., 2013; Owoeye et al., 2013). The Clinical Research Fellow/Registrar maintains regular contact with mental health teams to ensure identification of putative cases with first episode psychosis. Once a case has been identified, the individual is then assessed by the Clinical Research Fellow/Registrar as soon as possible in an appropriate setting such as a community clinic, outpatient unit, inpatient unit, or domiciliary visit as appropriate.

5.3.3 Assessment instruments

The following assessment instruments were used in CAMFEPS:

1. Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID)
2. Positive and Negative Syndrome Scale (PANSS)
3. Mini-Mental State Examination (MMSE)
4. Executive Interview (EXIT)
5. Premorbid Adjustment Scale
6. Quality of Life Scale
7. Beiser Scale
8. Simpson-Angus Scale
9. Abnormal Involuntary Movement Scale (AIMS)
10. Condensed Neurological Examination (CNE)
11. Neurological Evaluation Scale (NES)

12. Scale to Assess Unawareness of Mental Disorder (SUMD)

13. Edinburgh Handedness Inventory

14. Family history interview

5.3.4 Geographical variation by place at onset vs place at birth

5.3.4.1 Place at onset

In this study address at first presentation was considered a proxy for place at onset. This was obtained from clinical records and the corresponding ED for each address was identified using the Health Atlas Ireland database, a web-based source that enables geocoding of all addresses in the Republic of Ireland (Health Atlas Ireland). Place at onset was defined as each case’s domestic location over the 3-month period immediately prior to first presentation with a psychotic illness. For cases with more than one address in the study area over this period, the address at which he/she was living for more than 50% of the time was applied. Cases with a second address outside the study area were included only if they were living for more than 50% of the time in Cavan-Monaghan. Cases with no fixed address were excluded from the study. Cases of non-functional psychosis [i.e. substance-induced psychosis or psychosis due to a general medical condition] and those whose onset of illness was outside of Cavan-Monaghan were excluded from the study. In multiply affected families, only the first-born was included.

5.3.4.2 Place at birth

Parental location over the period of pregnancy and delivery was considered a proxy for place at birth. For each case, a copy of his/her birth certificate was
obtained from the Civil Registration Offices in Cavan and Monaghan and the ‘dwelling place of father’ extracted (dwelling place of mother is not recorded in Irish birth certificates except in the absence of a named father). As for place at onset, cases of non-functional psychosis [i.e. substance-induced psychosis or psychosis due to a general medical condition] and those who were born outside of Cavan-Monaghan were excluded from the study. In multiply affected families, only the first-born was included.

5.3.5 Neighbourhood-level characteristics and incidence of first episode psychosis by place at onset

ED-based measures were calculated using information from the 2002 census (Central Statistics Office, 2003), this being the census closest to the mid-point of the present study (1995-2007). These calculations were carried out with the assistance of Prof. Dennis Pringle, Department of Geography, National University of Ireland, Maynooth.

5.3.5.1 Material deprivation

Material deprivation was quantified using a deprivation index, similar to the Carstairs (Carstairs & Morris, 1991) and Townsend (Townsend et al., 1988) indices, which was developed by the Small Area Health Research Unit (SAHRU) in Trinity College Dublin (Kelly & Teljeur, 2004). This index was constructed for each ED by applying principal component analysis to a combination of selected census-based indicators, including unemployment, social class, type of house tenure and car ownership. EDs are divided into ten categories on an ordinal scale, with 1 being least deprived and 10 most deprived. For the present analyses, recognising the modest sample size of the study relative to the number
of EDs, the index was collapsed into five categories [1 = 1 & 2; 2 = 3 & 4; 3 = 5 & 6; 4 = 7 & 8; 5 = 9 & 10]. These analyses were carried out with the assistance of Prof. Dennis Pringle, Department of Geography, National University of Ireland, Maynooth.

5.3.5.2 Social fragmentation

The Social Fragmentation Index (SFI) was developed by Congdon for a study of suicide in London (Congdon, 1996). SFI was calculated by adding z scores of four census variables for each ED: 1) non-married adults, 2) single-person households, 3) population turnover and 4) private renting. For the present analyses, in keeping with prior ecological research that uses the SFI index (Allardyce et al., 2005), the index was collapsed into four categories, created by quartiles, with 1 being least socially fragmented and 4 most socially fragmented. These calculations were carried out with the assistance of Prof. Dennis Pringle, Department of Geography, National University of Ireland, Maynooth.

5.3.5.3 Urban-rural classification

This classification, developed by SAHRU for health services research at the small area level in Ireland, combines multiple variables, including population density, settlement size and proximity to urban centres (Teljeur & Kelly, 2008). EDs are divided into six categories on an ordinal scale, with 1 being most rural and 6 most urban. For multilevel analyses, the urban-rural classification (URC) was collapsed into three- and two-category variables: URC3 (1 = rural; 2 = village, 3 = town); and URC2 (1 = rural, 2 = village & town). URC3 was used for the ecological analysis. These calculations were carried out with the assistance
of Prof. Dennis Pringle, Department of Geography, National University of Ireland, Maynooth.

5.3.6 Neighbourhood-level socio-environmental factors and incidence of first episode psychosis by place at birth

5.3.6.1 Study design

A matched case-control design was used. Cases and controls were matched for age (to within one year) and sex: for each case, a copy of his/her birth certificate was obtained from the Civil Registration Offices in Cavan or Monaghan and the two same-sex entries above and the two same-sex entries below on the birth register were selected as controls. Two indices of socioeconomic status at birth were examined. Firstly, ‘Occupation of father’ was extracted from the birth certificate and a social class assigned according to the Census of Population Classification of Occupations for Ireland (Central Statistics Office, 1986), which consists of six categories I (highest) – VI (lowest). Farmers are assigned to a social class category based on farm acreage. Information on acreage was obtained from the Property Registration Authority in Dublin with the assistance of Dr. Martha Finnegan, Psychiatry Registrar, St. Patrick’s University Hospital, Dublin. Assigning social class from father’s occupation was carried out independently by two investigators: myself and Dr. Martha Finnegan. In instances where the social class could not be readily assigned or disagreement, this was resolved by consensus meetings that involved myself, Dr. Martha Finnegan, Prof. Paul Fearon, Consultant Psychiatrist, St. Patrick’s University Hospital, Dublin and the Research Supervisor Prof. John Waddington. Secondly, the social characteristics of the ED at birth were ascertained for ‘Dwelling-place of father’ on the birth certificate (dwelling place of the mother is not recorded on
Irish birth certificates, except in the absence of a named father); this entry was used as a proxy for parental location over the period of pregnancy.

5.3.6.2 Neighbourhood-level characteristics
ED-based measures were calculated with the assistance of Prof. Dennis Pringle using information from the 1971 census; this census was closest to the median year of birth of cases in the study cohort [1970].

5.3.6.2.1 Material deprivation
The deprivation index used in this analysis was based on the SAHRU index, which contains four indicators including unemployment, social class, type of house tenure and car ownership. The first three indicators were used from the 1971 census. However, as data on social class were not available at ED level until the 1986 census, 1986 social class data were used to calculate the deprivation index. The index was used to divide the EDs into four quartiles, with 1 being least deprived and 4 most deprived. These calculations were carried out with the assistance of Prof. Dennis Pringle, Department of Geography, National University of Ireland, Maynooth.

5.3.6.2.2 Social fragmentation
The social fragmentation index (SFI) was calculated with the assistance of Prof. Dennis Pringle by adding z scores of four census variables for each ED: 1) percentage of adults not married, 2) percentage of adults in single-person households, 3) population turnover and 4) percentage of households in private rented housing. As information on population turnover, as defined in the SFI, only became available from the 2002 census onwards, the absolute net population change over the 10-year period prior to the 1971 census was calculated with the
assistance of Prof. Dennis Pringle as a surrogate measure of population turnover. For the present analyses, the index was collapsed into four categories, created by quartiles, with 1 being least socially fragmented and 4 most socially fragmented. These calculations were carried out with the assistance of Prof. Dennis Pringle, Department of Geography, National University of Ireland, Maynooth.

5.3.6.2.3 Urban-rural classification

The SAHRU urban-rural classification (Teljeur & Kelly, 2008) was used, in which EDs are divided into six categories on an ordinal scale, with 1 being most rural and 6 most urban. This index was collapsed into three category variables (1 = rural, 2 = village, 3 = town) for ecological analysis. These calculations were carried out with the assistance of Prof. Dennis Pringle, Department of Geography, National University of Ireland, Maynooth.

Recognising that the SAHRU urban-rural classification uses data from the 2002 census, which may not be representative of the level of rurality in the study area around the time of birth of the study group, an urban-rural index was also calculated with the assistance of Prof. Dennis Pringle using a similar methodology as used to calculate the social fragmentation and deprivation indices. The following variables from the 1971 census were included in the index: population density, percentage of farmers, percentage with main water supply and percentage of people living in local authority housing.
5.4 Statistical analysis

5.4.1 Geographical variation study

Incidence rate was calculated with the assistance of Prof. Dennis Pringle for ‘all psychoses’ and diagnostic subgroups (i.e. males, females; non-affective, affective) from the number of cases in each area. The population at risk for the ‘place at onset’ group was determined from the 2002 census; this census was closest to the midpoint of the present study (1995-2007). The population at risk for ‘place at birth’ group was determined from the total population of Cavan-Monaghan who were aged 0-4 in the 1971 census; this census was closest to the median year of birth of the study group [1970]. Incidence is expressed as a case rate per 100,000 general population.

Two approaches were used to assess the geographical variation of incidence at ED level. First, Departures from a random distribution of cases between areas was evaluated using the $X^2$ test. This compares the observed number of cases in each area ($O_i$) against the expected number ($E_i$). The expected number of cases $E_i$ is given by $p_c/p$ (where $c$ is the total number of cases in the study area, $p$ is the total population at risk in the study area and $p_i$ is the population at risk in the $i^{th}$ area). The test statistic is given by:

$$X^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$$

where $n$ is the number of areas.

This could be tested for significance by reference to $X^2$ tables with $n-1$ degrees of freedom. However, the $X^2$ values in tables are unreliable when there are a large number of low expected values, so significance was assessed using a Monte Carlo approach. This entailed randomly allocating $c$ cases to areas, where $c$ is
the number of cases in the diagnostic subgroup and the probability of an area receiving each case is in proportion to its population at risk. Once the c cases had been allocated, a $X^2$ statistic was calculated using the above formula. This process was repeated 10,000 times to generate a probability distribution. If the $X^2$ value for the actual cases falls within the tail containing the 5 per cent highest values, then the distribution may be regarded as significant at $p \leq 0.05$.

Second, evidence for spatial heterogeneity in the distribution of EDs of high and low incidence was examined by Bayesian methods. The Bayesian approach overcomes the issue of the ‘small numbers problem’ for disorders of low incidence, such as schizophrenia, which results in unstable risk estimates due to stochastic variations if maximum likelihood methods are used (Pringle, 1996). A Bayesian model involves obtaining ‘a posterior distribution’ of relative risk estimates, which describes the distribution of possible values for the parameter conditional upon the observed data. Posterior distributions are obtained by combining ‘a prior distribution’, which refers to the initial assumption about the possible distribution of data, and the likelihood function, which is the Poisson distribution of cases conditional on the true incidence in each area (Pringle, 1996). Empirical Bayesian incidence estimates were calculated using a Gamma model developed by Clayton and Kaldor (as cited in Pringle, 1996). This model assumes that the relative risks $\theta_i$ follow a Gamma distribution with a scale parameter $\alpha$ and a shape parameter $\nu$ (i.e. mean $\nu/\alpha$ and variance $\nu/\alpha^2$) and that the observed number of cases $O_i$ are Poisson variates with an expectation $O_iE_i$ where $E_i$ is the number of cases that would be expected in area $i$ given its population at risk. $\alpha$ and $\nu$ are estimated using the following equations:
Having estimated \( \alpha \) and \( \nu \), the posterior distribution of \( \theta_i \) conditional on \( O_i \) is given by:

\[
\hat{\nu} = \frac{1}{\hat{\alpha}} \sum_{i} \frac{O_i + \hat{\nu}}{E_i + \hat{\alpha}} = \frac{1}{N} \sum_{i} \hat{\theta}_i
\]

\[
\frac{\hat{\nu}}{\hat{\alpha}^2} = \frac{1}{N-1} \sum_{i} \left( \frac{\hat{\alpha}}{E_i} \right) (\theta_i - \hat{\nu} / \hat{\alpha})^2
\]

These analyses were carried out with the assistance of Prof. Dennis Pringle using a Fortran programme.

5.4.2 Neighbourhood-level socio-environmental factors and incidence of first episode psychosis by place at onset

Recognising the modest size of our sample (216) relative to the total number of EDs (155), to maximise the statistical power of the study, two complementary approaches to data analysis were adopted.

First, in line with previous literature (Abas et al., 2006; Allardyce et al., 2005; O’Reilly et al., 2008), EDs were aggregated according to neighbourhood-level indices (deprivation scores, fragmentation quartiles and rurality categories) ignoring spatial contiguity. Age-standardised incidence rates (SIR) were calculated with the assistance of Prof. Dennis Pringle using software written by Prof. Pringle for each category and rate ratios (RR) [with 95% confidence intervals (CI)] were obtained by using category 1 for each neighbourhood-level characteristic as reference. Kendall’s rank correlation coefficients (\( \tau \)) were
calculated between incidence rates and category numbers to test whether there was a ‘dose-response’ relationship between incidence and the hypothesised environmental risk factors. These analyses were carried out with the assistance of Prof. Dennis Pringle, Department of Geography, National University of Ireland, Maynooth.

Second, a multilevel Poisson regression model (Kirkbride et al., 2007b, 2008a) (XTPOISSON command, Stata version 11.1), was applied with the assistance of Dr. James Kirkbride, University of Cambridge, by which area-based measures were treated as continuous z-standardised (deprivation, SFI) or categorical (URC) variables. This multivariate approach allowed adjusting more fully for potential confounding between individual- and neighbourhood-level variables. Incidence of psychosis was modelled, with variation in incidence quantified by fitting normally distributed random effects at the ED level. Correlation analysis was performed to test the strength of association between neighbourhood-level characteristics; these were entered in the model as fixed effects, using a forward-fitting modelling strategy. The natural logarithm of the denominator population, adjusted for the 12-year study period, was entered as an offset term in these models. Significance of fixed effects and their interactions was assessed by Likelihood Ratio Tests (LRTs). To inspect for the possibility of over-dispersion in our models at the ED level (more zero counts of cases than expected under a Poisson distribution), we re-fitted our final models under a zero-inflated-Poisson (ZIP) regression, using a Vuong test to test for evidence of over-dispersion. In all analyses a multilevel Poisson model was found to perform satisfactorily. These analyses were carried out with the assistance of Dr. James Kirkbride, University of Cambridge.
5.3.6 Neighbourhood-level socio-environmental factors and incidence of first episode psychosis by place at birth

Cross-tabulated categorical data were analysed using $X^2$ tests, with odds ratios (ORs) and 95% confidence intervals (95% CIs) calculated for all variables of interest. The Mann-Whitney U-test was also used to examine social class as an ordinal scale in cases vs controls. Logistic regression models were fitted to examine the relationship of caseness (i.e. the likelihood of being a case as opposed to a control) to individual- and neighbourhood-level characteristics, which were entered as continuous variables. Analysis of variance (ANOVA) was used to examine the relationship of age at first presentation to individual- and neighbourhood-level characteristics. These analyses were carried out with the assistance of a statistician, Mr. Anthony Kinsella, Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, using PASW Statistics 18 software.
Chapter 6

Results

6.1 Geographical variation by place at onset vs place at birth

During the first 12 years of the present study, May 1995-April 2007, CAMFEPS incepted 336 cases of any DSM-IV psychotic illness. After excluding non-functional cases \( n = 41 \), non-proband cases in multiply affected families \( n = 10 \), those whose onset of illness was outside the study area \( n = 28 \), and those without a fixed address in the study area \( n = 2 \), the total number of cases of functional psychotic illness [hereafter ‘all psychoses’] included in the place at onset analysis was 255 [144 male, 111 female]. Cases were further subdivided into two broad diagnostic categories: a) ‘non-affective psychoses’ [schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder, psychosis not otherwise specified: \( n = 132 \); 83 male, 49 female]; and b) ‘affective psychoses’ [bipolar disorder and major depressive disorder with psychotic features: \( n = 123 \); 61 male, 62 female]. The total number of cases of functional psychotic illness included in the place at birth analysis, after excluding an additional 69 cases who were born outside of Cavan-Monaghan or ED at birth could not be identified, was 216 [122 male, 94 female]. Of those, 112 cases were ‘non-affective psychoses’ [71 male, 41 female] and 104 ‘affective psychoses’ [51 male, 53 female].

6.1.1 Geographical variation by place at onset

Bayes estimates of incidence rates by place at onset for ‘all psychoses’ are shown in Fig. 3. The overall distribution of ‘all psychoses’ and the two diagnostic
subgroups appeared to show spatial homogeneity. When tested for departure from random distribution, the results were not statistically significant (Table 1).

![Fig. 3. Bayes estimates of incidence of ‘all psychoses’ by place at onset across Electoral Divisions of Cavan and Monaghan.](image)

**Table 1.** Variation in incidence of first episode psychosis by place at onset

<table>
<thead>
<tr>
<th>Category</th>
<th>X²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘All psychoses’</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>145.0</td>
<td>0.66</td>
</tr>
<tr>
<td>Female</td>
<td>152.0</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>148.6</td>
<td>0.56</td>
</tr>
<tr>
<td>‘Non-affective psychoses’</td>
<td>139.0</td>
<td>0.75</td>
</tr>
<tr>
<td>Male</td>
<td>136.6</td>
<td>0.79</td>
</tr>
<tr>
<td>Female</td>
<td>141.3</td>
<td>0.68</td>
</tr>
<tr>
<td>‘Affective psychoses’</td>
<td>139.5</td>
<td>0.84</td>
</tr>
<tr>
<td>Male</td>
<td>153.2</td>
<td>0.47</td>
</tr>
<tr>
<td>Female</td>
<td>127.1</td>
<td>0.86</td>
</tr>
</tbody>
</table>
6.1.2 Geographical variation by place at birth

Fig. 4 shows Bayes estimates of incidence of ‘all psychoses’ for the full sample. This deviates significantly from random distribution (Table 2). When ‘affective psychoses’ and ‘non-affective psychoses’ were studied separately, significant spatial variations were found for both diagnostic subgroups in men but not women (Figs. 5 & 6; Table 2).

Fig. 4. Bayes estimates of incidence of ‘all psychoses’ by place at birth across Electoral Divisions of Cavan and Monaghan.
Fig. 5. Bayes estimates of incidence of 'all psychoses' in males by place at birth across Electoral Divisions of Cavan and Monaghan.
Fig. 6. Bayes estimates of incidence of ‘all psychoses’ in females by place at birth across Electoral Divisions of Cavan and Monaghan.

Table 2. Variation in incidence of first episode psychosis by place at birth.

<table>
<thead>
<tr>
<th>Category</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘All psychoses’</td>
<td>198.3</td>
<td>0.0264*</td>
</tr>
<tr>
<td>Male</td>
<td>331.8</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Female</td>
<td>131.9</td>
<td>0.8290</td>
</tr>
<tr>
<td>‘Non-affective psychoses’</td>
<td>181.0</td>
<td>0.1062</td>
</tr>
<tr>
<td>Male</td>
<td>260.3</td>
<td>0.0020*</td>
</tr>
<tr>
<td>Female</td>
<td>106.9</td>
<td>0.9828</td>
</tr>
<tr>
<td>‘Affective Psychoses’</td>
<td>188.2</td>
<td>0.0737</td>
</tr>
<tr>
<td>Male</td>
<td>256.0</td>
<td>0.0059*</td>
</tr>
<tr>
<td>Female</td>
<td>159.6</td>
<td>0.3592</td>
</tr>
</tbody>
</table>

*p < 0.05
6.2 Neighbourhood-level characteristics and incidence of psychosis by place at onset

6.2.1 Material deprivation

For ‘all psychoses’, increase in level of deprivation was associated with increase in incidence rate among men but not women (Table 3). There was a significant reduction in risk for ‘all psychoses’ in women living in the second-least deprived areas. ‘Non-affective psychoses’ and ‘affective psychoses’ were then considered separately. For ‘non-affective psychoses’, the association between deprivation and incidence for males was found to be less consistent, whilst no association was again found for women. For ‘affective psychoses’, increase in level of deprivation was associated with a variable increase in incidence rate among men and a reduction in rate among women (Table 3).

6.2.2 Social fragmentation

For ‘all psychoses’, the highest rate of psychosis among women was in the most socially fragmented areas (Table 4); this pattern was evident for both ‘non-affective psychoses’ and ‘affective psychoses’ There were no significant associations between rate of psychosis and social fragmentation among men (Table 4).

6.2.3 Urban/rural classification

For ‘all psychoses’, the highest rates of psychosis among women were in the least rural areas (Table 5); this pattern was evident for ‘affective psychoses’ but less so for ‘non-affective psychoses’. There were no significant associations between rates of psychosis and urban/rural classification among men (Table 5).
## Table 3. Age-standardised incidence ratios (SIR) per 100,000 and rate ratios (RR) by deprivation index for place at onset.

| Rank | All psychoses |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |�

| Rank | All psychoses |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |�

| Rank | Non-affective psychoses |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |�

| Rank | Affective psychoses |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |�

1 Rank 1 (reference): least deprived; rank 5: most deprived. * p < 0.05.
Table 4. Age-standardised incidence ratios (SIR) per 100,000 and rate ratios (RR) by social fragmentation index for place at onset.

<table>
<thead>
<tr>
<th>Quartile&lt;sup&gt;1&lt;/sup&gt;</th>
<th>All psychoses</th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
</tr>
<tr>
<td>1</td>
<td>21.58 (17.97-25.19)</td>
<td>1</td>
<td>-</td>
<td>25</td>
<td>9785</td>
<td>14.10 (11.10-17.10)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>17.55 (14.28-20.81)</td>
<td>0.81 (0.64-1.04)</td>
<td>21</td>
<td>10232</td>
<td>11.25 (8.56-13.94)</td>
<td>0.80 (0.59-1.09)</td>
<td>12</td>
<td>9183</td>
</tr>
<tr>
<td>3</td>
<td>20.85 (17.30-24.40)</td>
<td>0.97 (0.77-1.22)</td>
<td>36</td>
<td>14593</td>
<td>12.79 (9.93-15.65)</td>
<td>0.91 (0.67-1.23)</td>
<td>21</td>
<td>14005</td>
</tr>
<tr>
<td>4</td>
<td>24.57 (20.72-28.41)</td>
<td>1.14 (0.91-1.43)</td>
<td>62</td>
<td>20555</td>
<td>24.29 (20.38-28.21)</td>
<td>1.72 (1.33-2.24)*</td>
<td>63</td>
<td>20612</td>
</tr>
<tr>
<td>Non-affective psychoses</td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
</tr>
<tr>
<td>1</td>
<td>12.31 (9.56-15.05)</td>
<td>1</td>
<td>-</td>
<td>14</td>
<td>9785</td>
<td>5.69 (3.75-7.63)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>10.23 (7.72-12.74)</td>
<td>0.83 (0.60-1.15)</td>
<td>12</td>
<td>10232</td>
<td>4.59 (2.84-6.34)</td>
<td>0.81 (0.50-1.31)</td>
<td>5</td>
<td>9183</td>
</tr>
<tr>
<td>3</td>
<td>12.79 (9.99-15.59)</td>
<td>1.04 (0.78-1.41)</td>
<td>22</td>
<td>14593</td>
<td>7.28 (5.10-9.46)</td>
<td>1.28 (0.83-1.98)</td>
<td>12</td>
<td>14005</td>
</tr>
<tr>
<td>4</td>
<td>13.68 (10.79-16.57)</td>
<td>1.11 (0.82-1.50)</td>
<td>35</td>
<td>20555</td>
<td>10.12 (7.56-12.67)</td>
<td>1.78 (1.18-2.67)*</td>
<td>26</td>
<td>20612</td>
</tr>
<tr>
<td>Affective psychoses</td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
</tr>
<tr>
<td>1</td>
<td>9.27 (6.88-11.66)</td>
<td>1</td>
<td>-</td>
<td>11</td>
<td>9785</td>
<td>8.41 (6.07-10.75)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>7.31 (5.18-9.45)</td>
<td>0.79 (0.54-1.15)</td>
<td>9</td>
<td>10232</td>
<td>6.66 (4.57-8.75)</td>
<td>0.79 (0.53-1.19)</td>
<td>7</td>
<td>9183</td>
</tr>
<tr>
<td>3</td>
<td>8.06 (5.82-10.30)</td>
<td>0.87 (0.60-1.25)</td>
<td>14</td>
<td>14593</td>
<td>5.51 (3.60-7.42)</td>
<td>0.66 (0.43-1.00)</td>
<td>9</td>
<td>14005</td>
</tr>
<tr>
<td>4</td>
<td>10.89 (8.30-13.48)</td>
<td>1.17 (0.84-1.65)</td>
<td>27</td>
<td>20555</td>
<td>14.17 (11.17-17.18)</td>
<td>1.69 (1.20-2.37)*</td>
<td>37</td>
<td>20612</td>
</tr>
</tbody>
</table>

<sup>1</sup> Quartile 1 (reference): most socially cohesive; quartile 4: most socially fragmented. * p < 0.05.
Table 5. Age-standardised incidence ratios (SIR) per 100,000 and rate ratios (RR) by urban/rural index for place at onset.

<table>
<thead>
<tr>
<th>Category(^1)</th>
<th>All psychoses</th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
</tr>
<tr>
<td>Category 1 (reference): most rural; category 3: least rural. * p &lt; 0.05.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>21.64 (18.02-25.25)</td>
<td>1</td>
<td>-</td>
<td>90</td>
<td>35210</td>
<td>15.53 (12.39-18.68)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>20.69 (17.15-24.22)</td>
<td>0.96</td>
<td>(0.76-1.21)</td>
<td>19</td>
<td>7512</td>
<td>19.24 (15.75-22.73)</td>
<td>1.24</td>
<td>(0.95-1.62)</td>
</tr>
<tr>
<td>3</td>
<td>22.08 (18.43-25.73)</td>
<td>1.02</td>
<td>(0.81-1.29)</td>
<td>35</td>
<td>12443</td>
<td>20.71 (17.09-24.33)</td>
<td>1.33</td>
<td>(1.03-1.73)</td>
</tr>
<tr>
<td>Non-affective psychoses</td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
</tr>
<tr>
<td>1</td>
<td>12.63 (9.85-15.41)</td>
<td>1</td>
<td>-</td>
<td>52</td>
<td>35210</td>
<td>6.76 (4.66-8.86)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>11.96 (9.25-14.66)</td>
<td>0.95</td>
<td>(0.70-1.29)</td>
<td>11</td>
<td>7512</td>
<td>10.39 (7.80-12.98)</td>
<td>1.54</td>
<td>(1.05-2.26)</td>
</tr>
<tr>
<td>3</td>
<td>12.07 (9.35-14.79)</td>
<td>0.96</td>
<td>(0.71-1.30)</td>
<td>20</td>
<td>12443</td>
<td>8.21 (5.90-10.52)</td>
<td>1.21</td>
<td>(0.81-1.82)</td>
</tr>
<tr>
<td>Affective psychoses</td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
</tr>
<tr>
<td>1</td>
<td>9.01 (6.65-11.37)</td>
<td>1</td>
<td>-</td>
<td>38</td>
<td>35210</td>
<td>8.78 (6.39-11.16)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>8.73 (6.40-11.05)</td>
<td>0.97</td>
<td>(0.68-1.39)</td>
<td>8</td>
<td>7512</td>
<td>8.85 (6.45-11.24)</td>
<td>1.01</td>
<td>(0.70-1.46)</td>
</tr>
<tr>
<td>3</td>
<td>10.01 (7.52-12.49)</td>
<td>1.11</td>
<td>(0.78-1.58)</td>
<td>15</td>
<td>12443</td>
<td>12.50 (9.67-15.33)</td>
<td>1.42</td>
<td>(1.01-2.01)</td>
</tr>
</tbody>
</table>
6.2.4 Multi-level analysis for place at onset

There were some significant relationships between neighbourhood variables; for example, material deprivation index was strongly positively correlated with social fragmentation ($r^2 = 0.63$, $p<0.01$). Relationships between individual-level variables, neighbourhood-level variables and incidence of ‘all psychoses’ are shown in Table 6. As expected, risk was highest among the 15-24 age group and declined over subsequent decades until around 65 years of age, after which risk increased slightly; decline in risk with age was less marked among women than among men. In the unadjusted multilevel model, increased levels of deprivation and social fragmentation were associated with higher incidence of psychosis. In the fully adjusted model (for age and sex), there was a relationship between increased level of deprivation and higher incidence rates of psychosis when stratified by sex, this effect being evident only among women. No such association was evident when the sample was restricted to those ages studied typically in first episode samples (15-64 years) (Table 7); a marginal interaction between age group and level of deprivation in the full sample (LRT $p = 0.08$) suggested further that that the association between level of deprivation and risk for psychosis derived particularly from the group aged 65-74 years. When ‘non-affective psychoses’ and ‘affective psychoses’ were analysed separately, no associations between any neighbourhood-level variable for place at onset and risk for psychosis was evident (Tables 8-11). There was a marginal association between increased levels of deprivation and risk for ‘affective psychoses’. This effect was not evident when the subjects were stratified by sex (Table 10).
Table 6. Multi-level modelling of individual- and neighbourhood-level socio-environmental risk factors for place at onset for all psychoses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects: IRR (95% CI)</th>
<th>Men: IRR (95% CI)</th>
<th>Women: IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Full</td>
<td>LRT p</td>
</tr>
<tr>
<td><strong>Individual-level variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>1</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>25-34</td>
<td>0.8 (0.5-1.1)</td>
<td>0.8 (0.6-1.1)</td>
<td>0.7 (0.4-1.0)</td>
</tr>
<tr>
<td>35-44</td>
<td>0.5 (0.4-0.8)</td>
<td>0.5 (0.6-0.8)</td>
<td>0.4 (0.3-0.7)</td>
</tr>
<tr>
<td>45-54</td>
<td>0.5 (0.3-0.8)</td>
<td>0.5 (0.6-0.8)</td>
<td>0.3 (0.2-0.6)</td>
</tr>
<tr>
<td>55-64</td>
<td>0.4 (0.3-0.7)</td>
<td>0.4 (0.3-0.7)</td>
<td>0.4 (0.2-0.7)</td>
</tr>
<tr>
<td>65-74</td>
<td>0.6 (0.4-1.0)</td>
<td>0.6 (0.4-1.0)</td>
<td>0.4 (0.2-0.8)</td>
</tr>
<tr>
<td>75+</td>
<td>0.9 (0.5-1.3)</td>
<td>0.9 (0.6-1.4)</td>
<td>0.8 (0.4-1.5)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women vs men</td>
<td>0.8 (0.6-1.0)</td>
<td>0.8 (0.6-1.0)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Neighbourhood-level variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFI</td>
<td>1.10 (1.01-1.20)</td>
<td>-</td>
<td>0.60</td>
</tr>
<tr>
<td>Deprivation</td>
<td>1.13 (1.03-1.24)</td>
<td>1.12 (1.03-1.23)</td>
<td>0.01</td>
</tr>
<tr>
<td>URC3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>-</td>
<td>0.86</td>
</tr>
<tr>
<td>Village</td>
<td>1.07 (0.74-1.54)</td>
<td>-</td>
<td>0.97 (0.59-1.60)</td>
</tr>
<tr>
<td>Town</td>
<td>1.19 (0.90-1.58)</td>
<td>-</td>
<td>1.07 (0.73-1.58)</td>
</tr>
<tr>
<td>URC2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>-</td>
<td>0.58</td>
</tr>
<tr>
<td>Less rural</td>
<td>1.15 (0.89-1.47)</td>
<td>-</td>
<td>1.04 (0.74-1.45)</td>
</tr>
</tbody>
</table>

IRR, incidence rate ratio (with 95% CI); LRT, likelihood ratio test; p value indicated whether a variable improved overall final model fit. IRR not reported for variables that did not significantly improve the final model at the p <0.05 threshold of significance. SFI, social fragmentation index; URC, urban-rural classification; Deprivation, material deprivation index.
Table 7. Multi-level modelling of individual- and neighbourhood-level socio-environmental risk factors for place at onset for all psychoses aged 15-64.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects: IRR (95% CI)</th>
<th>Men: IRR (95% CI)</th>
<th>Women: IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Full</td>
<td>LRT p</td>
</tr>
<tr>
<td><strong>Individual-level variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>1</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25-34</td>
<td>0.8 (0.5-1.1)</td>
<td>0.8 (0.6-1.3)</td>
<td>0.7 (0.4-1.0)</td>
</tr>
<tr>
<td>35-44</td>
<td>0.5 (0.4-0.8)</td>
<td>0.8 (0.6-1.5)</td>
<td>0.4 (0.3-0.7)</td>
</tr>
<tr>
<td>45-54</td>
<td>0.5 (0.3-0.8)</td>
<td>0.5 (0.6-1.7)</td>
<td>0.3 (0.2-0.6)</td>
</tr>
<tr>
<td>55-64</td>
<td>0.4 (0.3-0.7)</td>
<td>0.4 (0.5-1.5)</td>
<td>0.4 (0.2-0.7)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women vs men</td>
<td>0.8 (0.6-1.0)</td>
<td>0.8 (0.6-1.0)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Neighbourhood-level variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFI</td>
<td>1.09 (0.98-1.20)</td>
<td>-</td>
<td>0.56</td>
</tr>
<tr>
<td>Deprivation</td>
<td>1.10 (0.99-1.22)</td>
<td>1.09 (0.99-1.21)</td>
<td>0.09</td>
</tr>
<tr>
<td>URC3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>-</td>
<td>0.81</td>
</tr>
<tr>
<td>Village</td>
<td>1.15 (0.78-1.70)</td>
<td>-</td>
<td>1.13 (0.67-1.89)</td>
</tr>
<tr>
<td>Town</td>
<td>1.11 (0.80-1.52)</td>
<td>-</td>
<td>1.19 (0.78-1.80)</td>
</tr>
<tr>
<td>URC2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>-</td>
<td>0.76</td>
</tr>
<tr>
<td>Less rural</td>
<td>1.12 (0.85-1.48)</td>
<td>-</td>
<td>1.17 (0.81-1.67)</td>
</tr>
</tbody>
</table>

IRR, incidence rate ratio (with 95% CI); LRT, likelihood ratio test; p value indicated whether a variable improved overall final model fit. IRR not reported for variables that did not significantly improve the final model at the p <0.05 threshold of significance. SFI, social fragmentation index; URC, urban-rural classification; Deprivation, material deprivation index.
Table 8. Multi-level modelling of individual- and neighbourhood-level socio-environmental risk factors for place at onset for non-affective psychoses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects: IRR (95% CI)</th>
<th>Men: IRR (95% CI)</th>
<th>Women: IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Full</td>
<td>LRT p</td>
</tr>
<tr>
<td>Individual-level variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>25-34</td>
<td>0.8 (0.5-1.4)</td>
<td>NA</td>
<td>0.9 (0.5-1.5)</td>
</tr>
<tr>
<td>35-44</td>
<td>0.6 (0.4-1.1)</td>
<td>NA</td>
<td>0.4 (0.2-0.8)</td>
</tr>
<tr>
<td>45-54</td>
<td>0.4 (0.2-0.7)</td>
<td>NA</td>
<td>0.3 (0.1-0.7)</td>
</tr>
<tr>
<td>55-64</td>
<td>0.2 (0.1-0.5)</td>
<td>NA</td>
<td>0.2 (0.1-0.7)</td>
</tr>
<tr>
<td>65+</td>
<td>0.5 (0.3-0.9)</td>
<td>NA</td>
<td>0.5 (0.2-0.9)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women vs men</td>
<td>0.6 (0.4-0.9)</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>Neighbourhood-level variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFI</td>
<td>1.09 (0.97-1.23)</td>
<td>-</td>
<td>0.14</td>
</tr>
<tr>
<td>Deprivation</td>
<td>1.11 (0.98-1.26)</td>
<td>-</td>
<td>0.12</td>
</tr>
<tr>
<td>URC3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>-</td>
<td>0.82</td>
</tr>
<tr>
<td>Village</td>
<td>1.13 (0.70-1.86)</td>
<td>-</td>
<td>0.98 (0.51-1.87)</td>
</tr>
<tr>
<td>Town</td>
<td>1.10 (0.74-1.65)</td>
<td>-</td>
<td>1.06 (0.63-1.78)</td>
</tr>
<tr>
<td>URC2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>-</td>
<td>0.53</td>
</tr>
<tr>
<td>Less rural</td>
<td>1.12 (0.79-1.58)</td>
<td>-</td>
<td>1.02 (0.66-1.61)</td>
</tr>
</tbody>
</table>

IRR, incidence rate ratio (with 95% CI); LRT, likelihood ratio test; p value indicated whether a variable improved overall final model fit. IRR not reported for variables that did not significantly improve the final model at the p < 0.05 threshold of significance. NA, included in the final model but IRR not reported as there was some evidence of interaction (LRT p value: 0.07) between age and sex. SFI, social fragmentation index; URC, urban-rural classification; Deprivation, material deprivation index.
Table 9. Multi-level modelling of individual- and neighbourhood-level socio-environmental risk factors for place at onset for non-affective psychoses aged 15-64.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects: IRR (95% CI)</th>
<th>Men: IRR (95% CI)</th>
<th>Women: IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Full</td>
<td>LRT p</td>
</tr>
<tr>
<td><strong>Individual-level variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>25-34</td>
<td>0.8 (0.5-1.4)</td>
<td>NA</td>
<td>0.9 (0.5-1.5)</td>
</tr>
<tr>
<td>35-44</td>
<td>0.6 (0.4-1.1)</td>
<td>NA</td>
<td>0.4 (0.2-0.8)</td>
</tr>
<tr>
<td>45-54</td>
<td>0.4 (0.2-0.7)</td>
<td>NA</td>
<td>0.3 (0.1-0.7)</td>
</tr>
<tr>
<td>55-64</td>
<td>0.2 (0.1-0.5)</td>
<td>NA</td>
<td>0.2 (0.1-0.7)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women vs men</td>
<td>0.6 (0.4-0.9)</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td><strong>Neighbourhood-level variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SFI</strong></td>
<td>1.07 (0.93-1.22)</td>
<td>-</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Deprivation</strong></td>
<td>1.06 (0.92-1.22)</td>
<td>-</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>URC3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>-</td>
<td>0.84</td>
</tr>
<tr>
<td>Village</td>
<td>1.18 (0.70-1.98)</td>
<td>-</td>
<td>1.14 (0.59-2.21)</td>
</tr>
<tr>
<td>Town</td>
<td>1.05 (0.67-1.62)</td>
<td>-</td>
<td>1.11 (0.64-1.92)</td>
</tr>
<tr>
<td><strong>URC2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>-</td>
<td>0.66</td>
</tr>
<tr>
<td>Less rural</td>
<td>1.09 (0.75-1.59)</td>
<td>-</td>
<td>1.12 (0.70-1.79)</td>
</tr>
</tbody>
</table>

IRR, incidence rate ratio (with 95% CI); LRT, likelihood ratio test; p value indicated whether a variable improved overall final model fit. IRR not reported for variables that did not significantly improve the final model at the p <0.05 threshold of significance. NA, included in the final model but IRR not reported as there was some evidence of interaction (LRT p value: 0.04) between age and sex. SFI, social fragmentation index; URC, urban-rural classification; Deprivation, material deprivation index.
Table 10. Multi-level modelling of individual- and neighbourhood-level socio-environmental risk factors for place at onset for affective psychoses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects: IRR (95% CI)</th>
<th>Men: IRR (95% CI)</th>
<th>Women: IRR (95% CI)</th>
<th>Unadjusted</th>
<th>Full</th>
<th>LRT p</th>
<th>Unadjusted</th>
<th>Full</th>
<th>LRT p</th>
<th>Unadjusted</th>
<th>Full</th>
<th>LRT p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual-level variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>1</td>
<td>1</td>
<td>0.07</td>
<td>1</td>
<td>1</td>
<td>0.11</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td>0.7 (0.4-1.2)</td>
<td>0.7 (0.4-1.2)</td>
<td>0.4 (0.2-0.9)</td>
<td>0.4 (0.2-0.9)</td>
<td>1.1 (0.5-2.5)</td>
<td>1.1 (0.5-2.5)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>35-44</td>
<td>0.4 (0.2-0.8)</td>
<td>0.4 (0.2-0.8)</td>
<td>0.5 (0.2-1.1)</td>
<td>0.5 (0.2-1.1)</td>
<td>0.3 (0.1-0.9)</td>
<td>0.3 (0.1-0.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>0.6 (0.4-1.1)</td>
<td>0.6 (0.4-1.2)</td>
<td>0.4 (0.1-0.9)</td>
<td>0.4 (0.1-0.9)</td>
<td>1.1 (0.5-2.6)</td>
<td>1.1 (0.5-2.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>0.8 (0.4-1.5)</td>
<td>0.8 (0.4-1.5)</td>
<td>0.6 (0.2-1.4)</td>
<td>0.6 (0.2-1.4)</td>
<td>1.1 (0.5-2.8)</td>
<td>1.1 (0.5-2.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65+</td>
<td>1.0 (0.6-1.6)</td>
<td>1.0 (0.6-1.6)</td>
<td>0.7 (0.3-1.5)</td>
<td>0.7 (0.3-1.5)</td>
<td>1.4 (0.6-2.9)</td>
<td>1.4 (0.6-2.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women vs men</td>
<td>1.1 (0.7-1.5)</td>
<td>1.0 (0.7-1.5)</td>
<td>0.81</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Neighbourhood-level variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFI</td>
<td>1.10 (0.97-1.26)</td>
<td>-</td>
<td>0.88</td>
<td>1.04 (0.86-1.26)</td>
<td>-</td>
<td>0.66</td>
<td>1.15 (0.97-1.37)</td>
<td>-</td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deprivation</td>
<td>1.15 (1.00-1.32)</td>
<td>1.14 (1.00-1.31)</td>
<td>0.06</td>
<td>1.13 (0.93-1.36)</td>
<td>-</td>
<td>0.23</td>
<td>1.16 (0.97-1.39)</td>
<td>-</td>
<td>0.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URC3</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>-</td>
<td>0.85</td>
<td>1</td>
<td>-</td>
<td>0.95</td>
<td>1</td>
<td>-</td>
<td>0.42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Village</td>
<td>1.01 (0.57-1.78)</td>
<td>-</td>
<td>0.97 (0.45-2.08)</td>
<td>-</td>
<td>1.03 (0.47-2.24)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Town</td>
<td>1.32 (0.84-2.06)</td>
<td>-</td>
<td>1.09 (0.60-1.97)</td>
<td>-</td>
<td>1.49 (0.84-2.62)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URC2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>-</td>
<td>0.71</td>
<td>1</td>
<td>-</td>
<td>0.86</td>
<td>1</td>
<td>-</td>
<td>0.32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less rural</td>
<td>1.20 (0.82-1.76)</td>
<td>-</td>
<td>1.04 (0.62-1.75)</td>
<td>-</td>
<td>1.32 (0.80-2.19)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IRR, incidence rate ratio (with 95% CI); LRT, likelihood ratio test; p value indicated whether a variable improved overall final model fit. IRR not reported for variables that did not significantly improve the final model at the p <0.05 threshold of significance. SFI, social fragmentation index; URC, urban-rural classification; Deprivation, material deprivation index.
Table 11. Multi-level modelling of individual- and neighbourhood-level socio-environmental risk factors for place at onset for affective psychoses aged 15-64.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects: IRR (95% CI)</th>
<th>Men: IRR (95% CI)</th>
<th>Women: IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Full</td>
<td>LRT p</td>
</tr>
<tr>
<td><strong>Individual-level variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-24</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>25-34</td>
<td>0.7 (0.4-1.2)</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>35-44</td>
<td>0.4 (0.2-0.8)</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>45-54</td>
<td>0.6 (0.4-1.1)</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>55-64</td>
<td>0.8 (0.4-1.5)</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women vs men</td>
<td>1.0 (0.7-1.5)</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td><strong>Neighbourhood-level variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFI</td>
<td>1.11 (0.95-1.29)</td>
<td>-</td>
<td>0.22</td>
</tr>
<tr>
<td>Deprivation</td>
<td>1.15 (0.98-1.36)</td>
<td>-</td>
<td>0.10</td>
</tr>
<tr>
<td>URC3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Village</td>
<td>1.12 (0.60-2.10)</td>
<td>-</td>
<td>1.10</td>
</tr>
<tr>
<td>Town</td>
<td>1.21 (0.71-2.04)</td>
<td>-</td>
<td>1.31</td>
</tr>
<tr>
<td>URC2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>Less rural</td>
<td>1.17 (0.75-1.83)</td>
<td>-</td>
<td>1.23</td>
</tr>
</tbody>
</table>

IRR, incidence rate ratio (with 95% CI); LRT, likelihood ratio test; p value indicated whether a variable improved overall final model fit. IRR not reported for variables that did not significantly improve the final model at the p <0.05 threshold of significance. NA, included in the final model but IRR not reported as there was some evidence of interaction (LRT p value: 0.07) between age and sex. SFI, social fragmentation index; URC, urban-rural classification; Deprivation, material deprivation index.
6.3 Socioeconomic status at birth and risk for first episode psychosis

During the first 12 years of the present study, May 1995-April 2007, CAMFEPS incepted 336 cases of any DSM-IV psychotic illness. Cases of non-functional psychosis [i.e. substance-induced psychosis or psychosis due to a general medical condition] (n = 28), those who were adopted (n = 4), born outside Ireland (n = 49) or of parents having no fixed abode (n = 3) were excluded from the study. In those from multiply affected families (n = 11), only the first-born was included. Furthermore, some birth certificates could not be located due to missing information on the maiden name of married women (n = 11), and in other instances information available on the birth certificate did not allow the father’s occupation to be assigned (n = 44). In total, 186 cases of psychosis (106 men, 80 women) and 679 matched controls (385 men, 294 women) were included in the analysis; these were again subdivided into the broad diagnostic categories of ‘non-affective psychoses’ [100 cases (63 men, 37 women), 351 controls (219 men, 132 women)] and ‘affective psychoses’ [86 cases (43 men, 43 women), 328 controls (166 men, 162 women)].

6.3.1. Parental social class at birth and risk for first episode psychosis

For ‘all psychoses’, distribution of parental social class differed slightly between men and women across all subjects ($X^2 = 11.40, p < 0.05$) but did not differ between cases and controls ($p = 0.45$; Table 12). When considered as an ordinal scale, parental social class did not differ between cases and controls (Mann-Whitney U-test, $Z = -1.37, p = 0.17$). A similar profile was evident for ‘non-affective psychoses’ (men vs women, $p < 0.05$; no difference for cases vs controls), while for ‘affective psychoses’ there were no differences for either men vs women or cases vs controls.
In logistic regression models, adjusting for age and sex, for ‘non-affective psychoses’ no associations with social class were evident \( (p \geq 0.45; \text{Table 13}) \), while for ‘affective psychoses’ there was an association between parental social class III and reduced risk for psychosis \( (p \leq 0.05) \); this association altered only marginally on adjusting also for neighbourhood-level characteristics \( (p = 0.08; \text{Table 14}) \).

**6.3.2. Neighbourhood-level characteristics for place at birth and risk for first episode psychosis**

For ‘all psychoses’, increasing level of rurality was associated with reduced risk for psychosis \( (p \leq 0.05) \); this relationship altered only marginally on adjusting for social class \( (p = 0.07; \text{Table 15}) \). On considering ‘affective psychoses’ and ‘non-affective psychoses’ separately, a similar and more robust pattern was present for ‘affective psychoses’ \( (p \leq 0.05) \) but was absent for ‘non-affective psychoses’ \( (p \geq 0.48) \). There were no significant associations between neighbourhood levels of social fragmentation or deprivation at birth and risk for psychosis.

**6.3.3. Parental social class at birth and age at first presentation**

Distribution of age at first presentation by social class is shown in Table 16. On ANOVA, for ‘all psychoses’ age at first presentation increased markedly with lower socioeconomic status (effect of social class, \( p < 0.001 \)) in a manner that did not differ between the sexes (no effect of sex or social class x sex interaction); this profile was evident for both ‘non-affective psychoses’ (effect of social class, \( p < 0.01 \)) and ‘affective psychoses’ (effect of social class, \( p < 0.001 \)).
### Table 12. Distribution of parental social class at birth for cases and controls.

<table>
<thead>
<tr>
<th>Social class</th>
<th>Cases (%</th>
<th>Controls (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>All</td>
</tr>
<tr>
<td>I</td>
<td>6 (5.7)</td>
<td>3 (3.8)</td>
<td>9 (4.8)</td>
</tr>
<tr>
<td>II</td>
<td>13 (12.3)</td>
<td>6 (7.5)</td>
<td>19 (10.2)</td>
</tr>
<tr>
<td>III</td>
<td>5 (4.7)</td>
<td>9 (11.3)</td>
<td>14 (7.5)</td>
</tr>
<tr>
<td>IV</td>
<td>30 (28.3)</td>
<td>20 (25.0)</td>
<td>50 (26.9)</td>
</tr>
<tr>
<td>V</td>
<td>33 (31.1)</td>
<td>20 (25.0)</td>
<td>53 (28.5)</td>
</tr>
<tr>
<td>VI</td>
<td>19 (17.9)</td>
<td>22 (27.5)</td>
<td>41 (22.0)</td>
</tr>
</tbody>
</table>

Odds ratios (ORs) with 95% confidence intervals (95% CIs) for all psychoses; category 1 as reference.

### Table 13. Logistic regression model for relationship between parental social class at birth and risk for non-affective psychosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusteda</th>
<th>Final modela</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Social Class I</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Social Class II</td>
<td>0.53</td>
<td>0.67 (0.19-2.35)</td>
</tr>
<tr>
<td>Social Class III</td>
<td>0.87</td>
<td>0.91 (0.27-3.08)</td>
</tr>
<tr>
<td>Social Class IV</td>
<td>0.96</td>
<td>1.03 (0.35-3.07)</td>
</tr>
<tr>
<td>Social Class V</td>
<td>0.66</td>
<td>1.28 (0.43-3.76)</td>
</tr>
<tr>
<td>Social Class VI</td>
<td>0.98</td>
<td>1.02 (0.33-3.16)</td>
</tr>
<tr>
<td>URC-1971</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SFI</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Deprivation</td>
<td>0.67</td>
<td>1.03 (0.89-1.20)</td>
</tr>
</tbody>
</table>

Odds ratios (ORs) with 95% confidence intervals (95% CIs); category 1 as reference. URC, urban-rural classification; SFI, social fragmentation index; Deprivation, material deprivation index. aAdjusted for age and sex.
**Table 14.** Logistic regression model for relationship between parental social class at birth and risk for affective psychosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th>Final model&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Social Class I</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Social Class II</td>
<td>0.43</td>
<td>0.58 (0.15-2.26)</td>
<td>0.37</td>
<td>0.51 (0.12-2.21)</td>
</tr>
<tr>
<td>Social Class III</td>
<td>0.05*</td>
<td>0.21 (0.05-1.02)</td>
<td>0.08</td>
<td>0.23 (0.04-1.18)</td>
</tr>
<tr>
<td>Social Class IV</td>
<td>0.45</td>
<td>0.61 (0.17-2.17)</td>
<td>0.44</td>
<td>0.58 (0.15-2.27)</td>
</tr>
<tr>
<td>Social Class V</td>
<td>0.46</td>
<td>0.62 (0.17-2.22)</td>
<td>0.39</td>
<td>0.54 (0.14-2.16)</td>
</tr>
<tr>
<td>Social Class VI</td>
<td>0.65</td>
<td>0.74 (0.20-2.72)</td>
<td>0.68</td>
<td>0.74 (0.18-3.02)</td>
</tr>
<tr>
<td>URC-1971</td>
<td></td>
<td></td>
<td>0.04*</td>
<td>0.96 (0.92-1.00)</td>
</tr>
<tr>
<td>SFI</td>
<td>0.67</td>
<td></td>
<td>0.97</td>
<td>(0.84-1.12)</td>
</tr>
<tr>
<td>Deprivation</td>
<td>0.81</td>
<td></td>
<td>0.98</td>
<td>(0.86-1.12)</td>
</tr>
</tbody>
</table>

Odds ratios (ORs) with 95% confidence intervals (95% CIs); category 1 as reference. URC, urban-rural classification; SFI, social fragmentation index; Deprivation, material deprivation index. <sup>a</sup>Adjusted for age and sex. * p ≤ 0.05

**Table 15.** Logistic regression models for relationship between neighbourhood-level characteristics for place at birth and risk for psychosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt; OR (95% CI)</th>
<th>Adjusted&lt;sup&gt;b&lt;/sup&gt; OR (95% CI)</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt; OR (95% CI)</th>
<th>Adjusted&lt;sup&gt;b&lt;/sup&gt; OR (95% CI)</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt; OR (95% CI)</th>
<th>Adjusted&lt;sup&gt;b&lt;/sup&gt; OR (95% CI)</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt; OR (95% CI)</th>
<th>Adjusted&lt;sup&gt;b&lt;/sup&gt; OR (95% CI)</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt; OR (95% CI)</th>
<th>Adjusted&lt;sup&gt;b&lt;/sup&gt; OR (95% CI)</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt; OR (95% CI)</th>
<th>Adjusted&lt;sup&gt;b&lt;/sup&gt; OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>URC-1971</td>
<td>0.97 (0.94-1.00)</td>
<td>0.05*</td>
<td>0.97 (0.95-1.00)</td>
<td>0.07</td>
<td>0.99 (0.95-1.03)</td>
<td>0.48</td>
<td>0.99 (0.95-1.03)</td>
<td>0.57</td>
<td>0.96 (0.92-1.00)</td>
<td>0.04*</td>
<td>0.96 (0.92-1.00)</td>
<td>0.05*</td>
</tr>
<tr>
<td>SFI</td>
<td>0.96 (0.87-1.06)</td>
<td>0.40</td>
<td>0.96 (0.86-1.06)</td>
<td>0.37</td>
<td>0.95 (0.82-1.09)</td>
<td>0.43</td>
<td>0.95 (0.82-1.09)</td>
<td>0.45</td>
<td>0.97 (0.84-1.12)</td>
<td>0.70</td>
<td>0.97 (0.84-1.12)</td>
<td>0.66</td>
</tr>
<tr>
<td>Deprivation</td>
<td>1.01 (0.92-1.11)</td>
<td>0.79</td>
<td>1.01 (0.92-1.11)</td>
<td>0.88</td>
<td>1.05 (0.91-1.21)</td>
<td>0.53</td>
<td>1.04 (0.90-1.20)</td>
<td>0.60</td>
<td>0.99 (0.87-1.12)</td>
<td>0.83</td>
<td>0.99 (0.87-1.12)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Odds ratios (ORs) with 95% confidence intervals (95% CIs). URC, urban-rural classification; SFI, social fragmentation index; Deprivation, material deprivation index. <sup>a</sup>Adjusted for age and sex. <sup>b</sup>Adjusted for age, sex and social class. * p ≤ 0.05
Table 16. Age at first presentation by parental social class at birth.

<table>
<thead>
<tr>
<th>Social class</th>
<th>All psychoses</th>
<th>Non-affective psychoses</th>
<th>Affective psychoses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean age (SD)</td>
<td>N</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>9</td>
<td>22.8 (6.0)</td>
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SD, Standard Deviation
Chapter 7

Discussion

7.1 Geographical variation

7.1.1 Introduction

Spatial epidemiology is the description and analysis of geographically indexed health data in relation to environmental, demographic, behavioural, socioeconomic, genetic and infectious risk factors (Elliott & Wartenberg, 2004). It is an important field of research that helps our understanding of the aetiology of disease and assists policy makers in deciding preventive strategies and provision of services (Pringle, 1996). While there is substantial evidence indicating significant geographical variation in rates of schizophrenia at macroscopic (national and regional) levels, there is a dearth of literature on spatial variation at the microscopic or small-area level. The body of literature on small-area variation comes primarily from urban settings, with rural areas featuring mainly in urban-rural comparisons. Little is known about associations between the spatial environment and rates of psychosis within rural settings. In this study, I set out to investigate whether such associations exist within a wholly rural context in Ireland. The main findings of the present study are that the geographical distribution of incidence of first episode psychosis by place at onset appears to be homogenous in this predominantly rural Irish context; conversely, the geographical distribution of incidence of all psychoses and the diagnostic subcategories by place at birth appears to
follow a non-random distribution for men but not women. These findings will be discussed below.

7.1.2 Geographical variation by place at onset

7.1.2.1 Comparison with previous research

The lack of spatial heterogeneity of affective psychoses accords with the body of literature on the subject. However, the homogenous distribution of cases of non-affective psychoses by place at onset in our study area contrasts with the wealth of ecological literature that comes mainly from urban settings; a consistent findings for these studies is the concentration of non-affective psychoses in socially deprived inner city areas (Faris & Dunham, 1939; Giggs & Cooper, 1987; Hare, 1956; Kirkbride et al., 2007b; Levy & Rowitz, 1973; Maylath et al., 1989). It is not possible to directly compare our findings with prior research due to difference in the statistical methods utilised. The majority of studies on small-area research have used conventional statistical methods that are susceptible to error or what is known as the ‘small numbers’ problem; a relatively rare disorder such as schizophrenia will yield a very small number of cases at the small-area level, which in turn will produce unstable risk estimates that could be explained by stochastic variations (Pringle, 1996). Furthermore, conventional statistical methods do not take into account spatial patterning, as counts in neighbouring units may be more similar than those in units further apart (Kirkbride et al., 2007a). To overcome these methodological challenges, I have employed a Bayesian statistical model, a suggested approach that allows for spatial dependency and gives smoothed estimates of relative risk in each geographical unit (Elliott & Wartenberg, 2004; Kirkbride et al., 2007a). To the best of our knowledge, only three
studies have used a Bayesian approach to examine geographical variation in incidence of psychosis at the small-area level (Kirkbride et al., 2007a, 2014; Szoke et al., 2016). Two studies from London have found evidence for spatial variation in incidence of non-affective psychosis but did not identify any variation in incidence of affective psychoses (Kirkbride et al., 2007a, 2014). Conversely, a more recent study by Szoke and colleagues from the Southeast of Paris found evidence of spatial patterning for broad and affective psychoses but not for non-affective psychoses (Szoke et al., 2016). These findings, albeit from a small number of studies that were primarily conducted in urban settings, would indicate that the spatial variation of psychotic disorders at small-area level is not consistently present in all settings and may be influenced by underlying environmental factors.

Prior studies from the present study region have demonstrated significant variation in the prevalence of schizophrenia by place at onset at the ED level (Pringle et al., 1995; Scully et al., 2004; Youssef et al., 1991, 1999). For example, Scully and colleagues examined spatial variation in the prevalence of schizophrenia in 32 EDs in County Monaghan and found significant deviation from a Poisson model for random occurrence in space (Scully et al., 2004). This study, however, considered prevalence rather than incidence, did not use a Bayesian approach and did not take into account the possibility of residual autocorrelation and/or over-dispersion of the outcome data (Pignon et al., 2016). Another study by Pringle and colleagues of 36 EDs in County Cavan, that adjusted for spatial autocorrelation, found evidence for significant variation in the prevalence of schizophrenia by place at onset (Pringle et al., 1995). Other than what could be explained by methodological differences, it is
possible that our findings are due to temporal changes in whatever environmental factors were at play in earlier research from the study region. It is also possible that prevalence estimates are influenced by other risk factors that are not present in close proximity to the onset of the disorder (Pignon et al., 2016).

7.1.2.2 Methodological considerations
In this study appropriate statistical techniques suitable for small-area research were used. Also, methodology has been improved over earlier research from the study region by using incidence data of a much larger sample that involves prospective accrual of cases of first episode psychosis. While one cannot dismiss the possibility of lack of statistical power as an explanation for the absence of spatial variation in incidence in relation to place at onset, this is highly unlikely as it was possible to detect spatial variation by place at birth even though the number of cases was rather smaller.

7.1.2.3 Meaning of findings
The absence of any significant spatial variation in the incidence of psychotic disorders in this rural Irish context raises a number of possibilities. First, it is possible that those environmental risk factors that operate in an urban environment are absent or minimal in a rural setting. Second, rather than eliminating the possibility of the presence of environmental risk factors proximal to the onset of psychosis, it is possible that environmental risk factors are distributed uniformly or randomly in our study area. This is evidenced by the considerable socioeconomic homogeneity of the study region. Further evidence comes from research in urban areas demonstrating
that heterogeneity in incidence of non-affective psychosis is mostly explained by neighbourhood social characteristics such as income inequality, deprivation and population density (Kirkbride et al., 2014). Third, It is also possible that strong social networks and support that are usually present in a rural setting act as protective factors that negate the effects of socio-environmental risk factors present in an urban setting.

7.1.3 Geographical variation by place at birth

7.1.3.1 Comparison with previous research

Our finding of a significant variation in incidence by place at birth for men accords with previous reports from the study region that have demonstrated significant heterogeneity in the prevalence of schizophrenia by place at birth (Scully et al., 2004; Youssef et al., 1991, 1999). However, in these earlier studies geographical variation by place at birth was evident for both sexes and appeared to be limited to the diagnosis of schizophrenia and not for bipolar disorder. Very few other studies have examined issues of small-area variation in incidence of psychotic disorders by place at birth. A study by Torrey and colleagues from Denmark utilised a national case register of patients with schizophrenia in 217 geographical areas. In this study all evidence for geographical clustering could be explained by genetic factors and urbanicity (Torrey et al., 2001). Two studies from urban areas in the UK have shown that patients with schizophrenia were more likely to be born in socially deprived areas (Castle et al., 1993; Harrison et al., 2001).
7.1.3.2 Methodological considerations

Several methodological issues that are pertinent to our findings have been discussed in detail previously (Scully et al., 2004); in short, in the face of strict catchment area policy in Ireland, the possibility of case leakage is greatly reduced. Therefore, it is unlikely that in electoral divisions with low counts this would be a result of case leakage. Second, the possibility of differential out-migration from the study area seems to be unlikely as the region has generally low levels of geographical mobility, with the majority of patients both being born and becoming ill in the same region. Third, it is possible any evidence of geographical clustering is a result of familial aggregation of cases. However, to control for this a conservative approach was used, by selecting only the first-born in multiply affected families. While this does not eliminate the possibility of familial aggregation, its likelihood is considerably reduced.

7.1.3.3 Interpretation of findings

Taken together, the lack of spatial heterogeneity in incidence by place at onset and the evidence for heterogeneity by place at birth points towards a role of environmental factors operating in intrauterine life or early childhood to increase risk for psychosis. Several area-level (contextual) and individual-level (compositional) environmental risk factors have been implicated in the aetiology of psychotic disorders; for example, the role of socio-environmental risk factors such as being born in socially deprived areas. Individual-level environmental factors that may contribute to risk for psychosis early in life include maternal viral infection (Brown & Patterson, 2011), lead exposure (Opler et al., 2004) and dietary factors (McGrath et al., 2011). However, it is difficult to envisage such factors differing substantially across this relatively
small region in Ireland. While one cannot be certain about the underlying mechanisms that are responsible for this heterogeneity in incidence by place at birth, it is likely that a combination of genetic and environmental factors are at play.

7.2 Neighbourhood-level characteristics and risk for first episode psychosis by place at onset

7.2.1 Introduction

Socio-environmental risk factors (SERFs) are generally studied at two levels: (1) area-based (contextual) characteristics such as deprivation, social fragmentation and, more recently, social capital, and (2) individual–level (compositional) factors such as ethnicity, social class, social adversity and cannabis use. To our knowledge, this is the first study to examine associations between neighbourhood-level socio-environmental risk factors and incidence of first episode psychosis within a rural setting. Unlike the majority of other studies, this study did not impose any upper age limit and attempted to identify ‘all’ cases presenting with a first episode psychosis so as to incept an epidemiologically representative population across the lifespan. Two complementary approaches to data analysis were adopted: first, by aggregating EDs according to their social characteristics (Abas et al., 2006; Allardyce et al., 2005; O’Reilly et al., 2008); second, by applying multilevel modelling. The main findings are considered below.
7.2.2 Comparison with previous research

7.2.2.1 Material deprivation

It is important to point out that, unlike many studies that define deprivation in a broader sense that included aspects of both material and social deprivation, in this study the conceptual approach suggested by Townsend and colleagues was adopted, in which material deprivation entails a lack of services, goods, resources, amenities and physical environment that are customary in the community in question. Social deprivation, on the other hand, involves non-participation in relationships, roles, customs and functions, and a lack of the rights and responsibilities implied by membership of a society (Townsend et al., 1988).

7.2.2.1.1 Ecological analysis

Ecological analysis identified a variable association between extent of material deprivation and incidence of psychosis, primarily among men. Previous ecological studies have demonstrated that the relationship between deprivation and psychosis is not necessarily linear (Allardyce & Boydell, 2006; Croudace et al., 2000). Moreover, comparison with prior ecological research on the relationship between deprivation and incidence of psychosis is complicated by the fact that different indices are used, including single measurements such as unemployment or composite measures such as the index used in our study. In a study that used a similar approach to the present research, Allardyce and colleagues found an association between material deprivation as measured by Carstairs scores and first admission rates for psychosis in Scotland (Allardyce et al., 2005). In this study the relationship between deprivation and psychosis did not differ between urban and rural...
areas. Conversely, a study by Thornicroft and colleagues from Northern Italy found the relationship between deprivation and service utilisation for psychosis to be present in an urban but not in a rural area (Thornicroft et al., 1993). Another study from Maastricht, the Netherlands, failed to find an association between neighbourhood socioeconomic disadvantage and the treated incidence of schizophrenia (Drukker et al., 2006). These findings suggest that material deprivation may not play a substantive role in the heterogeneity of incidence of psychotic disorders, especially in rural settings.

7.2.2.1.2 Multi-level analysis

One of the main limitations of ecological analysis is inability to differentiate between compositional and contextual factors (Allardyce & Boydell, 2006). The use of multi-level statistical modelling allows us to disentangle the effects of individual from contextual factors. In our analyses, multi-level modelling revealed an association between extent of deprivation and risk for ‘all psychoses’ for the whole sample, though this effect may have been restricted to older women, beyond the age range considered in most studies of first episode psychosis; this limits comparability with the literature. Very few studies have used multi-level modelling techniques to investigate the relationship between deprivation and psychosis and findings generally support attenuation of neighbourhood effects once individual-level factors are controlled for (Silver et al., 2002; van Os et al., 2000).
7.2.2.2 Social fragmentation

7.2.2.2.1 Ecological analysis

Implicating a role for neighbourhood disorganisation/fragmentation in the aetiology of psychosis can be traced back to the work of Faris and Dunham in Chicago in the first half of the 20th century (Faris & Dunham, 1939). In subsequent years several studies have used single and composite census-based measurements to examine this relationship. This study used the SFI, which was calculated by adding z scores of four census variables for each ED: 1) non-married adults, 2) single-person households, 3) population turnover and 4) private renting. In this sense the SFI is considered a marker for social deprivation. Ecological analysis revealed an association between extent of social fragmentation and incidence of psychosis, primarily among women. This finding is less robust than previously reported in ecological analyses that have shown a strong association between area-level SFI and rates of psychosis (Allardyce et al., 2005; Curtis et al., 2006). For example, in the study by Allardyce and colleagues from Scotland, there was a dose-response relationship between social fragmentation and first-admission rate for psychosis (Allardyce et al., 2005).

7.2.2.2.2 Multi-level analysis

On multi-level analysis, social fragmentation was not associated with incidence of psychosis once material deprivation had been included, though these were highly correlated factors. This contrasts with previous studies that have used multi-level modelling techniques and found a significant effect of area-level social fragmentation after adjusting for individual-level factors (van Os et al., 2000; Zammit et al., 2010). These studies indicate a more robust
association between area-level social fragmentation and rate of psychosis, primarily in urban settings.

7.2.2.3 Urban-rural classification

One of the most consistent findings in psychiatric epidemiology is a differential in rates of psychosis between urban and rural areas, with urbanicity being considered to confer a two-fold increase in risk for psychosis (Kelly et al., 2010; March et al., 2008). As there is no universally agreed definition for urbanicity, studies have used different methods to define urbanicity, the commonest of which is population density. In Ireland, Teljeur and Kelly developed an urban-rural classification for health services research at the small area level. This classification combines multiple variables, including population density, settlement size and proximity to urban centres (Teljeur & Kelly, 2008). This urban-rural classification was used to examine whether the differential gradient in incidence of psychotic disorders extends beyond the traditional urban-rural divide to within a predominantly rural context.

7.2.2.3.1 Ecological analysis

Ecological analysis identified a significant association between level of rurality and incidence of all psychoses, primarily in women, with the highest risk being in the least rural category. When the diagnostics subgroups were investigated separately, this effect persisted in affective psychoses for women but not in men. This finding contrasts with the body of literature. For example, a previous comparison of incidence data from the present study with findings from an urban study that used very similar methodology revealed that the incidence of schizophrenia in males in Dublin was almost twice that of rural
males; a similar pattern was evident for females; conversely, the incidence of affective psychosis was higher in rural compared to urban areas for both men and women (Kelly et al., 2010). One would have expected the urban/rural differences in incidence of psychosis to continue at the same pattern within the rural environment. For example, in a study by Szöke and colleagues from France the incidence of all psychoses and diagnostic subgroups was higher in the urban area compared to the rural area (Szöke et al., 2014). When the rural area was subdivided according to town size, the same pattern was observed, with higher incidence in the more urbanised parts of the rural area.

7.2.2.3.2 Multi-level analysis

In the multi-level analysis there was no significant association between level of rurality and incidence of psychosis after adjusting for age and deprivation. To date, no studies that used the urban-rural classification in multi-level modelling analysis have been reported. However, studies that examined population density, an important component of the urban-rural classification, have produced mixed results: while an earlier study by Kirkbride and colleagues did not find population density to be associated with incidence of psychosis in London (Kirkbride et al., 2007b), a later study with a much larger sample showed a significant association (Kirkbride et al., 2014).

7.2.2.4 Sex

Our findings include a number of sex-related associations that were apparent across diagnostic categories, not confined to a single index and evident using different analytical approaches. This is in line with published studies that have demonstrated sex differences in the association between neighbourhood
characteristics and health-related outcomes. For example, a large population-based case-control study of risk for myocardial infarction in Sweden revealed the contextual effects of material deprivation and social fragmentation to be stronger in women compared to men (Stjärne et al., 2004); similarly, sex differences have been reported in ecological studies of self-rated health (Kavanagh et al., 2006; Stafford et al., 2005). Stafford and colleagues proposed possible explanations for such sex differences: (1) men and women may differ in their perception of the local environment, (2) men and women are exposed to different stressors within neighbourhoods, and (3) due to differences in social roles, women may be more vulnerable to certain aspects of the local environment (Stafford et al., 2005). There is some evidence supporting the differential effect of neighbourhood social environment to be particularly detrimental to women’s mental health from studies of common mental disorders such as depression (Bassett & Moore, 2013). Typically, studies of the relationship between neighbourhood-level characteristics and risk for psychosis adjust for sex as a potential confounder. This limits the ability to compare sex-related findings in the present study with the literature.

7.2.3 Methodological considerations

Multi-level analyses allowed us to quantify the impact of neighbourhood-level factors on incidence rates in our sample. While multi-level models suggested only weak neighbourhood (random) effects, our study was sufficiently powered to detect evidence for an association between material deprivation and psychosis after adjusting for individual level covariates. These multi-level models were appropriate for count data and were fitted appropriately, given the possibility of over-dispersion. Our study is subject to a number of
limitations common to ecological research: first, we cannot assume that cases living in neighbourhoods with a given level of a putative risk factor were themselves exposed to that level of risk factor; second, the cross-sectional design of ecological studies precludes assessing the direction of causality in any associations, such that we cannot exclude a role for social drift. A longitudinal study design may help address the issue of social drift. However, it has been hypothesised that social drift may well extend to generations beyond patients and their fathers (Goldberg & Morrison, 1963). This study did not include data at an individual level on some possible confounders, such as social class. Some of the present findings could be mediated by aggregation of individual-level characteristics, though the study controlled for two very important factors: age and sex. However, in previous large population studies the effect of neighbourhood-level social fragmentation has remained after adjusting for individual-level characteristics (Silver et al., 2002; Zammit et al., 2010). Finally, the 2002 census may not be truly representative of the social characteristics of Cavan-Monaghan over the 12-year period of the study. To address this, analyses were repeated using data from the 2006 census; this did not materially alter the results.

7.2.4 Meaning of findings

A modest association between material deprivation and incidence of psychosis was observed, primarily in older women. This finding suggests that women may be particularly sensitive to deprivation during late rather than early life. Alternatively, they may reflect cumulative exposure to deprivation over the life course in women or, perhaps, stronger social drift for women who go on to develop psychosis later in life as they become more marginalised in
rural communities; however, longitudinal data would be necessary to test such hypotheses. It will also be important for future research to avoid imposing arbitrary upper age cut-offs and include older adults in epidemiological studies of psychotic disorders. Our overall finding in relation to material deprivation would indicate that in a rural context, it is not strongly associated with the incidence of psychosis proximal to the onset of the disorder.

As a modest association between social fragmentation and incidence of psychosis was evident here on ecological analysis but not using multi-level modelling, this may reflect lower levels of, or less variability in, social fragmentation in rural compared to urban areas. A previous nation-wide study from Ireland has demonstrated the lowest scores for social fragmentation to be in rural EDs, with the highest scores reported in cities other than Dublin (Corcoran et al., 2007). This accords with the notion that neighbourhood-level characteristics such as social fragmentation explain the differential in rates between urban and rural areas (Allardyce et al., 2005; Zammit et al., 2010). It is also possible that in a rural environment there are protective neighbourhood social factors such as social cohesion and social capital that buffer against the effects of social fragmentation. Again, it is also possible the timing of exposure to neighbourhood-level social fragmentation is relevant to periods other than close proximity to the onset of psychosis.

While ecological analysis also indicated that women living in the least rural areas of the study were at increased risk for psychosis, this association was not evident in multi-level analyses after taking age and deprivation into account. While there is a strong body of evidence indicating higher rates of
psychosis in urban areas (Harrison et al., 2003; Kelly et al., 2010; McGrath et al., 2004; Pedersen & Mortensen, 2001a), future studies should examine further the extent to which socio-environmental variation in risk for psychosis may extend beyond the traditional dichotomous urban/rural divide and be subject to gradations within both urban and rural areas.

In ecological analyses the associations between incidence of psychosis and neighbourhood indices of social fragmentation and rurality showed a similar profile for affective and non-affective psychoses. While one cannot exclude the possibility of misclassification of cases, this may be unlikely as standardised assessment methods were employed for diagnosis using DSM-IV criteria. While the absence of significant findings using multilevel modelling is cautionary, other ecological studies indicate that the relationship between contextual characteristics and mental illness is not confined to non-affective psychoses and extends to affective disorders (Curtis et al., 2006; Silver et al., 2002). Finally, sex-related findings accord with previous ecological research that indicates neighbourhoods may affect women and men differently. Future research should explore this issue further.

7.2.5 Conclusions

Our primary finding is an association between more deprived social contexts and higher rates of psychotic disorder in a predominantly rural setting, after adjustment for age and sex. However, there was less evidence for such associations than is typically reported in urban settings (Kirkbride et al., 2007b). Together, these findings suggest that there may be a continuum of risk for psychosis with socio-environmental risk factors across the rural-urban
divide, to include essentially rural environments. However, they suggest that such exposures may have greater impact in more urban settings. Future epidemiological and health services research in rural areas (see, for example, the SEPEA study (Kirkbride et al., 2012b)) should take into account potential variations in risk within rural areas and consider sex differences in relation to contextual effects.

7.3 Socioeconomic status at birth and risk for first episode psychosis

7.3.1 Introduction

One of the main challenges for neighbourhood research is the difficulty in disentangling cause from effect. Therefore, it could be argued that increased rates of psychosis in socially deprived neighbourhoods are a result of social drift of patients to those areas after the onset of their symptoms (the causation vs selection debate). Ideally, studies examining the relationship between the neighbourhood social environment and rates of psychosis should be able to capture both the timing and duration of such exposure. In reality, this is methodologically difficult. Thus far, few studies have attempted to overcome this methodological limitation by examining the relationship between socioeconomic position by place at birth and psychosis risk later in life. However, the substantial majority of contemporary, quantitative studies investigating any relationship between socioeconomic position at birth and risk for schizophrenia have been carried out in primarily urban areas or using national/large regional datasets that conflate the urban-rural divide. Thus, features of urbanicity are potential modulators of or confounders in such relationships and may either sharpen or blunt their identification.
To address this issue requires a study that is conducted in a wholly rural setting. CAMFEPS provides a rare opportunity to investigate risk for psychotic illness in relation to social class in the absence of any major urban centres. Additionally, few studies have examined relationships between the social environment (other than social class and the urban-rural divide) at the time of birth and risk for psychosis at the neighbourhood level, other than those also carried out in primarily urban areas or using national datasets (Brown, 2011; Eaton, 1985; Kwok, 2014). Therefore, in this study the focus is on the relationship between individual- and neighbourhood-level socioeconomic indicators proximal to the time of birth and risk for a first psychotic episode.

### 7.3.2. Main findings

In this rural region of Ireland no overall relationship between parental social class and risk for first episode psychosis was found. Neither was any relationship found when ‘non-affective’ and ‘affective’ psychoses were examined separately, subject to one exception: social class III was associated with reduced risk for ‘affective psychosis’. No material effect of deprivation or social fragmentation at birth on risk for psychotic illness was detected. However, a modest association between increasing rurality and decrease in risk for first episode psychosis was identified that, as for the above association with social class III, appeared more evident for ‘affective psychosis’ than for ‘non-affective psychosis. The most striking finding was a prominent relationship between lower parental social class and older age at first presentation.
7.3.3 Interpretation of findings in relation to previously published work

7.3.3.1 Social class at birth

In this study the methodological design was the same as for the study by Harrison and colleagues conducted in an urban centre in the UK (Harrison et al., 2001). The present findings contrast with that study as they found a significant association between social class at birth and risk for schizophrenia in adulthood. However, other studies have produced mixed results. For example, in the landmark study by Goldberg and Morrison, the social class of fathers of patients with schizophrenia was comparable to the general population (Goldberg & Morrison, 1963). More importantly, our findings are similar to those reported by Mulvany and colleagues who conducted a case-control study of 352 pairs of patients with schizophrenia and sex-matched controls in Dublin (Mulvany et al., 2001). In this study, the risk of schizophrenia was not increased in those from lower social classes. These findings are consistent with the recent systematic review of 14 studies that has concluded that there is not enough evidence to support a relationship between social class at birth and psychosis (Kwok, 2014). There are several possible explanations for divergent findings in the relationships between individual-level socioeconomic status at birth and risk for psychosis. First, it is possible that such differences are due to methodological variations between studies, such as the choice of social indicator used; individual socioeconomic position may be measured in several ways such as parental education, income, and social class. However, the methodology of our study is similar to that of Harrison et al. (Harrison et al., 2001), including the use of social class (according to father's occupation) as an indicator of socioeconomic position.
Second, it could be that socio-environmental risk factors around the time of birth and early childhood operate differentially across countries. Socioeconomic status is a proxy measure of a yet unidentifiable mediating pathway. Therefore, it is plausible that inconsistencies in the association between socioeconomic status at birth and risk for psychosis are a result of variability in such unmeasured factor(s).

There are several candidate mechanisms through which socioeconomic status at birth may influence risk for psychosis. For example, there is evidence from the literature, including a systematic review of longitudinal population-based studies, that socioeconomic status at birth is associated with risk of cannabis misuse in adolescence (Daniel et al., 2009; Legleye et al., 2012). Cannabis misuse is an established risk factor for psychosis (Arseneault et al., 2004; Moore et al., 2007; Semple et al., 2005). Another possible mediating variable is low birth weight, which has been demonstrated to be a risk factor for schizophrenia (M. Cannon et al., 2002); several studies, including a systematic review, have reported an association between individual-level socioeconomic status and low birth weight (Blumenshine et al., 2010; Gray et al., 2014; Luo et al., 2006). Finally, there is the possibility that other socio-environmental risk factors are more detrimental to the pathobiology of psychotic disorders; in a large population-based study from Sweden, while social adversity in childhood accounted for 20% of the attributable risk for schizophrenia, this was mostly related to social indicators at the household level, including living in a rented apartment, household receiving social welfare benefits, single-parent household and parental unemployment (Wicks et al., 2005). It has been suggested that, rather than
the gradient of socioeconomic position, it is conditions of social isolation and exclusion that influence risk for schizophrenia and other psychoses in childhood (Wicks et al., 2005).

Interestingly, the association between intermediate social class III and reduced risk for psychosis, particularly for ‘affective psychosis’, is similar to the aforementioned study by Mulvany and colleagues where intermediate social class IV was associated with reduced risk. This suggests that in rural regions there may be some characteristic of social class III [other non-manual and farmers with 50-99 acres (20.2 – 40.1 hectares)] that decreases risk for psychotic illness in a manner that shifts from ‘non-affective psychosis’ to ‘affective psychosis’ along the urban-rural divide. One can cautiously speculate that social class III in rural regions and social class IV [skilled manual and farmers with 30–49 acres (12.1 – 19.8 hectares] in more urban regions may represent a favourable, intermediate social milieu associated with fewer of the stressors that might characterise social class I/II [professional/managerial] and social class V/VI [semi-skilled manual or farmers with < 30 acres (12.1 hectares)]. Such an intermediate social class may optimise the stress-buffering effects of personal control (mastery), self-esteem and social support known to be associated with reduced risk for ill-health (Thoits, 2010). Furthermore, an overall shift in the relative incidence of ‘non-affective psychosis’ vs ‘affective psychosis’ between the present rural region and the more urban region of Mulvany et al. (Mulvany et al., 2001) has been reported (Kelly et al., 2010). This supports the proposition above that factors varying along the urban-rural continuum can predispose differentially to ‘non-affective psychosis’ vs ‘affective psychosis’.
7.3.3.2 Neighbourhood characteristics by place at birth

7.3.3.2.1 Material deprivation and social fragmentation

The lack of association between neighbourhood-level of material deprivation and risk for psychotic illness contrasts with published work. For example, in the study by Harrison and colleagues in an urban region in the UK, area–level deprivation at birth was significantly associated with increased risk for developing schizophrenia in later life (Harrison et al., 2001). Similarly, a large population-based study from Israel that used multi-level modelling reported higher rates of schizophrenia among cases that were born in poorer residential areas in Jerusalem after adjusting for individual-level variables (Werner et al., 2007).

The lack of association between area-level social fragmentation and psychosis is also at odds with previous studies. Castle and colleagues, using a case-control design, established that patients with schizophrenia were more likely to be born in socially deprived neighbourhoods in London compared to controls (Castle et al., 1993). It is not immediately clear how neighbourhood-levels of deprivation and fragmentation influence risk for psychosis later in life but proposed mediating pathways include social factors such as social exclusion and lack of social support and biological pathways such as nutritional deprivation in utero (Werner et al., 2007; Wicks et al., 2005). As neighbourhood-level SERF variables have been shown to influence risk for psychotic illness in primarily urban areas in relation to onset (Kirkbride et al., 2007b; 2014), the underlying mediators may be attenuated in rural regions and/or of greater impact proximal to the emergence of diagnostic symptoms and first presentation. It is also possible that census-based indices such as
the deprivation index and SFI are less suitable for assessing levels of
depprivation in rural areas. It has been argued that some of the individual
variables in these indices may better capture levels of deprivation in urban
than in rural areas (Allardyce et al., 2005; Pringle, 2002).

7.3.3.2 Urban-rural classification

The lack of association between level of rurality and risk for psychosis is at
odds with published literature. The significant association between exposure
to urbanicity early in life and the risk for developing schizophrenia is one of
the most consistent findings in psychiatric epidemiology. This evidence mainly
comes from large population-based studies from Scandinavian countries (see
Introduction). These studies have demonstrated that the relationship
between urbanicity early in life and risk for schizophrenia meets several of the
criteria set forth by Hill (Hill, 1965) for establishing causality, including
consistency, dose-response relationship and temporality (Kelly et al., 2010;
March et al., 2008). Further, there is evidence that risk for schizophrenia is
attenuated in those who move from urban to rural areas in childhood
(Pedersen & Mortensen, 2001a). While the underlying biological mechanisms
through which urbanicity increases risk for psychosis is yet to be identified,
several mechanisms have been proposed, including toxins, infection and
social stress (March et al., 2008). It is noteworthy that many of the studies
demonstrating a significant association between urbanicity at birth and
schizophrenia defined urbanicity based on population density (Marcelis et al.,
1999; Pedersen & Mortensen, 2001a) and it has been shown that there is a
linear association between city size and risk for schizophrenia (Pedersen &
Mortensen, 2001a). In the present study an effect of ‘urbanicity’ was not
evident within this rural setting. If this finding is not a result of a measurement error, it is possible that there is a threshold below which the effect of urbanicity is attenuated or absent.

7.3.3.3 Social class at birth and age at first presentation

As for the association with intermediate social classes III/IV, the relationship between lower parental social class and older age at first presentation was previously reported in a more urban region of Ireland (Mulvany et al., 2001); in that study, mean ages at first presentation were 25 for class I, 29 for class IV and 34 for class VI. In the present rural region, this effect was considerably more prominent, i.e. mean ages at first presentation were 23 for class I, 34 for class IV and 44 for class VI. In the USA, Brown and colleagues studied the social class of origin of 153 first admission cases of non-affective psychosis (Brown et al., 2000b). While there was a significant difference in symptomatology between those of lower social class of origin compared to higher social classes, there was no significant difference in age between the two groups.

As discussed by Mulvany and colleagues (Mulvany et al., 2001), it is possible that age at onset differs between the social classes, or that family practitioners delay in referring patients from lower social classes. However, it is more likely that lower social class may be associated with delayed engagement with health services, as is the case for several general medical situations; these include: seeking antenatal care, with subsequent delivery of a baby of low birth weight (Gray et al., 2014; Luo et al., 2006); seeking medical attention for children and extent of illness endured before seeking
help (Department of Health and Social Security, 1980). Lower social class might be associated with increased difficulty in accessing psychiatric services (Birtchnell, 1971) (but see Cooper, 1961), or higher social class might be associated with being more informed about psychosis and/or more aware of deviations in social, academic or occupational functioning (Horwitz, 1987; Roberts, 1980). Lower social class may be associated with increased tolerance and acceptance of psychotic behaviour and a sense of reduced control or powerlessness (Bosma et al., 1999; Loebel et al., 1992). It cannot be excluded that older age in patients from lower parental social classes could result in their never reaching health services or dying before treatment could be initiated.

Societal factors and help-seeking behaviour provide better explanation for differences in age at onset between the social classes compared to other biological and environmental variables. For example, studies have demonstrated that obstetric complications, which are known to be associated with lower social class, are associated with an earlier age at onset of psychosis (O’Donoghue et al., 2015; Rubio-Abadal et al., 2015). Similarly, there is evidence from the literature, including a meta-analytic review, that cannabis use is associated with an earlier age at onset of psychosis (Large et al., 2011; O’Donoghue et al., 2015; Tosato et al., 2013).

While some of these putative explanatory factors might be more evident in rural relative to urban settings, this should be juxtaposed with Cavan-Monaghan Mental Health Service operating a community, home-based treatment model in close association with family practitioners (McCauley et
al., 2003; Nkire et al., 2015) and into which CAMFEPS is fully integrated. That lower social class may be associated with later presentation to family practitioners, as espoused by Mulvany and colleagues (Mulvany et al., 2001) is supported by evidence (Clarke et al., 1999) that lower social class is associated with increased duration of untreated psychosis (DUP) and should be prioritised in terms of efforts to reduce DUP.

7.3.4 Strengths and limitations of the study

Strengths of the CAMFEPS dataset include the epidemiological completeness of the data: the Irish mental health service operates a strict catchment area policy, such that patients presenting to services other than those relating to their home address are re-directed to their catchment area; we were able to ascertain cases who chose to present privately or whose presentation resulted in a forensic admission; we were able to obtain information from case records/treating teams for cases who declined formal assessment. Therefore, the likelihood of case leakage is considerably reduced. A common methodological challenge for ecological studies is reliance on hospital registers and case record diagnoses as outcome measures; in our study, cases were accrued prospectively and operational diagnostic criteria were used. The ethnic homogeneity and lack of in-migration in the Cavan-Monaghan region allow for examination of neighbourhood-level effects independent of migration, a potential problem for urban-based studies. Additionally, this study uses analyses that allow the examination of socioeconomic indices at the level of the individual as well as neighbourhood. Another strength of the study is the use of general population controls rather
than psychiatric controls. Moreover our controls were age and sex matched to our cases.

As with all such studies, there is no information on the outcome of the control population utilised here; however, the very small number of cases of psychosis that might be expected to emerge among the controls would bias the study towards false-negative rather than false-positive findings. A number of cases were excluded because of missing information, due to factors such as having been born in the United Kingdom. Because of non-inclusion of certain items in historical censuses, a small number of socioeconomic indicators required modification to fit the availability of census data. Further, that some of the neighbourhood indices were collapsed into smaller categories may have led to spurious findings. The number of statistical tests applied may also have increased the possibility of false-positive findings.

A further limitation is the use of census-based data as a measure of area characteristics. Composite measures such as the social fragmentation index are artificial constructs based on indicators whose selection is dictated by availability of census data (Congdon, 2004). It is also possible that census-based indicators such as private renting and single-person households may not capture social fragmentation similarly in urban and rural areas (Allardyce et al., 2005). Although every effort was made to identify every new case in the study area over a 12-year period, the total number of cases is not large; caution must therefore be exercised in the interpretation of the results, especially when analysing sub-groups in the total sample (e.g. male/female, affective/non-affective cases). Ascertaining an appropriate denominator in
such population-based research also remains a challenge. We attempted to control for genetic relatedness by including only the first-born in multiply affected families, but this may not control adequately for the role of family history in clustering of cases.

7.3.5 Conclusions

The diversity of previous findings on the relationship between parental social class and risk for psychotic illness (Brown, 2011; Eaton, 1985; Kwok, 2014), likely reflects diversity in methodologies and settings in which those methods were applied. The present study utilised prospectively accrued cases with matched population controls in a setting in which two major confounds, urbanicity and in-migration, are absent or minimal, and report no overall influence of social class on risk for psychotic illness. However, one can speculate on a heuristic but reproducible finding, at least in Ireland, that an intermediate socioeconomic milieu at birth may be optimal vis-à-vis both more ‘advantaged’ and ‘disadvantaged’ circumstances. This study also indicates no effects for the neighbourhood-level characteristics of deprivation and social fragmentation, but a modest effect for extent of rurality, indicating that the urban-rural divide (Kelly et al., 2010; Vassos et al., 2012) should be looked upon as a continuum that applies across even a wholly rural (and, thus, possibly a wholly urban) setting. Furthermore, the notion of ‘non-affective psychosis’ vs ‘affective psychosis’ should be considered also in terms of dimensions of psychopathology rather than solely as distinct, diagnostic aggregates, both generally (van Os & Kapur, 2009) and specifically within the present rural region (Owoeye et al., 2013).
While our findings for social class were modest in relation to risk for psychosis, they were substantive in relation to age at first presentation. On the basis of studies conducted primarily in urban settings, it has been suggested that, rather than a gradient of socioeconomic position, it is conditions of social isolation and exclusion that influence risk for schizophrenia and other psychoses (Castle et al., 1993). However, the present findings in a rural setting indicate that such conditions are less influential in relation to risk for psychosis, while a gradient of socioeconomic position may be more influential on delay in presentation for treatment. Future studies should evaluate the reproducibility and effect sizes of such relationships in comparison with other studies that may arise.
References


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Health Atlas Ireland
https://www.healthatlasireland.ie/
(accessed May 2017)


Appendix
Neighbourhood-level socio-environmental factors and incidence of first episode psychosis by place at onset in rural Ireland: The Cavan–Monaghan First Episode Psychosis Study [CAMFEPS]

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1 Deceased.

A B S T R A C T

Background: Little is known about associations between the social environment and risk for psychosis within rural settings. This study sought to investigate whether such associations exist within a rural context using a prospective dataset of unusual epidemiological completeness.

Method: Using the Cavan–Monaghan First Episode Psychosis Study database of people aged 16 years and older, both ecological analyses and multilevel modelling were applied to investigate associations between incidence of psychosis by place at onset and socio-environmental risk factors of material deprivation, social fragmentation and urban–rural classification across electoral divisions.

Results: The primary finding was an association between more deprived social contexts and higher rates of psychotic disorder, after adjustment for age and sex [all psychoses: incidence rate ratio (IRR) = 1.12, 95% CI (1.03–1.23)].

Conclusions: These findings support an association between adverse socio-environmental factors and increase in risk for psychosis by place at onset within a predominantly rural environment. This study suggests that social environmental characteristics may have an impact on risk across the urban–rural gradient.

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1. Introduction

The past two decades have witnessed a revival of interest in the role of the social environment in the aetiology of psychotic disorders (Allardyce and Boydell, 2006; Cantor-Graae, 2007; Kirkbride et al., 2007). Socio-environmental risk factors are generally studied at two levels: (1) area-based (contextual) characteristics such as deprivation, social fragmentation and more recently social capital, and (2) individual-level (compositional) factors such as ethnicity, social class, social adversity and cannabis use. A classic example of contextual research is the seminal study by Faris and Dunham in Chicago in the 1930s (Faris and Dunham, 1939). Using first-admission data from psychiatric hospitals over a 12-year period, higher rates of schizophrenia were observed in inner city areas characterised by greater levels of social disorganisation and residential mobility; conversely, rates of ‘manic-depressive’ psychosis (i.e. bipolar disorder) appeared to follow a more random distribution. More recently, several studies have replicated the findings of Faris and Dunham: measures of social fragmentation, including residential mobility and the proportion of single and divorced people in the neighbourhood, were associated with high rates of psychosis (van Os et al., 2000; Silver et al., 2002); similarly, this pattern was evident when a composite measure (the social fragmentation index) was used (Allardyce et al., 2005).

Interactions with neighbourhood-level socio-environmental risk factors appear to be strongest in urban settings (Thornicroft et al., 1993; Allardyce et al., 2005; Zammit et al., 2010). Thus, it has been argued that neighbourhood-level variables may be responsible for differential rates of psychosis between urban and rural environments (Allardyce et al., 2005; Zammit et al., 2010). In Ireland, differential associations
between urban and rural areas were found between neighbourhood-level characteristics and rates of self-harm and forensic admissions (O’Neill et al., 2005; Corcoran et al., 2007). The body of literature on contextual research comes from urban settings, with rural areas featuring mainly in urban–rural comparisons. Little is known about associations between the social environment and rates of psychosis within rural settings. In this study, we set out to investigate whether such associations exist within a wholly rural context in Ireland using a dataset of unusual epidemiological completeness.

2. Method

2.1. Study cohort

Subjects were participants in the Cavan–Monaghan First Episode Psychosis Study (CAMFEPS). This is a prospective study that seeks the closest approximation to identification of ‘all’ incident cases presenting with a first episode of any psychotic disorder in two rural counties in Ireland, Cavan and Monaghan, since 1995, as described previously in detail (Baldwin et al., 2005; Owoeye et al., 2013; Kingston et al., 2013).

In outline, the study involves the following ascertainment procedures: (a) cases identified from all treatment teams in the catchment areas, (b) cases from the catchment areas who present privately to St. Patrick’s Hospital or St. John of God Hospital, Dublin, which together account for >98% of all national private psychiatric admissions, and (c) cases from the catchment areas having forensic admission to the Central Mental Hospital, Dublin. The primary criterion for entry to the study is a first lifetime episode of any psychotic illness at age 16 or above, with no upper age cut-off. DSM-IV diagnosis is made at inception, together with psychopathological and cognitive assessments, reported elsewhere (Owoeye et al., 2013; Kingston et al., 2013), with repeat DSM-IV diagnosis made at 6 months; there are no exclusion criteria other than a previously treated episode of psychosis or psychosis occurring with a prior, overriding diagnosis of gross neurodegenerative disease. This study was approved by the Research Ethics Committees of (initially) the North Eastern Health Board and (subsequently to reorganisation) the Health Service Executive Dublin North East Area, St. Patrick’s Hospital, St. John of God Hospital and the Central Mental Hospital, to include (a) subjects giving informed consent to formal assessment and (b) obtaining diagnostic/demographic information from case notes/treating teams for subjects declining formal assessment.

Residence at onset was defined as each subject’s domestic location over the 3-month period immediately prior to first presentation with a psychotic illness. For subjects with more than one address in the study area over this period, the address at which he or she was living for more than 50% of the time was applied. Subjects with a second address outside the study area were included only if they were living for more than 50% of the time in Cavan–Monaghan.

2.2. Setting

Cavan and Monaghan are two contiguous counties with a population of 109,139 [55,821 males and 53,318 females] at the 2002 census. The region is predominantly rural, consisting of dispersed farms with a scatter of villages and small towns, in the absence of any major urban areas (Central Statistics Office, 2003). The largest towns are the county towns, Cavan and Monaghan, with populations of 5572 and 5557 respectively in 2002. Only one other town had a population of more than 3000 [Carrickmacross, population 3614]. Both counties are ethnically homogeneous, with the vast majority of the population being white Irish. The study is based within Cavan–Monaghan Mental Health Service, a community-based service model comprising two community mental health teams, including home-based treatment teams, a specialist service for the elderly and a community rehabilitation team. Central to the delivery of health services in this model is the use of home-based treatment as an alternative to hospital admission (McCausley et al., 2003; Iqbal et al., 2012). Electoral divisions (EDs) constitute the smallest administrative sub-regions below county level for which census population data are available. The study region contains a total of 155 EDs having a population mean per ED of 697 in 2002 (Central Statistics Office, 2003).

2.3. Neighbourhood-level characteristics

ED-based measures were calculated using information from the 2002 census (Central Statistics Office, 2003); this census was closest to the midpoint of the present study (1995–2007).

2.3.1. Material deprivation

Material deprivation was quantified using a deprivation index, similar to the Carstairs (Carstairs and Morris, 1991) and Townsend (Townsend et al., 1988) indices often used in the UK, that was developed by the Small Area Health Research Unit (SAHRU) in Trinity College Dublin (Kelly and Teljeur, 2004). The material deprivation index has been previously used in a variety of contexts, including studies of the availability of psychiatric services (O’Keane et al., 2004), forensic admissions (O’Neill et al., 2005), benzodiazepine consumption (Quigley et al., 2006) and self-harm (Corcoran et al., 2007). This index was constructed for each ED by applying principal components analysis to a combination of selected census-based indicators, including unemployment, social class, type of house tenure and car ownership. EDs are divided into ten categories on an ordinal scale, with 1 being least deprived and 10 most deprived. For the present analyses, these were collapsed into five categories [1 = 1 & 2; 2 = 3 & 4; 3 = 5 & 6; 4 = 7 & 8; 5 = 9 & 10]. Mean deprivation scores and standard deviations (SDs) for the three categories of rurality utilised (see Section 2.3.3 Urban–rural classification) were: rural, −0.37 (0.69); village, 0.52 (0.82); and town, 1.80 (0.67).

2.3.2. Social fragmentation

The social fragmentation index (SFI) was developed for a study of suicide in London (Congdon, 1996). We calculated SFI by adding 2 scores of four census variables for each ED: 1) non-married adults, 2) single-person households, 3) population turnover and 4) private renting. For the present analyses, the index was collapsed into four categories, created by quartiles, with 1 being least socially fragmented and 4 most socially fragmented. Mean fragmentation scores and standard deviations (SDs) for the three categories of rurality utilised (see Section 2.3.3 Urban–rural classification) were: rural, −0.59 (1.96); village, 1.90 (1.36); and town, 4.96 (2.74).

2.3.3. Urban–rural classification

This classification, developed by SAHRU for health services research at the small area level in Ireland, combines multiple variables, including population density, settlement size and proximity to urban centres (Teljeur and Kelly, 2008); EDs are divided into six categories on an ordinal scale, with 1 being most rural and 6 most urban. For ecological analyses, the urban–rural classification (URC) was collapsed into a three-category variable: URC3 (1 = rural; 2 = village; 3 = town). For multilevel analyses, both URC3 and URC2 (1 = rural, 2 = village & town) were used.

2.4. Statistical analysis

We adopted two complementary approaches to data analysis: First, in accordance with previous literature (Allardycz et al., 2005; Abas et al., 2006; O’Reilly et al., 2008), we aggregated EDs according to neighbourhood-level indices (deprivation scores, fragmentation quartiles and rurality categories), ignoring spatial contiguity. Age-standardised incidence rates (SIRs) were calculated for each category and rate ratios (RRs), with 95% confidence intervals (95% CIs) and associated probabilities, were obtained using category 1 for each neighbourhood-level characteristic as the reference category.
Second, a multilevel Poisson regression model [XTPOISSON command, Stata version 11.1; Kirkbride et al., 2007, 2008] was applied, by which area-based measures were treated as continuous z-standardised (deprivation, SFI) or categorical (URC) variables. This approach allowed us to adjust more fully for potential confounding by individual- and neighbourhood-level variables. Incidence of psychosis was modelled, with variation in incidence quantified by fitting normally distributed random effects at the ED level (i.e. a random intercepts model). Neighbourhood-level characteristics were entered as fixed effects, using a forward-fitting modelling strategy. The natural logarithm of the denominator population, adjusted for the 12-year study period, was entered as an offset term in these models. Significance testing of fixed effects and their interactions was conducted using likelihood ratio tests (LRTs). To inspect for the possibility of over-dispersion in our models at the ED level (more zero counts of cases than expected under a Poisson distribution), we re-fitted our final models under a zero-inflated-Poisson (ZIP) regression, using a Vuong test to test for evidence of over-dispersion. In all analyses a multilevel Poisson model was found to perform satisfactorily (data available on request).

3. Results

During the first 12 years of the present study, May 1995–April 2007, CAMFEPS incepted 336 cases of any DSM-IV psychotic illness. Cases of non-functional psychosis [i.e. substance-induced psychosis or psychosis due to a general medical condition], those with no non-functional psychosis [i.e. substance-induced psychosis or psychosis on account of a general medical condition] were excluded from the study. As genetic risk in first-degree relatives is, in general, considerably larger than risk associated with environmental factors, a conservative approach was adopted to control for genetic relatedness as a potential confound in evaluating putative environmental factors related to small area variation in rate: in multiply affected families, only the first-born was included (Yousef et al., 1999; Scully et al., 2004). Thus, the total number of cases of functional psychotic illness (hereafter ‘all psychoses’) included in this analysis was 255 [144 males, 111 females]. Cases were further subdivided into two broad diagnostic categories: a) ‘non-affective psychoses’ [primarily schizophrenia and schizoaffective disorder: n = 132; 83 males, 49 females]; and b) ‘affective psychoses’ [bipolar disorder and major depressive disorder with psychotic features: n = 123; 61 males, 62 females].

3.1. Ecological analysis

3.1.1. Material deprivation

For ‘all psychoses’, increase in level of deprivation was associated ordinaly with increase in incidence rate among men but not women (Table 1). When ‘non-affective psychoses’ and ‘affective psychoses’ were considered separately, similar but less robust patterns were found (data available on request).

3.1.2. Social fragmentation

For ‘all psychoses’, the highest rate of psychosis among women was in the most socially fragmented areas; this pattern was evident for both ‘non-affective psychoses’ [RR 1.78 (1.18–2.67)] and ‘affective psychoses’ [RR 1.69 (1.20–2.37)]. There were no significant associations between rate of psychosis and social fragmentation among men (Table 2).

3.1.3. Urban/rural classification

For ‘all psychoses’, the highest rates of psychosis among women were in the least rural areas; this pattern was evident for ‘affective psychoses’ [RR 1.42 (1.01–2.01)] but not for ‘non-affective psychoses’. There were no significant associations between rates of psychosis and urban/rural classification among men (Table 3).

3.2. Multilevel analysis

Relationships between individual-level variables, neighbourhood-level variables and incidence of ‘all psychoses’ are shown in Table 4. As expected, risk was highest among the 15–24 age group and declined over subsequent decades until around 65 years of age, after which risk increased slightly; decline in risk with age was less marked among women than among men, in accordance with previous findings (Kirkbride et al., 2006).

In the unadjusted multilevel model, no significant neighbourhood variation (i.e. random effects) in incidence rates was apparent. Despite this, however, we did observe a relationship between increased level of deprivation and higher incidence rates of psychosis in our fully adjusted model (for age and sex); when stratified by sex, this effect was evident only among women. No such association was evident when the sample was restricted to those ages studied typically in first episode samples (15–64 years); a marginal interaction between age group and level of deprivation in the full sample (LRT, p = 0.08) suggested further that the association between level of deprivation and risk for psychosis derived primarily from the group aged 65–74 years. When ‘non-affective psychoses’ and ‘affective psychoses’ were analysed separately, no associations between any neighbourhood-level variable and risk for psychosis were evident (data available on request).

4. Discussion

To our knowledge, this is the first study to examine associations between neighbourhood-level socio-environmental risk factors and incidence of first episode psychosis within a rural setting. Unlike the majority of other studies, we did not impose any upper age limit and attempted to identify ‘all’ cases presenting with a first episode psychosis so as to incept an epidemiologically representative population across the lifespan. We adopted, and thus were able to compare, two complementary approaches to data analysis. First, by aggregating EDs according to their social characteristics; this is a widely adopted ecological approach (Allardycse et al., 2005; Abas et al., 2006; O’Reilly et al., 2008) that reveals non-linear relationships where they exist and does not depend on any assumptions applicable to multilevel techniques. Second, by applying multilevel modelling; this more incisive approach allows exploration of variation in the incidence of first episode psychosis at more than one level (Kirkbride et al., 2007, 2008). The main findings are considered below.

Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
<td>n</td>
<td>Population</td>
<td>SIR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>2</td>
<td>19.77 (16.31–23.23)</td>
<td>1.19</td>
<td>(0.92–1.53)</td>
<td>21</td>
<td>8944</td>
<td>12.28 (9.47–15.08)</td>
</tr>
<tr>
<td>3</td>
<td>20.00 (16.52–23.47)</td>
<td>1.20</td>
<td>(0.93–1.55)*</td>
<td>33</td>
<td>14019</td>
<td>17.18 (13.88–20.49)</td>
</tr>
<tr>
<td>4</td>
<td>21.41 (17.81–25.00)</td>
<td>1.29</td>
<td>(1.00–1.66)*</td>
<td>33</td>
<td>12849</td>
<td>17.01 (13.72–20.30)</td>
</tr>
<tr>
<td>5</td>
<td>26.31 (22.23–30.29)</td>
<td>1.58</td>
<td>(1.25–2.01)*</td>
<td>46</td>
<td>13737</td>
<td>19.60 (16.08–23.12)</td>
</tr>
</tbody>
</table>

Category 1: least deprived (reference); category 5: most deprived.

* p < 0.05.
4.1. Material deprivation

Ecological analysis identified a variable association between extent of deprivation and incidence of psychosis, primarily among men; previous ecological studies have demonstrated that the relationship between deprivation and psychosis is not necessarily linear (Croudace et al., 2000; Allardyce and Boydell, 2006). Multilevel modelling revealed an association between extent of deprivation and risk for ‘all psychoses’ for the whole sample, though this effect may have been restricted to older women, beyond the age range considered in most studies of first episode psychosis. These findings suggest that women may be particularly sensitive to deprivation during late rather than early life. Alternatively, they may reflect cumulative exposure to deprivation over the life course in women or, perhaps, stronger social drift for women who go on to develop psychosis later in life as they become more marginalised in rural communities; however, longitudinal data would be necessary to test such hypotheses. Our data suggest that socio-environmental factors influence incidence rates in rural as well as urban communities. Although the impact of such factors may be greater in more urban regions, our results nonetheless hold material import for health service planning, public health and, more tentatively, etiological research.

4.2. Social fragmentation and rurality

Ecological analysis revealed an association between extent of social fragmentation and incidence of psychoses, primarily among women. In multilevel analyses, social fragmentation was not associated with the rate of psychosis once material deprivation has been included, though they were highly correlated factors \( r^2 = 0.63, p < 0.01 \). Whether social fragmentation or material deprivation constitutes the more salient exposure remains a matter of debate but studies conducted in other settings indicate a more robust association between area-level social fragmentation and rate of psychosis, primarily in urban settings (Allardycase et al., 2005; Zammit et al., 2010). As a modest association between social fragmentation and incidence of psychosis was evident here on ecological analysis but not using multilevel modelling, future studies should examine further the extent to which this may reflect lower levels of, or less variability in, social fragmentation in rural compared to urban areas. A previous nation-wide study from Ireland has demonstrated the lowest scores for social fragmentation to be in rural EDs, with the highest scores reported in cities other than Dublin (Corcoran et al., 2007).

4.3. Gender

While ecological analysis also indicated that women living in the least rural areas of our study were at increased risk for psychosis, this association was not evident in multilevel analyses after taking age and deprivation into account. While there is a strong body of evidence indicating higher rates of psychosis in urban areas (Pedersen and Mortensen, 2001; Harrison et al., 2003; McGrath et al., 2004; Kelly et al., 2010), future studies should examine further the extent to which socio-environmental variation in risk for psychosis may extend beyond the traditional dichotomous urban/rural divide and be subject to gradations within both urban and rural areas.

In ecological analyses the associations between incidence of psychosis and neighbourhood indices of social fragmentation and rurality showed a similar profile for affective and non-affective psychoses. This contrasts with findings by Faris and Dunham (1939). While we cannot exclude the possibility of misclassification of cases, we believe this to be unlikely as standardised assessment methods were employed for diagnosis using DSM-IV criteria. While the absence of significant findings using multilevel modelling is cautionary, other ecological studies indicate that the relationship between contextual characteristics and mental illness is not confined to non-affective psychoses and extends to affective disorders (Silver et al., 2002; Curtis et al., 2006).

4.4. Methodological considerations

Our findings include a number of gender-related associations that were apparent across diagnostic categories, not confined to a single index and evident using either analytical approach. A large population-based case–control study of risk for myocardial infarction in Sweden revealed gender differences in contextual effects of material deprivation and social fragmentation (Stjärne et al., 2004); similarly, gender differences have been reported in ecological studies of self-rated health (Stafford et al., 2005; Kavanagh et al., 2006). Possible explanations for such gender differences are that men and women differ in perception of and exposure and vulnerability to the local environment (Stafford et al., 2005).

Table 2

<table>
<thead>
<tr>
<th>Category</th>
<th>Men</th>
<th>SIR CI (range)</th>
<th>RR CI</th>
<th>n</th>
<th>Population</th>
</tr>
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<td>1</td>
<td>21.58 (17.97–25.19)</td>
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<td>25</td>
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<td>2</td>
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<td>24.57 (20.72–28.41)</td>
<td>1.14</td>
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<tr>
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<tr>
<td>1</td>
<td>1</td>
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<td>15</td>
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Table 3

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<th>Population</th>
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<td>3</td>
<td>3</td>
<td>22.08 (18.43–25.73)</td>
<td>1.02</td>
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<tr>
<td>Women</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>15.53 (12.39–18.68)</td>
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<td>59</td>
<td>32,249</td>
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<tr>
<td>2</td>
<td>2</td>
<td>19.2367 (15.75–22.73)</td>
<td>1.24</td>
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<td>7,453</td>
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<td>3</td>
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<td>20.7117 (17.09–24.33)</td>
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<td>35</td>
<td>13,084</td>
</tr>
</tbody>
</table>

Category 1: most rural (reference); category 3: least rural.

p < 0.05.
were able to ascertain cases who chose to present privately or whose presentation resulted in a forensic admission; we were able to obtain information from case records/treating teams for subjects who declined formal assessment. Therefore, the likelihood of case leakage is considerably reduced. A common methodological challenge for ecological studies is reliance on hospital registers and case record diagnoses as outcome measures; in our study, cases were accrued prospectively and operational diagnostic criteria were used. The ethnic homogeneity and lack of in-migration in the Cavan–Monaghan region allow for examination of neighbourhood-level effects independent of migration, a potential problem for urban-based studies. Multilevel analyses allowed us to quantify the impact of neighbourhood-level factors on incidence rates in our sample. While multilevel models suggested only weak neighbourhood (random) effects, our study was sufficiently powered to detect evidence for an association between material deprivation and psychosis after controlling for individual level covariates. These multilevel models were appropriate for count data and were fitted appropriately, given the possibility of over-dispersion.

### 4.4.2. Limitations

Our study is subject to a number of limitations common to ecological research. First, we cannot assume that people with first episode psychosis living in neighbourhoods with a given level of a putative risk factor were themselves exposed to that level of risk (the ‘ecological fallacy’). Second, the cross-sectional design of ecological studies precludes aggregation of individual-level characteristics, though we controlled for two very important factors: age and sex. However, in previous large population studies the effect of neighbourhood-level social fragmentation has remained after controlling for individual-level characteristics (Silver et al., 2002; Zammit et al., 2010). The comparison of two analytical approaches revealed both convergence on certain relationships and some differences in specifics; this emphasises how conclusions drawn can be influenced by the analytical approach adopted. A potential limitation is differential migration. For example, it is possible that areas of high incidence are related to outmigration of healthy subjects or, alternatively, that areas of low incidence are related to outmigration of those at risk for psychosis. On demographic grounds, over the period during which the present data were collected (1995–2007), such selective migration is unlikely to be so substantive as to generate the present profile of results. However, the absence of information on the mental health of those who may have left the study area is cautionary. A further limitation is the use of census-based data as a measure of area characteristics. Composite measures such as the social isolation index are artificial constructs based on indicators whose selection is dictated by availability of census data (Congdon, 2004). It is also possible that census-based indicators such as private renting and single-person households may not capture social fragmentation similarly in urban and rural areas (Allardice et al., 2005). We attempted to control for genetic relatedness by including only the first-born in multiply affected families, but this may not control adequately for the role of family history in clustering of cases. Finally, the 2002 census may not be truly representative of the social characteristics of Cavan–Monaghan over the 12-year period of the study. To address this, we repeated analyses using data from the 2006 census; this did not materially alter our results (data available on request).

Our primary finding is an association between more deprived social contexts and higher rates of psychotic disorder in a predominantly rural setting, after adjustment for age and sex. However, there was less evidence for such associations than is typically reported in urban settings (Kirkbride et al., 2007). Together, these findings suggest that there may be a continuum of risk of psychosis with socio-environmental risk factors across the rural–urban divide, to include essentially rural environments. However, they suggest that such exposures may have greater impact in more urban settings. Future epidemiological and health services research in rural areas (see, for example, the SEPEA study (Kirkbride et al., 2012)) should take into account potential variations in risk within rural areas and consider gender differences in relation to contextual effects.

<table>
<thead>
<tr>
<th>Variable Strata</th>
<th>All subjects: IRR (95% CI)</th>
<th>Men: IRR (95% CI)</th>
<th>Women: IRR (95% CI)</th>
</tr>
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<td>Unadjusted</td>
<td>Full</td>
<td>LRT p</td>
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<td><strong>Individual-level variables</strong></td>
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<tr>
<td>Age</td>
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<td>1</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>25–34</td>
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<td>0.8 (0.6–1.1)</td>
<td>0.7 (0.4–1.0)</td>
</tr>
<tr>
<td>35–44</td>
<td>0.5 (0.4–0.8)</td>
<td>0.5 (0.6–0.8)</td>
<td>0.4 (0.3–0.7)</td>
</tr>
<tr>
<td>45–54</td>
<td>0.5 (0.3–0.8)</td>
<td>0.5 (0.6–0.8)</td>
<td>0.3 (0.2–0.6)</td>
</tr>
<tr>
<td>55–64</td>
<td>0.4 (0.3–0.7)</td>
<td>0.4 (0.3–0.7)</td>
<td>0.4 (0.2–0.7)</td>
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<td>65–74</td>
<td>0.6 (0.4–1.0)</td>
<td>0.6 (0.4–1.0)</td>
<td>0.6 (0.4–1.0)</td>
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<tr>
<td>75+</td>
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<td>0.9 (0.6–1.4)</td>
<td>0.8 (0.4–1.5)</td>
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<tr>
<td><strong>Neighbourhood-level variables</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SFI 1 SD change</td>
<td>1.10 (1.01–1.20)</td>
<td>1.04 (0.92–1.17)</td>
<td>1.17 (1.04–1.32)</td>
</tr>
<tr>
<td>Deprivation 1 SD change</td>
<td>1.13 (1.03–1.24)</td>
<td>1.10 (0.97–1.25)</td>
<td>1.16 (1.03–1.36)</td>
</tr>
<tr>
<td>SFI 1.25 SD change</td>
<td>1.17 (1.07–1.28)</td>
<td>1.15 (1.01–1.31)</td>
<td>1.22 (1.07–1.40)</td>
</tr>
<tr>
<td>SFI 1.5 SD change</td>
<td>1.19 (1.09–1.31)</td>
<td>1.17 (1.03–1.33)</td>
<td>1.25 (1.08–1.44)</td>
</tr>
<tr>
<td>SFI 2 SD change</td>
<td>1.22 (1.13–1.32)</td>
<td>1.21 (1.07–1.38)</td>
<td>1.30 (1.14–1.49)</td>
</tr>
<tr>
<td>NECR 1 Rural</td>
<td>1</td>
<td>1</td>
<td>0.94</td>
</tr>
<tr>
<td>NECR 1 Village</td>
<td>1.07 (0.74–1.54)</td>
<td>0.97 (0.59–1.60)</td>
<td>1.13 (0.66–1.94)</td>
</tr>
<tr>
<td>NECR 1 Town</td>
<td>1.19 (0.90–1.58)</td>
<td>1.17 (0.73–1.58)</td>
<td>1.36 (0.90–2.07)</td>
</tr>
<tr>
<td>NECR 1 Less rural</td>
<td>1.15 (0.89–1.47)</td>
<td>1.04 (0.74–1.45)</td>
<td>1.28 (0.88–1.85)</td>
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</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects: IRR (95% CI)</th>
<th>Men: IRR (95% CI)</th>
<th>Women: IRR (95% CI)</th>
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<td></td>
</tr>
<tr>
<td>NECR 2 SD change</td>
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<td></td>
</tr>
</tbody>
</table>

IRR, incidence rate ratio (with 95% CI); LRT, likelihood ratio test; p value indicates whether a variable improved overall model fit. IRR not reported for variables that did not significantly improve the final model at the p < 0.05 threshold of significance. SFI, social fragmentation index; NECR, urban–rural classification; Deprivation, material deprivation index; SD, standard deviation.
Role of funding source
The Cavan–Monaghan First Episode Psychosis Study (CAMEFPS) was supported by the Stanley Medical Research Institute and Cavan–Monaghan Mental Health Service. J.B. Kirkbride was supported by a Sir Henry Wellcome Research Fellowship from the Wellcome Trust (grant number WT085540).

Contributors
Sam Omer contributed to the conception and design of the study, and collection, analysis and interpretation of the data, drafted the manuscript and ensured final approval of the version to be published. James Kirkbride contributed to the analysis and interpretation of the data, revising the manuscript and final approval of the version to be published. Vincent Russell contributed to the conception and design of the study, revising the manuscript and final approval of the version to be published.

Conflict of interest
None of the authors have any conflict of interest relating to this manuscript.

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References
Socioeconomic status at birth and risk for first episode psychosis in rural Ireland: Eliminating the features of urbanicity in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS)

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Environmental factors
Case-control
Social context

A B S T R A C T
Background: There is a paucity of research on the relationship between social environment at birth and risk for psychosis in rural settings. This study examined the relationship between individual- and neighbourhood-level socioeconomic indicators proximal to the time of birth and risk for a first psychotic episode in a rural context using a prospective dataset of unusual epidemiological completeness.

Methods: A matched case-control design was used. 186 cases were identified from the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS) and 679 age- and sex-matched controls from the same rural setting were identified and analysed for relationships with individual and neighbourhood-level socioeconomic indicators at the level of Electoral Divisions.

Results: While neither the distribution nor the ordinal scale of parental social class differed between cases and controls, logistic regression revealed both parental social class III and increasing level of rurality to be associated (p ≤ 0.05) with reduced risk for affective psychosis. There was a prominent relationship (p < 0.001) between lower parental social class and older age at first presentation [mean age at first presentation for all psychoses: social class I, 22.8; social class VI, 44.3].

Conclusions: These findings indicate modest effects of individual- and neighbourhood-level socioeconomic indicators and risk for psychosis by place at birth within a rural environment. Thus, these factors are not confined to large urban settings and apply across the urban-rural continuum. The substantive finding in relation to age at first presentation may indicate that a gradient of socioeconomic position is influential on delay in presentation to mental health services.

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1. Introduction

There is a wealth of literature on the relationship between socioeconomic position and psychosis. In a study of insanity in Massachusetts in 1855, Edward Jarvis stated “there is a manifestly larger ratio of the insane among the poor, and especially among those who are paupers, than among the independent and more prosperous classes” (Jarvis, 1971). In Ireland in 1911, Dawson observed that the geographical distribution of insanity in Ireland was associated strongly with rates of puerperism (Dawson, 1911). Over the subsequent century, numerous studies have investigated such relationships and, as examination of socioeconomic status at the time of presentation may be confounded by an effect of illness, several have used social class at birth as an indicator of socioeconomic position. While the majority of socioeconomic studies have reported higher rates of schizophrenia among those of lower social class, a not insubstantial minority have found no such relationship or even an inverse relationship (Brown, 2011; Eaton, 1985; Kwok, 2014). For those studies reporting a significant relationship, the well
recognised debate as to the relative roles of social causation vs social drift endures (Dohrenwend et al., 1992; van Os and McGuffin, 2003).

More recently, considerable interest has focussed on another possible relationship: that being born and/or having one’s early upbringing in an urban as opposed to a rural area is associated with increased risk for schizophrenia (Kelly et al., 2010; Pedersen and Mortensen, 2001; Vassos et al., 2012). The substantial majority of contemporary, quantitative studies investigating any relationship between social class and risk for schizophrenia have been carried out in primarily urban areas or using national/large regional datasets that confine the urban-rural divide. Thus, features of urbanicity are potential modulators of or confounders in such relationships and may either sharpen or blunt their identification.

To address this issue requires a study that is conducted in a wholly rural setting. The Cavan-Monaghan First Episode Psychosis Study (Baldwin et al., 2005; Kingston et al., 2013; Omer et al., 2014; Owowe et al., 2013) incepts cases from the rural Irish counties of Cavan and Monaghan and provides a rare opportunity to investigate risk for psychotic illness in relation to social class in the absence of any major urban centres. Additionally, few studies have examined relationships between the social environment (other than social class and the urban-rural divide) at the time of birth and risk for psychosis at the neighbourhood level, other than those also carried out in primarily urban areas or using national datasets (Brown, 2011; Eaton, 1985; Kwok, 2014). Therefore, in this study we focus on the relationship between individual- and neighbourhood-level socioeconomic indicators proximal to the time of birth and risk for a first psychotic episode.

2. Methods

2.1. Study cohort

Subjects were participants in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). This is a prospective study of ‘all’ incident cases presenting with a first episode of any psychotic disorder in two rural counties in Ireland, total population 109,139 [55,821 males and 53,318 females] at the 2002 census. Details of this setting, case ascertainment and assessment have been described previously in detail (Baldwin et al., 2005; Kingston et al., 2013; Omer et al., 2014; Owowe et al., 2013). This study was approved by the Research Ethics Committees of (initially) the North Eastern Health Board and (subsequent to reorganisation) the Health Service Executive Dublin North East Area, St. Patrick’s Hospital, St. John of God Hospital and the Central Mental Hospital, to include (a) subjects giving informed consent to formal assessment and (b) obtaining diagnostic/demographic information from case notes/treating teams for subjects declining formal assessment.

2.2. Study design

A matched case-control design was used. Cases and controls were matched for age (to within one year) and sex; for each case, a copy of his/her birth certificate was obtained from the civil registration offices in Cavan or Monaghan and the two same-sex entries above and the two below on the birth register were selected as controls.

Two indices of socioeconomic status at birth were examined. Firstly, ‘occupation of father’ was extracted from the birth certificate and a social class assigned according to the Census of Population Classification of Occupations for Ireland (Central Statistics Office, 1986); this consists of six categories 1 (highest)—VI (lowest). Secondly, the social characteristic of the area of residence at birth was ascertained from ‘Dwelling-place of father’ on the birth certificate (dwelling place of the mother is not recorded on Irish birth certificates, except in the absence of a named father); this entry was used as a proxy for parental location over the period of pregnancy. Neighbourhood-level indices of material deprivation, social fragmentation and urban-rural classification at the level of electoral divisions (ED) were obtained from census data. EDs constitute the smallest administrative sub-regions below county level for which census population data are available, with the study region containing a total of 155 EDs.

2.3. Neighbourhood-level characteristics

ED-based measures were calculated using information from the 1971 census for Ireland; this census was closest to the median year of birth of the study group [1970].

2.3.1. Material deprivation

The deprivation index was based on an index developed by the Small Area Health Research Unit (SAHRU), Trinity College Dublin (Kelly and Teljeur, 2004). It contains four indicators for each ED: (a) unemployment, (b) social class, (c) type of house tenure, and (d) car ownership. (a), (c) and (d) were calculated using 1971 census data; as data on social class were not available at ED level until the 1986 census, 1986 social class data were used for (b).

2.3.2. Social fragmentation

The social fragmentation index (SFI) was developed for a study of suicide in London (Congdon, 1996). We calculated SFI by adding z scores of four indicators for each ED: (a) percentage of adults not married, (b) percentage of adults in single-person households, (c) population turnover, and (d) percentage of households in private rented housing. (a), (b) and (d) were calculated using 1971 census data; as data on population turnover, as defined in the SFI, were not available at the ED level until the 2002 census, we calculated population change over the 10-year period prior to the 1971 census as a surrogate measure for (c).

2.3.3. Urban-rural classification

We used the SAHRU urban-rural classification in which EDs are divided into six categories on an ordinal scale, with 1 being most rural and 6 most urban (Teljeur and Kelly, 2008). Recognising that the SAHRU urban-rural classification uses data from the 2002 census, which may not be fully representative of the level of rurality in the study area around the time of birth of the study group, we also constructed an urban-rural classification using the following variables from the 1971 census: population density, percentage of farmers, percentage with mains water supply and percentage of people living in local authority housing.

2.4. Statistical analysis

Cross-tabulated categorical data were analysed using χ² tests, with odds ratios (ORs) and 95% confidence intervals (95% CIs) calculated for all variables of interest. The Mann-Whitney U test was also used to examine social class as an ordinal scale in cases vs controls. Logistic regression models were fitted to examine the relationship of caseness (i.e. the likelihood of being a case as opposed to a control) to individual- and neighbourhood-level characteristics. Analysis of variance (ANOVA) was used to examine the relationship of age at first presentation to individual- and neighbourhood-level characteristics. Data were analysed using PASW Statistics 18 software.

3. Results

During the first 12 years of the present study, May 1995–April 2007, CAMFEPS incepted 336 cases of any DSM-IV psychotic illness. Cases of non-functional psychosis [i.e. substance-induced psychosis or psychosis due to a general medical condition] (n = 28), those who were adopted (n = 4), born outside the study area (n = 49) or of parents having no fixed abode (n = 3) were excluded from the study. In those from multiply affected families (n = 11), only the first-born was included (Omer et al., 2014). Furthermore, some birth certificates could not be
located due to missing information on the maiden name of married women (n = 11), and in other instances information available on the birth certificate did not allow the father’s occupation to be assigned (n = 44). In total, 186 cases of psychosis (106 men, 80 women) and 679 matched controls (385 men, 294 women) were included in the analysis. Cases were subdivided into two broad diagnostic categories: (a) ‘non-affective psychoses’ [primarily schizophrenia and schizoaffective disorder: 100 cases (63 men, 37 women), 351 controls (219 men, 132 women)]; and (b) ‘affective psychoses’ [bipolar disorder and major depressive disorder with psychotic features: 86 cases (43 men, 43 women), 328 controls (166 men, 162 women)].

### 3.1. Parental social class and risk for first episode psychosis

For ‘all psychoses’, distribution of parental social class differed slightly between men and women across all subjects ($\chi^2 = 11.40, p \leq 0.05$) but did not differ between cases and controls ($p = 0.45$; Table 1). When considered as an ordinal scale, parental social class did not differ between cases and controls (Mann-Whitney U test, $Z = −1.37, p = 0.17$). A similar profile was evident for ‘non-affective psychoses’ (men vs women, $p \leq 0.05$; no difference for cases vs controls), while for ‘affective psychoses’ there were no differences for either men vs women or cases vs controls.

In logistic regression models, adjusting for age and sex, for ‘non-affective psychoses’ no associations with social class were evident ($p \geq 0.45$), while for ‘affective psychoses’ there was an association between parental social class III and reduced risk for psychosis ($p \leq 0.05$); this association altered only marginally on adjusting also for neighbourhood-level characteristics ($p = 0.08$; Table 2).

### 3.2. Neighbourhood-level characteristics and risk for first episode psychosis

For ‘all psychoses’, increasing level of rurality was associated with reduced risk for psychosis ($p \leq 0.05$); this relationship altered only marginally on adjusting for social class ($p = 0.07$; Table 3). On considering ‘affective psychoses’ and ‘non-affective psychoses’ separately, a similar and more robust pattern was present for ‘affective psychoses’ ($p \leq 0.05$) but was absent for ‘non-affective psychoses’ ($p \geq 0.48$). There were no significant associations between neighbourhood levels of social fragmentation or deprivation at birth and risk for psychosis.

### 3.3. Parental social class and age at first presentation

Distribution of age at first presentation by social class is shown in Table 4. For ‘all psychoses’, age at first presentation increased markedly with lower socioeconomic status (effect of social class, $p < 0.001$) in a manner that did not differ between the sexes (no effect of sex or social class × sex interaction); this profile was evident for both ‘non-affective psychoses’ (effect of social class, $p < 0.01$) and ‘affective psychoses’ (effect of social class, $p < 0.001$).

### Table 1

Distribution of parental social class for cases and controls.

<table>
<thead>
<tr>
<th>Social class</th>
<th>Cases (%)</th>
<th>Controls (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>All</td>
</tr>
<tr>
<td>I</td>
<td>6 (5.7)</td>
<td>3 (3.8)</td>
<td>9 (4.8)</td>
</tr>
<tr>
<td>II</td>
<td>13 (12.3)</td>
<td>6 (7.5)</td>
<td>19 (10.2)</td>
</tr>
<tr>
<td>III</td>
<td>5 (4.7)</td>
<td>9 (11.3)</td>
<td>14 (7.5)</td>
</tr>
<tr>
<td>IV</td>
<td>30 (28.3)</td>
<td>20 (25.0)</td>
<td>50 (26.9)</td>
</tr>
<tr>
<td>V</td>
<td>33 (31.1)</td>
<td>20 (25.0)</td>
<td>53 (28.5)</td>
</tr>
<tr>
<td>VI</td>
<td>19 (17.9)</td>
<td>22 (27.5)</td>
<td>41 (22.0)</td>
</tr>
</tbody>
</table>

Odds ratios (ORs) with 95% confidence intervals (95% CIs); category 1 as reference.

### Table 2

Logistic regression model for relationship between social class and risk for affective psychosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted**</th>
<th>Final model**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social class</td>
<td>P OR (95% CI)</td>
<td>P OR (95% CI)</td>
</tr>
<tr>
<td>I</td>
<td>– 1 –</td>
<td>– 1 –</td>
</tr>
<tr>
<td>II</td>
<td>0.43 0.58  (0.15–2.26)</td>
<td>0.37 0.51 (0.12–2.21)</td>
</tr>
<tr>
<td>III</td>
<td>0.05† 0.21 (0.05–1.02)</td>
<td>0.08 0.23 (0.04–1.18)</td>
</tr>
<tr>
<td>IV</td>
<td>0.45 0.61 (0.17–2.17)</td>
<td>0.44 0.58 (0.15–2.27)</td>
</tr>
<tr>
<td>V</td>
<td>0.46 0.62 (0.17–2.22)</td>
<td>0.39 0.54 (0.14–2.16)</td>
</tr>
<tr>
<td>VI</td>
<td>0.65 0.74 (0.20–2.72)</td>
<td>0.68 0.74 (0.18–3.02)</td>
</tr>
<tr>
<td>URC-1971</td>
<td>0.04* 0.06 (0.92–1.00)</td>
<td>0.67 0.97 (0.84–1.12)</td>
</tr>
<tr>
<td>SFI</td>
<td></td>
<td>0.81 0.98 (0.86–1.12)</td>
</tr>
</tbody>
</table>

Odds ratios (ORs) with 95% confidence intervals (95% CIs); * category 1 as reference.

### 4. Discussion

#### 4.1. Main findings

In this rural region of Ireland we found no overall relationship between parental social class and risk for first episode psychosis. Neither was any relationship found when ‘non-affective’ and ‘affective’ psychoses were examined separately, subject to one exception: social class III was associated with reduced risk for ‘affective psychosis’. We could detect no material effect of deprivation or social fragmentation at birth on risk for psychotic illness. However, we did identify a modest association between increasing rurality and decrease in risk for first episode psychosis, that, as for the above association with social class III, appeared more evident for ‘affective psychosis’ than for ‘non-affective psychosis. The most striking finding was a prominent relationship between lower parental social class and older age at first presentation.

#### 4.2. Interpretation of findings in relation to previously published work

The association between intermediate social class III and reduced risk for psychosis, particularly for ‘affective psychosis’, is similar to a previous study in a more urban region of Ireland, where intermediate social class IV was associated with reduced risk (Mulvany et al., 2001). This suggests that in rural areas there may be some characteristic of social class III [other non-manual and farmers with 50–99 acres (20.2–40.1 ha)] that decreases risk for psychotic illness in a manner that shifts from ‘non-affective psychosis’ to ‘affective psychosis’ along the urban-rural divide. We propose that social class III in rural regions and social class IV [skilled manual and farmers with 30–49 acres (12.1–19.8 ha)] in more urban regions may represent a favourable, intermediate social milieu associated with fewer of the stressors that might characterise social class I/II [professional/managerial] and social class V/VI [semi-skilled manual or farmers with < 30 acres (12.1 ha)]. Such an intermediate social class may optimise the stress-buffering
effects of personal control (mastery), self-esteem and social support known to be associated with reduced risk for ill-health (Thors, 2010). Furthermore, we have previously reported (Kelly et al., 2010) an overall shift in the relative incidence of regional vs urban rural region of Mulvany et al. (2001). This supports the proposition above that factors varying along the urban-rural continuum can predispose differentially to non-affective psychosis vs affective psychosis.

The lack of association between neighbourhood-level characteristics of deprivation and social fragmentation and risk for psychotic illness contrasts with published work. As such variables have been shown to influence risk for psychotic illness in primarily urban areas in relation to onset (Kirkbride et al., 2007, 2014), the underlying mediators may be attenuated in rural regions and/or of greater impact proximal to the emergence of diagnostic symptoms and first presentation. It is also possible that census-based indices such as the deprivation index and SFI are less suitable for assessing levels of deprivation in rural areas. It has been argued that the individual variables in these indices may better capture levels of deprivation in urban than in rural areas (Allardyce et al., 2005; Pringle, 2002).

As for the association with intermediate social classes III/IV, the relationship between lower parental social class and older age at first presentation was previously reported in a more urban region of Ireland (Mulvany et al., 2001): mean ages at first presentation were 25 for class I, 29 for class IV and 34 for class VI. In the present rural region, this effect was considerably more prominent, i.e. mean ages at first presentation were 23 for class I, 34 for class IV and 44 for class VI. As discussed by Mulvany et al. (2001), it is possible that age at onset differs between the social classes, or that family practitioners delay in referring patients from lower social classes. However, it is more likely that lower social class may be associated with delayed engagement with health services, as is the case for several general medical situations; these include: seeking antenatal care, with subsequent delivery of a baby of low birth weight (Gray et al., 2014; Luo et al., 2006); seeking medical attention for children and extent of illness endured before seeking help (Department of Health and Social Security, 1980). Lower social class might be associated with increased difficulty in accessing psychiatric services (Birtchnell, 1971; but see Cooper, 1961) or higher social class might be associated with being more informed about psychosis and/or more aware of deviations in social, academic or occupational functioning (Horwitz, 1987; Roberts, 1980). Lower social class may be associated with increased tolerance and acceptance of psychotic behaviour and a sense of reduced control or powerlessness (Rosma et al., 1999; Loebel et al., 1992). It cannot be excluded that older age in patients from lower parental social classes could result in their never reaching health services or dying before treatment could be initiated. While some of these putative explanatory factors might be more evident in rural relative to urban settings, this should be juxtaposed with Cavan–Monaghan Mental Health Service operating a community, home-based treatment model in close association with family practitioners, as espoused by Mulvany et al. (2001), is supported by evidence (Clarke et al., 1999) that lower social class is associated with increased duration of untreated psychosis (DUP) and should be prioritised in terms of efforts to reduce DUP.

### 4.3. Strengths and limitations of the study

Strengths of the CAMFEPS dataset include prospective accrual, epidemiological completeness, ethnic homogeneity and minimal immigration of cases, as described in detail elsewhere (Baldwin et al., 2005; Kingston et al., 2013; Omer et al., 2014; Owoeye et al., 2013). Thus, its wholly rural setting allows examination of the relationship between socioeconomic indicators and risk for psychosis independent of two potential confounders that are typically encountered in other studies, i.e. in-migration and urbanicity. Additionally, this study uses analyses that allow the examination of socioeconomic indices at the level of the individual as well as neighbourhood.

As with all such studies, we have no information on the outcome of our control population; however, the very small number of cases of

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Logistic regression models for relationship between neighbourhood-level characteristics and risk for psychosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>All psychoses</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
</tr>
<tr>
<td></td>
<td>P OR (95% CI)</td>
</tr>
<tr>
<td>URC-1971</td>
<td>0.05⁎</td>
</tr>
<tr>
<td>SFI</td>
<td>0.40</td>
</tr>
<tr>
<td>Deprivation</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Odds ratios (ORs) with 95% confidence intervals (95% CIs). URC, urban-rural classification; SFI, social fragmentation index; deprivation, material deprivation index.

⁎ Adjusted for age, sex and social class.

** Table 4 | Age at first presentation by parental social class. |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Social class</td>
<td>All psychoses</td>
</tr>
<tr>
<td></td>
<td>Mean age (SD)</td>
</tr>
<tr>
<td>I</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>Women</td>
</tr>
<tr>
<td>II</td>
<td>All</td>
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<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>Women</td>
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<tr>
<td>III</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>Women</td>
</tr>
<tr>
<td>IV</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>Women</td>
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<tr>
<td>V</td>
<td>All</td>
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<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>Women</td>
</tr>
<tr>
<td>VI</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>Women</td>
</tr>
</tbody>
</table>

SD, standard deviation.

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psychosis that might be expected to emerge among the controls would bias the study towards false-negative rather than false-positive findings. A number of cases were excluded because of missing information, due to factors such as having been born in the United Kingdom. Because of non-inclusion of certain items in historical censuses, a small number of socioeconomic indicators required modification to fit the availability of census data.

4.4. Implications for future research, policy and practice

The findings of our study indicate that the urban-rural variable should be looked upon as a continuum rather than a divide, such that one’s position along that continuum appears to be influential even within what is classified as a ‘rural’ region (see also Omer et al., 2014). Furthermore, the notion of ‘non-affective psychosis’ vs ‘affective psychosis’ should be considered also in terms of dimensions of psychopathology rather than solely as distinct, diagnostic aggregates, both generally (van Os and Kapur, 2009) and specifically within the present rural region (Owowe et al., 2013).

4.5. Conclusions

The diversity of previous findings on the relationship between parental social class and risk for psychotic illness (Brown, 2011; Eaton, 1985; Kwok, 2014) likely reflects diversity in methodologies and settings in which those methods were applied (see Section 1). In the present study we utilise prospectively accrued cases with matched population controls in a setting in which two major confounds, urbanicity and in-migration, are absent or minimal, and report no overall influence of social class on risk for psychotic illness. However, we speculate on a heuristic but reproducible finding, at least in Ireland, that an intermediate socioeconomic milieu at birth may be optimal vis-à-vis both more ‘advantaged’ and ‘disadvantaged’ circumstances. We also report no effects for the neighbourhood-level characteristics of deprivation and social fragmentation, but a modest effect for extent of rurality, indicating that the urban-rural divide (Kelly et al., 2010; Vassos et al., 2012) should be looked upon as a continuum that applies across even a wholly rural (and, thus, possibly a wholly urban) setting.

While our findings for social class were modest in relation to risk for psychosis, they were substantive in relation to age at first presentation. On the basis of studies conducted primarily in urban settings, it has been suggested that, rather than a gradient of socioeconomic position, it is conditions of social isolation and exclusion that influence risk for schizophrenia and other psychoses (Castle et al., 1993). However, the present findings in a rural setting indicate that such conditions are less influential in relation to risk for psychosis, while a gradient of socioeconomic position may be more influential on delay in presentation for treatment.

Conflict of interest

All authors declare they have no conflict of interest.

Role of funding source

The Cavan-Monaghan First Episode Psychosis Study (CAMFEPS) was supported by the Stanley Medical Research Institute and Cavan-Monaghan Mental Health Service.

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All作者 declares they have no conflict of interest.

Contributions

Sami Omer contributed to the conception and design of the study, collection, analysis and interpretation of the data, drafted the manuscript and ensured final approval of the version to be published. Martha Finnegan contributed to the collection, analysis and interpretation of the data, revising the manuscript and final approval of the version to be published. Anthony Kinsella contributed to the analysis and interpretation of the data, revising the manuscript and final approval of the version to be published. Paul Fearon contributed to the analysis and interpretation of the data, revising the manuscript and final approval of the version to be published. Vincent Russell contributed to the conception and design of the study, revising the manuscript and final approval of the version to be published. Edadbaid O’Callaghan contributed to the conception and design of the study: his tragic death precluded giving final approval of the version to be published. John Waddington contributed to the conception and design of the study, collection, analysis and interpretation of the data, revising the manuscript and final approval of the version to be published.


