Very late-onset schizophrenia-like psychosis: incidence, risk factors and subsequent dementia

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I, Jean Stafford, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature …….. Date ……..

Summary

Introduction

People aged 65 years and above are frequently excluded from research on the epidemiology of non-affective psychotic disorders; consequently, little is known about the incidence of psychotic disorders in older people. In this thesis, I characterised the incidence of very late-onset schizophrenia-like psychosis (VLOSLP) in relation to socio-demographic factors, and I investigated the association between VLOSLP and subsequent dementia.

Methods

In Chapter 2, I conducted a systematic review and meta-analysis to synthesise published data on VLOSLP incidence. In Chapter 4, I investigated the incidence of VLOSLP in a Swedish population-based cohort. I conducted a matched cohort study to examine the rate of subsequent dementia in VLOSLP in Chapter 5. In Chapter 6, I assessed the feasibility of a case-control study examining social isolation, loneliness and social cognition in VLOSLP.

Results

In Chapters 2 and 4, I demonstrated a substantial burden of VLOSLP incidence, with a higher rate in women and migrants. Additionally, in Chapter 4, I found a higher rate of VLOSLP in those with a lower disposable income and those with no partner or children. The rate of subsequent dementia was higher in those with VLOSLP relative to age and calendar-period matched comparisons in Chapter 5. In Chapter 6, I found that the feasibility of the case-control study was limited due to challenges in recruiting patients with VLOSLP.

Discussion

In this thesis, I characterised the incidence of VLOSLP and identified several potential socio-demographic risk factors and outcomes associated with VLOSLP. My findings indicate that VLOSLP may be more common than was previously realised and suggest that the association between the environment and psychosis may persist into late life, opening up new areas for future investigation. Findings of a higher rate of dementia following VLOSLP may be relevant to clinicians in considering monitoring and treatment options.

Impact statement

It has long been recognised that a subset of individuals present with a non-affective psychotic disorder for the first time later in life, known as very late-onset schizophrenia-like psychosis (VLOSLP) in those with first onset at age 60 years old or above. However, older people are frequently excluded from research on the epidemiology of psychotic disorders, hence little is known about the incidence of VLOSLP, or associated risk and protective factors. Additionally, while there is ongoing debate about the relationship between VLOSLP and neurodegeneration, few longitudinal studies have investigated this association.

Findings from this thesis addressed these knowledge gaps, contributing to the academic literature in several ways. First, Chapters 2 and 4 helped to complete the life-course picture of the incidence of psychotic disorders, suggesting that VLOSLP may be more common than was previously thought. I found that the rate of VLOSLP increased with age, with a sharper increase for women, which may have implications for policy and service planning. In Chapter 4, I demonstrated associations between VLOSLP incidence and several environmental factors, including migration, low income, and having no partner or children, with some weaker evidence of a higher rate in those who had experienced the death of a child in infancy. Findings emphasised the role of the environment in understanding psychosis risk, suggesting that social adversity may contribute to risk for psychotic disorders into late life. This opens up new avenues for investigation within VLOSLP research, particularly the need to identify possible mechanisms underlying these associations.

In Chapter 5, I found a substantially higher rate of subsequent dementia among those with VLOSLP, which was robust to adjustment for confounders and remained after considering potential sources of bias. However, findings did not support the idea that VLOSLP can be entirely explained by neurodegeneration. These results are likely to be relevant to old age psychiatrists in considering treatment and monitoring of patients with VLOSLP. In Chapter 6, I described key challenges in recruiting patients with VLOSLP in primary data collection studies, and I highlighted potential directions for future research, including the need for qualitative research to identify barriers and facilitators of recruitment in those with VLOSLP, the potential for pooling smaller datasets focussed on VLOSLP, and the possibility of

including measures of VLOSLP symptoms or diagnoses in ongoing cohort studies, where possible.

Adapted versions of two Chapters from this thesis (Chapters 2 and 4) have been published and an additional paper is in preparation for publication. I have presented findings from this thesis at national and international conferences including: Schizophrenia International Research Society, International Federation of Psychiatric Epidemiology, MQ Mental Health Science Meeting, Perspectives on Migration: Mental Health and Wellbeing Conference, and the UCL Population Health Symposium. This thesis has led to my involvement in several relevant research networks, including the Social Connections, Cohesion and Health Group, through which I led a successful small grant application to the Grand Challenges. I have also become an Early Career Researcher Representative for the UKRI Loneliness and Social Isolation in Mental Health Network.

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Contents

List of figures

List of tables

Acronyms

ACC: Anterior cingulate cortex
AD: Alzheimer's Disease
AIC: Akaike Information Criterion
AIHQ: Ambiguous Intentions Hostility Questionnaire
APA: American Psychiatric Association
CI: Confidence interval
CMHT: Community Mental Health Team
CRP: C-Reactive Protein
DSM: Diagnostic and Statistical Manual of Mental Disorders
EIP: Early Intervention in Psychosis
FEP: First episode psychosis
fMRI: Functional magnetic resonance imaging
GALES: Geriatric Adverse Life Events Scale
GP: General practitioner
GWAS: Genome-wide association study
HADS: Hospital Anxiety and Depression Scale
HR: Hazard ratio
IR: Incidence rate
IRR: Incidence rate ratio
ICD: International Statistical Classification of Diseases and Related Health Problems
IPR: National Inpatient Register
IQR: Interquartile range
KI: Karolinska Institutet
LISA: Longitudinal Integration Database for Statistics
LSNS-R: Lubben Social Network Scale – Revised
LOS: Late-onset schizophrenia
LRT: Likelihood ratio test
MRC: Medical Research Council
NAPD: Non-affective psychotic disorder
NART: National Adult Reading Test
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
NPR: National Patient Register
OPCRIT: Operational Criteria Checklist
OR: Odds ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PYAR: Person-years at risk
RTB: Total Population Register
SCAN: Schedules for Clinical Assessment in Neuropsychiatry
SCID: Structured Interview of DSM-IV
SES: Socio-economic status
SMI: Severe mental illness
STATIV: Integration register
UCL: University College London
UCLA: University of California Los Angeles
VLOSLP: Very late-onset schizophrenia-like psychosis
WAIS: Wechsler Adult Intelligence Scale
WHO: World Health Organisation

Chapter 1 Introduction

1.1 Overall introduction and thesis remit

Although non-affective psychotic disorders typically emerge during adolescence or early adulthood (Kessler et al., 2007), it has long been recognised that a subset of individuals present with schizophrenia-like symptoms for the first time later in life. This is referred to as very late-onset schizophrenia-like psychosis (VLOSLP) in those with first onset at age 60 years old or above (Howard, Rabins, Seeman, & Jeste, 2000). However, older people have been consistently excluded from research on the epidemiology of psychotic disorders, hence little is known about the incidence of non-affective psychotic disorders later in life. Additionally, while epidemiological research has played a key role in elucidating potential risk factors for younger, more typical age-at-onset psychotic disorders, few epidemiological studies have investigated potential risk and protective factors for VLOSLP. Further, although there is ongoing debate about the aetiology of VLOSLP and its potential association with cognitive decline, longitudinal research focussed on this topic is sparse.

To address these gaps in the literature, in this thesis I aim to characterise the overall incidence of very late-onset schizophrenia-like psychosis (VLOSLP) using Swedish population register data, to investigate potential socio-demographic risk factors for VLOSLP, and to examine the relationship between VLOSLP and subsequent dementia. In **Chapter 1**, I broadly overview the literature on the biopsychosocial underpinnings of non-affective psychotic disorders and VLOSLP, and their association with dementia. In **Chapter 2**, I synthesise previously published data on the incidence of VLOSLP via systematic review and meta-analysis. In **Chapter 3**, I set out the methods for two Swedish population-based cohort studies (Chapters 4 and 5), which aim to address the gaps in the literature identified in Chapters 1 and 2. **Chapter 4** examines the incidence of VLOSLP in relation to socio-demographic factors, while **Chapter 5** investigates the relationship between VLOSLP and subsequent dementia. In addition, **Chapter 6** describes a feasibility case-control study to investigate levels of social isolation, loneliness and social cognitive impairments in individuals with VLOSLP. In the final Chapter (**Chapter 7)**, I summarise and contextualise findings, and discuss possible clinical, research and policy-level implications.

In order to set this thesis in context, first, this chapter provides a broad introduction to the literature on non-affective psychotic disorders and very late-onset psychotic disorders from a biopsychosocial perspective. Second, I discuss the epidemiology of psychotic disorders, and potential risk factors for psychotic disorders across the life course, with a particular focus on social isolation and loneliness. Third, I provide a broad overview of the literature on the epidemiology of dementia and its association with psychotic disorders.

1.2 Introduction to non-affective psychotic disorders

To contextualise my findings regarding risk factors and outcomes associated with VLOSLP, which are presented in Chapters 2, 4, 5 and 6, this section begins with a broad introduction to non-affective psychotic disorders and VLOSLP, and the ways in which they have been conceptualised in this thesis.

Non-affective psychotic disorders are serious, debilitating mental health conditions and are among the main contributors to the global burden of disease (Whiteford et al., 2013). Psychosis as a clinical entity dates back to Kraepelin's dementia praecox (1899), later adapted by Eugen Bleuler (1911), among others, who coined the term ‘schizophrenia’. As currently conceptualised, symptoms of non-affective psychotic disorders include positive symptoms, such as delusions, which refer to strongly held false inferences about an external reality that persist despite strong evidence to refute these inferences, and hallucinations, which describe sensory perceptions in the absence of corresponding external stimuli (American Psychiatric Association (APA), 2013). Other symptoms of non-affective psychotic disorders include disorganised thinking and speech, and negative symptoms such as lack of motivation and emotional expression. Cognitive impairment is also considered to be a core component of non-affective psychotic disorders (Bora, 2015). Non-affective psychotic disorders are often preceded by a prodromal phase where changes in thinking and social and cognitive functioning emerge at subclinical levels. The course of psychotic disorders can be continuous or episodic, with the possibility of full or partial remission (APA, 2013).

Non-affective psychotic disorders encompass various diagnoses, including schizophrenia, schizophreniform disorder, and brief and transient psychoses, with different diagnoses given depending on the combination, severity and persistence of symptoms (Table 1.1). The

two main classification systems used to diagnose mental health conditions are the International Statistical Classification of Disease and Health Related Problems, 10th revision (ICD-10) (World Health Organisation, 1992), and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (APA, 2013). Although ICD and DSM classifications of mental health conditions overlap considerably, there are notable differences between them. The ICD is intended to be used worldwide, includes physical and mental health diagnoses, focusses on clinical utility, and provides diagnostic descriptions rather than operational criteria, whereas the DSM was developed in the US, although it is also used in many other regions, focusses specifically on mental health conditions, and uses operational criteria for diagnoses (Tyrer, 2014). Throughout the studies included in this thesis, I have defined non-affective psychotic disorders using ICD diagnoses, as set out in Table 1.1.

A dimensional approach can be applied to the conceptualisation of non-affective psychotic disorders, with schizophrenia representing the severe end of the spectrum, linked with the poorest outcomes (Van Os, 2016), while diagnoses at the milder end of the spectrum may reflect transient or quasi-psychotic symptoms, eccentric behaviour and milder anomalies of thinking (Table 1.1). More broadly, there is debate as to whether mild psychotic-like symptoms which are relatively common in the general population (Freeman et al., 2005; Johns & Van Os, 2001) are on a continuum with more severe, diagnosable psychotic disorders or whether these should be considered as distinct entities (David, 2010; Jablensky, 2010).

Psychotic disorders are associated with a range of adverse outcomes across domains, which impact not only the individual experiencing psychosis, but also carers (Kuipers, 1993) and society (Guest & Cookson, 1999). Individuals with psychotic disorders are less likely to be in full time employment (Rinaldi et al., 2010) and are more likely to be homeless (Odell & Commander, 2000), to have poor physical health (Osborn, 2001), and to report smaller social networks compared to the general population (Gayer-Anderson & Morgan, 2013). Strikingly, mortality rates are substantially higher among those with serious mental illness compared to the general population (Saha, Chant, & McGrath, 2007). A recent study reported a mortality hazard ratio of 2.08 (95% confidence interval (CI): 1.98–2.19) among those with schizophrenia relative to the general population in the UK, with evidence that the mortality gap is increasing over time (Hayes, Marston, Walters, King, & Osborn, 2017).

Table 1.1 ICD-10 diagnostic codes for non-affective psychotic disorders

ICD code	Diagnosis	Description[a]
F20	Schizophrenia	• Distortions in thinking and perception. • Inappropriate or blunted affect. • Symptoms include thought insertion or withdrawal, thought broadcasting, delusional perception, delusions of control, influence or passivity, and negative symptoms. • Intellectual capacity and clear consciousness maintained, but cognitive deficits may emerge over time. • Not diagnosed in the presence of extensive depressive or manic symptoms, with overt brain disease, or during states of drug intoxication or withdrawal.
F21	Schizotypal disorder	• Eccentric behaviour and anomalies of thinking and affect, without definite characteristics of schizophrenia. • Symptoms include eccentric behaviour, social withdrawal, paranoid ideas, thought disorder, perceptual disturbance and quasi-psychotic symptoms.
F22	Persistent delusional disorder	• Long-standing, clear and persistent delusion(s). • May co-occur with occasional or transitory auditory hallucinations.
F23	Acute and transient psychotic disorder	• Heterogeneous group of psychotic symptoms with acute onset, without evidence of organic causation. • Recovery usually occurs within a few weeks or months.
F24	Induced delusional disorder	• Delusional disorder shared by two or more people with close emotional links.
F25	Schizoaffective disorders	• Combines affective and schizophrenic symptoms not justifying diagnosis of schizophrenia, or manic or depressive psychosis.
F28	Other nonorganic psychotic disorder	• Delusional or hallucinatory disorders not justifying a diagnosis of other conditions listed in this table.
F29	Unspecified nonorganic psychosis	• Psychosis not otherwise specified with no evidence of organic causation.

[a]Adapted from ICD-10 (WHO, 1992)

1.3 Introduction to very late-onset psychotic disorders

Although non-affective psychotic disorders typically have onset during adolescence or early adulthood (Kessler et al., 2007), research suggests that a substantial minority of individuals have a first episode of psychosis in old age (Howard et al., 2000). Psychotic symptoms in late-life do not necessarily reflect a psychiatric condition and can co-occur with various medical conditions including delirium (Webster & Holroyd, 2000), dementia (Rubin, Drevets, & Burke, 1988), Parkinson's Disease (Aarsland, Larsen, Cummings, & Laake, 1999) and with

visual impairment in Charles Bonnet Syndrome (Menon, Rahman, Menon, & Dutton, 2003), among other conditions. As in younger adults, older people may also present with subthreshold psychotic symptoms which do not necessarily reflect psychopathology (Badcock, Dehon, & Larøi, 2017). However, in this thesis I have focussed specifically on the emergence of functional non-affective psychotic disorders in old age without a clear organic basis. Further, I focussed on those diagnosed with a first episode of non-affective psychotic disorder after age 60, rather than those with a chronic psychotic disorder persisting into old age. In Section 1.5.2, I have discussed the epidemiology of VLOSLP as distinct from non-affective psychotic disorders with a younger, more typical age-at-onset.

Non-affective psychotic disorders with a late age-at-onset have been recognised in research and clinical practice for decades, although the corresponding terminology and age limits have changed over time. Bleuler was among the first to describe psychotic disorders in those aged 40 years old and above (1943), and the term 'late paraphrenia' was subsequently used to define the condition in those aged 55-60 years old and above (Roth & Morrissey, 1951). The DSM-III-R distinguished late-onset psychotic disorders in those aged 45 years old and above from schizophrenia in those below age 45 years old, although this was excluded from future versions of the DSM. Following an International Consensus, the terms 'late-onset schizophrenia' (LOS) and 'very late-onset schizophrenia-like psychosis' (VLOSLP) were adopted in reference to those who first present with non-affective psychosis after age 40 and age 60, respectively (Howard et al., 2000). It should be noted that LOS and VLOSLP refer to non-affective psychotic disorders, rather than affective psychotic disorders, such as bipolar disorder or psychotic depression.

There is ongoing debate in the literature as to whether VLOSLP represents the same condition as schizophrenia with a more typical age-at-onset, or whether it should be regarded as a distinct subtype with a different presentation, aetiology and outcomes (Vahia et al., 2010). Differences in symptoms have been observed between age-at-onset groups, with individuals with VLOSLP presenting with more delusional symptoms and fewer negative symptoms compared to those with a more typical age-at-onset (Howard, Castle, Wessely, & Murray, 1993), although this has not been found consistently (Hanssen et al., 2015). Additionally, research suggests that those with VLOSLP may have a higher level of functioning in educational, occupational and social domains than patients with a more

typical age-at-onset (Castle, Wessely, Howard, & Murray, 1997), although research in this area is sparse.

1.4 Biological underpinnings of psychotic disorders

Recent conceptual models suggest that the aetiology of psychotic disorders is heterogeneous, multi-factorial and complex, acknowledging the contributions of genetics, brain abnormalities, psychological mechanisms, and environmental factors (Howes & Murray, 2014). Although this thesis focusses primarily on socio-demographic risk factors for psychotic disorders, in the following sections, I briefly introduce the biopsychosocial underpinnings of psychotic disorders and how these may be integrated at different levels, with the aim of contextualising findings within the broader literature. It is also important to consider the underlying biology of non-affective psychotic disorders in relation to their potential association with subsequent dementia, as introduced in Section 1.9.

1.4.1 Genetics

Schizophrenia is highly heritable, with a pooled heritability estimate of 81% (95%CI: 73%-90%) in a meta-analysis (Sullivan, Kendler, & Neale, 2003), although this estimate may also reflect underlying gene-environment interaction (Van Os, Kenis, & Rutten, 2010). A recent genome-wide association study (GWAS) identified 108 loci conferring a small amount of risk for schizophrenia, highlighting its polygenic nature (Ripke et al., 2014). In addition, a higher burden of large, rare and *de novo* copy number variants (CNV) has been identified in those with schizophrenia (Kavanagh, Tansey, Donovan, & Owen, 2015). Rare CNVs have also been implicated in neurodevelopmental disorders such as autism (Sanders et al., 2011), and are associated with advanced paternal age (Hehir-Kwa et al., 2011). The CNV most consistently associated with schizophrenia is the 22q11.2 deletion (Bassett & Chow, 2008). 20-30% of carriers of this CNV have schizophrenia, although only 0.2-0.6% of individuals with schizophrenia carry the 22q11.2 deletion (Murphy, Jones, & Owen, 1999). While little research has examined the genetic underpinnings of VLOSLP, there is evidence of a lower morbid risk of schizophrenia among relatives in those with VLOSLP compared to those with more typical age-at-onset psychotic disorders (Howard et al., 1997; Pearlson et al., 1989). This suggests that VLOSLP may differ in aetiology from psychotic disorders with a younger,

more typical age-at-onset. However, further research is needed to investigate the genetic underpinnings of VLOSLP in larger samples.

1.4.2 Pathophysiology

A core mechanism proposed to underpin psychotic symptoms is dopamine dysregulation, a hypothesis which emerged in the 1950s on the discovery of antipsychotic drugs which block dopamine D2/3 receptors, and which remains central to recent models of psychosis (Howes et al., 2012). Broadly, research suggests that dopamine may signal 'salience', indicating that a given stimulus is important or personally relevant (Kapur, Mizrahi, & Li, 2005). Kapur (2003) proposed that excess dopamine release could lead to psychotic symptoms via 'aberrant salience', or a heightened feeling of personal significance in response to commonplace internal and external events. Further, applying a Bayesian understanding of the brain to psychotic symptoms, it has been posited that dopamine dysfunction may lead to abnormalities in prediction error: the mismatch between expected and actual inputs which we use to make sense of the world (Frith & Friston, 2013). This could lead to difficulties in learning, problem solving and prioritisation of stimuli, potentially contributing to hallucinations and delusions (Corlett, Frith, & Fletcher, 2009).

Building on the dopamine hypothesis, abnormalities in other neurotransmitter systems have also been implicated in the aetiology of psychotic disorders, including glutamate and gamma-Aminobutyric acid (GABA) (Lisman et al., 2008), the main excitatory and inhibitory neurotransmitters in the brain, respectively. In line with this, a recent meta-analysis of proton magnetic resonance spectroscopy studies found evidence of excess glutamate in the basal ganglia, and glutamine, a glutamate metabolite, in the thalamus in those with schizophrenia (Merritt, Egerton, Kempton, Taylor, & Mcguire, 2016). The leading explanation for this is that N-methyl-D-aspartic acid (NMDA) receptor hypofunction leads to excess glutamate, contributing to psychotic symptoms (Olney, Newcomer, & Farber, 1999). This is supported by the observation that NMDA receptor antagonists, such as phencyclidine, can cause psychotic symptoms, including hallucinations, delusions and, most notably, negative symptoms (Stone, Morrison, & Pilowsky, 2007). Arguably, models of schizophrenia which include both dopaminergic and glutamatergic dysfunction best explain the full spectrum of psychotic symptoms (Howes, Mccutcheon, & Stone, 2015).

1.4.3 Structural and functional neuropathology

Additionally, varied structural and functional brain abnormalities have been identified in those with psychotic disorders. The most consistent structural finding to date is of reduced grey matter volume in those with schizophrenia (Glahn et al., 2008; Wright et al., 2000). Further, in functional neuroimaging studies, those with psychotic disorders have shown different patterns of activation in regions associated with executive functioning and working memory relative to those without psychotic disorders (Glahn et al., 2005; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). In addition, a meta-analysis found evidence of pathology in white matter tracts, which connect brain regions into functional networks, in those with schizophrenia suggesting potential disconnect between grey matter regions, including between the frontal lobe, thalamus and cingulate gyrus, and between the frontal lobe, insula, hippocampus-amygdala, temporal and occipital lobes (Ellison-wright & Bullmore, 2009). Neuroimaging studies in LOS and VLOSLP have identified subtle brain abnormalities similar to those found in younger patients, including enlarged ventricle volume (Krull, Press, Dupont, Harris, & Jeste, 1991; Van Assche, Morrens, Luyten, Van de Ven, & Vandenbulcke, 2017), volume reductions in the left temporal lobe and superior temporal gyrus (Howard et al., 1995; Pearlson et al., 1993), and white matter pathology (Van Assche et al., 2017).

1.4.4 Inflammation and immune functioning

Immune system dysfunction and chronic neuroinflammation have been suggested as potential mechanisms which may underlie psychotic disorders (Khandaker et al., 2015). In particular, it has been posited that microglial hyperactivation may contribute to schizophrenia risk via an increase in inflammatory cytokines and potential disruption to the blood-brain barrier, which may lead to cognitive dysfunction (Kirkpatrick & Miller, 2013). In support of this, the rate of psychotic disorders is higher among offspring of mothers who experienced prenatal infection, and in individuals exposed to early childhood infection or autoimmune conditions (Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011). Additionally, a recent schizophrenia GWAS identified several genes implicated in the immune system (Miller et al., 2011; Ripke et al., 2014).

Further, differences in blood concentrations of acute phase proteins such as C-Reactive Protein (CRP) and inflammatory cytokines including interleukin-6 have been found in those

with psychotic disorders, including drug-naïve first-episode patients (Miller et al., 2011; Miller, Culpepper, & Rapaport, 2014; Potvin et al., 2008; Suvisaari et al., 2011). These findings extend to LOS and VLOSLP, with higher levels of CRP found in these groups in a Danish register-based study (Wium-Andersen, Ørsted, & Nordestgaard, 2014). However, chronic inflammation is a non-specific marker of a range of illnesses including cardio-vascular disease, Alzheimer's disease, and depression (Suvisaari & Mantere, 2013), and it is unclear whether inflammation and schizophrenia are causally associated. Additionally, potential confounders of this association include poor physical health, medication use, smoking, and drug use, which are not consistently accounted for in previous studies (Kirkpatrick & Miller, 2013).

1.4.5 Biological mechanisms underlying VLOSLP

As highlighted above, research on the underlying biology of VLOSLP is sparse. However, several additional explanatory theories have been put forward which may be pertinent to the VLOSLP group. Interestingly, it has been posited that schizophrenia may be a syndrome of accelerated biological ageing, which could explain the higher rate of physical health problems, dementia and mortality in this group (Kirkpatrick, Messias, Harvey, Fernandez-Egea, & Bowie, 2008). Additionally, there has been interest in the decline in oestrogen in mid-life as a potential mechanism underlying the higher preponderance of women with LOS and VLOSLP. Oestrogen is considered to have anti-dopaminergic properties, which may protect against psychotic disorders in younger women, with an increase in risk following the menopause (Riecher-Rössler & Hafner, 1993). Interestingly, an animal study found that in vivo oestrogen treatment led to reduced striatal dopamine response in female, but not male rats (Disshon & Dluzen, 2000). However, there is little evidence to date to support this mechanism in humans. It is also possible that psychosocial stressors increase risk for late-life psychotic disorders in women, although this has received less attention as a potential explanation in the literature.

1.4.6 Summary of biological underpinnings of psychotic disorders

This section broadly overviewed the literature on several key biological processes posited to underlie psychotic disorders, with the aim of setting this thesis in context. Importantly, the biological pathways described in this section may be driven by psychological and

environmental factors, such as exposure to viruses and infections, the urban environment, migration, traumatic life events, and social stress (Howes & Murray, 2014). In turn, the environmental factors described in the following sections are inseparable from the psychological and biological pathways through which they are likely to operate.

1.5 Introduction to the epidemiology of psychotic disorders

1.5.1 Epidemiology and environmental risk factors for psychotic disorders

In recent decades, epidemiological research has played a key role in quantifying the burden of psychotic disorders across different regions and in elucidating potential environmental risk factors for psychotic disorders. A systematic review which pooled estimates across 46 countries estimated the point prevalence of schizophrenia to be 4.6 per 1000, and lifetime prevalence was estimated to be 4.0 per 1000 (Saha, Chant, Welham, & Mcgrath, 2005). In England, a systematic review estimated the pooled incidence of non-affective psychotic disorders to be 23.2 (95%CI: 18.3–25.9) and schizophrenia to be 15.2 (95%CI: 11.9–19.5) per 100,000 person-years at-risk (Kirkbride et al., 2012). Additionally, a recent international meta-analysis reported the pooled incidence of all psychotic disorders to be 26.6 per 100,000 person-years at-risk (95%CI: 22.0-31.7), with high heterogeneity in estimates between studies (Jongsma, Turner, Kirkbride, & Jones, 2019). In those aged under 65, incidence rates of non-affective psychotic disorders have been found to peak in late adolescence or early adulthood, with higher rates among men than women (Aleman, Kahn, & Selten, 2003; Jongsma et al., 2019; Kirkbride et al., 2012). However, there is fairly consistent evidence of a second peak in the incidence of psychotic disorders among women during middle age (Hafner, Heiden, Maurer, Fatkenheuer, & Loffler, 1993; Hambrecht, Maurer, Häfner, & Sartorius, 1992; Jongsma et al., 2018; Kirkbride et al., 2006; Pedersen et al., 2014), with some exceptions (Van der Werf et al., 2014).

Importantly, reporting an overall prevalence or incidence rate may mask heterogeneity in rates which, in the case of psychotic disorders, has been observed in relation to factors such as age, sex, region, calendar period, and a range of socio-demographic variables (Jongsma et al., 2018; Jongsma et al., 2019; March et al., 2008; McGrath et al., 2004). Unravelling patterns of heterogeneity in psychotic disorder incidence may yield valuable insight into potential risk factors.

Correspondingly, there is now a considerable body of epidemiological research implicating the role of the environment in the development of psychotic disorders. Identified potential environmental risk factors for psychotic disorders include cannabis use (Arseneault, Cannon, Witton, & Murray, 2004), bullying, and early adversity (Varese et al., 2012). Additionally, urbanicity, particularly being born in an urban environment, has been associated with an increased risk of psychotic disorders (Fett, Lemmers-jansen, & Krabbendam, 2019; Marcelis, Takei, & Os, 1999; Mortensen et al., 1999). Recent data from the World Health Survey suggested that the association between urbanicity and psychotic disorders may not extend to lower and middle-income countries (DeVylder et al., 2018). However, as highlighted by Kirkbride, Keyes, and Susser (2018), this study focussed on psychotic experiences, or psychotic disorders assessed via a single self-report item, which is problematic given the potential for reporting bias, and given that psychotic experiences have relatively low positive predictive value for future psychotic disorders. In light of these limitations, there is a need for further investigation of variation in the association between urbanicity and psychotic disorders by region, which may help to elucidate proxy variables underlying this association and, in turn, potentially modifiable risk factors for psychotic disorders.

One of the most robustly replicated environmental risk factors for psychotic disorders to date is migration, with higher rates of psychotic disorders consistently observed among migrants compared to baseline populations across a range of regions and migrant groups (Dykxhoorn, Hollander, Lewis, Magnusson, et al., 2019; Jongsma et al., 2019; Kirkbride et al., 2012; McGrath et al., 2004). These findings do not appear to be due to higher rates of psychotic disorders in migrants' countries of origin (Cantor-Graae & Selten, 2005). Several lines of evidence suggest that ethnic minority status may be of particular importance, with consistently higher rates of psychotic disorders observed among black and minority ethnic (BME) groups (Fearon et al., 2006; Kirkbride et al., 2008). Interestingly, this finding has been observed among both first and second-generation migrants (Bourque, Ven, & Malla, 2011). Additionally, ethnic density may play a role, in that the incidence of psychotic disorders in non-white ethnic minorities is higher in regions where fewer such minorities live (Boydell et al., 2001). This could be explained by shared adverse environmental exposures, including increased exposure to interpersonal threat, hostility, discrimination and social exclusion related to visible minority status (Akdeniz et al., 2014; Bourque et al., 2011; Morgan,

Knowles, & Hutchinson, 2019; Veling et al., 2007). It is also possible that the association between migration and psychotic disorder reflects diagnostic bias related to cultural misunderstandings, in that clinicians may diagnose psychotic disorders inappropriately where someone is experiencing a brief reactive or mood disorder, or a culturally appropriate response to a distressing experience. However, several follow-up studies have examined this possibility, mainly in a UK context, with little evidence of diagnostic bias in relation to black Caribbean migrants to the UK (Morgan et al., 2017; Selten, van der Ven, & Termorshuizen, 2018). Nonetheless, this is an important possibility to consider and requires further investigation in migrants from different regions relative to different reference groups.

Several exposures related to neurodevelopment have also been associated with psychotic disorders in epidemiological studies, including obstetric complications (Cannon, Jones, & Murray, 2002), infections in early childhood or in utero (Miller et al., 2011) as described above, and exposure to famine in utero (Susser, Hoek, & Brown, 1998). Further, the risk of psychotic disorders is higher among those with poorer social, cognitive and motor skills in childhood (Dickson, Laurens, Cullen, & Hodgins, 2012; Jones, Rodgers, Murray, & Marmot, 1994; Rapoport, Giedd, & Gogtay, 2012). These findings contributed to the neurodevelopmental hypothesis of psychotic disorders (Murray & Lewis, 1987), which has been updated over several decades to incorporate evidence around the role of aberrant brain development in adolescence and social adversity in psychosis risk (Murray, Bhavsar, Tripoli, & Howes, 2017). Castle and Murray (1991) posited that the neurodevelopmental psychosis phenotype was more common among men, given that they tend to have an earlier age-at-onset of psychotic disorder than women, a more severe presentation and poorer functional outcomes. By contrast, Castle and Murray (1991) argued that late-onset schizophrenia and VLOSLP were less likely to have neurodevelopmental origins, given the female predominance and relatively preserved functioning found in these groups. However, there is little empirical evidence regarding the association between VLOSLP and neurodevelopment.

1.5.2 Epidemiology and environmental risk factors for VLOSLP

Most epidemiological research to date has focussed on psychotic disorders emerging before age 65 years old, whereas the epidemiology of psychotic disorders in older people has remained relatively neglected. Epidemiological studies of VLOSLP have mainly focussed on prevalence, with 1-year estimates ranging from 0.1%-0.5% (Howard et al., 2000). Less research has focussed on incidence and how this varies in relation to putative risk factors for VLOSLP. Most studies examining risk factors for VLOSLP have been cross-sectional, with small, unrepresentative samples, making it difficult to draw valid conclusions. Such studies have implicated several putative risk factors for VLOSLP, the most robust of which is of a higher preponderance of VLOSLP in women relative to men (Almeida, Howard, Levy, & David, 1995; Castle & Murray, 1991; Howard, Almeida, & Levy, 1994). However, given that most previous studies in this area have been cross-sectional, it is possible that this finding partly reflects differential mortality rates by sex (i.e. competing risks), as men are more likely to experience early mortality. In Chapters 5 and 7, I discuss the potential role of mortality as a competing risk in relation to VLOSLP.

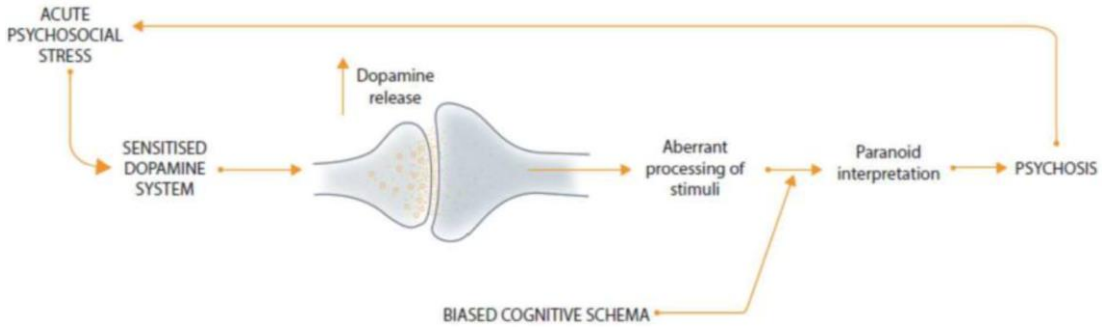
Other potential risk factors for VLOSLP include sensory impairment (Prager & Jeste, 1993), early adversity (Fuchs, 1994), social isolation (Pearlson et al., 1989), and premorbid subthreshold schizotypal traits (Kay & Roth, 1961). However, research investigating these risk factors is sparse; in particular, epidemiological evidence focussed on VLOSLP incidence is lacking. Consequently, little is known about how many people are first diagnosed with psychotic disorders later in life, whether incidence rates increase with age and how this varies by sex. Additionally, little is known about whether risk factors for developing psychotic disorders in old age differ from those implicated in psychotic disorders with a more typical age-at-onset. To address this gap in knowledge, I have conducted a systematic review to synthesise published data on the incidence of VLOSLP (Chapter 2). This may provide insight into the aetiology of late-life psychotic disorders, or gaps in the literature requiring examination.

1.6 Integrating biopsychosocial risk factors for psychotic disorders

The aetiology of psychotic disorders is considered to be complex, heterogeneous and multifactorial. Although I have largely focussed on social and environmental risk factors for

VLOSLP in this thesis, it is important to note that environmental factors operate in the context of genetic and psychological processes. The integrated sociodevelopmental-cognitive model of psychosis posits that environmental risk factors and psychosocial stress contribute to the development of psychotic symptoms via dopamine dysfunction as the 'final common pathway' (Figure 1.1) (Howes & Murray, 2014). It should be noted that this model focusses on psychotic disorders with a younger, more typical age-at-onset and therefore may not be applicable or valid in relation to VLOSLP. Nonetheless, this model serves as a useful starting point in conceptualising the biological and psychological mechanisms through which social and environmental factors may impart risk for psychotic disorders. Application of this model to VLOSLP would also require consideration of factors such as neurodegeneration and cognitive decline.

Figure 1.1 Integrated sociodevelopmental-cognitive model (from Howes & Murray, 2014)



The integrated sociodevelopmental-cognitive model posits that hyper-sensitisation of the dopamine system may lead to aberrant salience and a paranoid interpretation of events. Further, at the cognitive level, exposure to adverse events may alter the way in which we perceive and relate to our environment, for example, leading to cognitive biases such as hyper-vigilance to potential threat (Reininghaus et al., 2016), heightened stress sensitivity (Myin-Germeys & Van Os, 2007), and paranoia (Freeman & Garety, 2014).

In support of this, various cognitive and neural mechanisms have been proposed to underlie the association between psychotic disorders and environmental risk factors such as urbanicity, migration and trauma. For instance, in an fMRI study, urban living was found to be associated with increased amygdala activity, which has been linked with salience and threat response, while urban upbringing was associated with greater activation in the perigenual anterior cingulate cortex (ACC), a region associated with negative affect and

stress processing (Lederbogen et al., 2011). Further, another neuroimaging study found that those with ethnic minority status showed higher perceived chronic stress and increased activation in the perigenual ACC in response to social stress relative to the German baseline population (Akdeniz et al., 2014), and perceived group discrimination was correlated with perigenual ACC activation in those with ethnic minority status. However, both studies were conducted in healthy individuals and require further testing in clinical samples. In addition, two case-control studies conducted in Canada and the UK, respectively, found that striatal stress-induced dopamine release and dopamine synthesis capacity were higher in immigrants relative to non-immigrants in antipsychotic naïve patients with schizophrenia, those at clinical high risk, and healthy volunteers (Egerton et al., 2017). Further, in an fMRI study, individuals of black ethnicity showed greater amygdala activation to outgroup faces relative to those of white British ethnicity (McCutcheon et al., 2018). Taken together, these findings provide some tentative initial clues about potential mechanisms which may underlie associations between psychotic disorders and environmental risk factors including migration and urbanicity, particularly social stress and hyper-vigilance to social threat.

1.7 Introduction to social isolation, loneliness and psychotic disorders

The biopsychosocial model of psychotic disorders is also relevant to Chapter 6 of this thesis, in which I focussed on two neglected but potentially important risk factors for VLOSLP: loneliness and social isolation, which are increasingly recognised as important public health concerns (Gerst-Emerson & Jayawardhana, 2015). To address this gap in the literature, I aimed to conduct a feasibility study to examine levels of social isolation and loneliness in individuals with VLOSLP (Chapter 5). The following section provides a broad overview of the literature on social isolation and loneliness in relation to psychotic disorders and VLOSLP.

1.7.1 Social isolation and loneliness

Loneliness and social isolation are distinct, yet over-lapping constructs which are modestly correlated and often show independent associations with health (Cacioppo & Hawkley, 2009; Cornwell & Waite, 2009; Coyle & Dugan, 2012; Hawkley, Thisted, Masi, & Cacioppo, 2010). Social isolation implies being cut-off from other people, whereas loneliness refers to *perceived* social isolation, or a discrepancy between desired and achieved levels of social interaction (Badcock et al., 2015; Hawkley & Cacioppo, 2003). It is possible to experience

high levels of social isolation without feeling lonely, and conversely, to feel lonely while surrounded by other people (Coyle & Dugan, 2012).

Individuals can become socially isolated at any age, although older people are thought to be particularly at risk due to reductions in social network size following retirement, physical and cognitive decline, loss of family and friends and sensory impairment (Nicholson, 2012; Prager & Jeste, 1993). Social isolation may occur due to difficulties in forming meaningful social connections (Spitzberg & Hurt, 1987), and through loss of connections due to factors such as migration, separation, and disability and/or illness (Grenade & Boldy, 2008). Social isolation is associated with a range of negative health outcomes such as cardiovascular disease, stroke (Valtorta, Kanaan, Gilbody, Ronzi, & Hanratty, 2016), cognitive decline (Boss, Kang, & Branson, 2015; Cacioppo & Hawkley, 2009), and mortality (Eng, Rimm, Fitzmaurice, & Kawachi, 2002; Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015).

Loneliness can also affect people at any age (Qualter et al., 2015). In older people, risk factors associated with loneliness include disability, widowhood, limited contact with friends, emotional instability, introversion, poor physical and mental health (Victor, Scambler, Bowling, & Bond, 2005), and lower levels of social engagement earlier in life (Dahlberg, Andersson, & Lennartsson, 2018). To some extent, loneliness can be viewed as an intrinsic part of the human condition and is experienced transiently by most people (Masi, Chen, Hawkley, & Cacioppo, 2011). A degree of loneliness can even be viewed as adaptive. It motivates us to seek out social contact with others and to meet our need for social interaction (Cacioppo & Hawkley, 2009), which is regarded as central to human wellbeing (Steptoe, Shankar, Demakakos, & Wardle, 2013). However, while transient loneliness can be viewed as adaptive, chronic loneliness is a highly aversive experience associated with a range of negative health outcomes, many of which have been observed even after accounting for social isolation, including, cognitive decline (Holwerda et al., 2014), elevated blood pressure (Hawkley et al., 2010), coronary heart disease (Valtorta et al., 2016), and a higher mortality rate (Luo, Hawkley, Waite, & Cacioppo, 2012).

1.7.2 Social isolation, loneliness and psychotic disorders

Social isolation is consistently found to be common among those with psychotic disorders (Badcock et al., 2015; Gayer-Anderson & Morgan, 2013; Stain et al., 2012), who tend to

report smaller social networks and fewer confidants than healthy comparison groups (Harley & Boardman, 2012; Sündermann, Onwumere, Bebbington, & Kuipers, 2013). This may reflect withdrawal due to negative symptoms and amotivation, absorption in positive symptoms, including paranoia, difficulties in forming relationships (Lim, Gleeson, Alvarez, & Penn, 2018), stigma from others and/or self-stigma (Corrigan, Watson, & Barr, 2006).

On the other hand, social isolation could be a risk factor for psychotic disorders. The social defeat hypothesis posits that long-term exposure to social adversity, including social exclusion and rejection, could increase risk for schizophrenia via social stress and sensitization of the mesolimbic dopamine system, a mechanism discussed in the previous section (Selten & Cantor-graae, 2007; Selten & Cantor-Graae, 2005; Selten, van der Ven, Rutten, & Cantor-Graae, 2013). Alternatively, the social deafferentation theory posits that those who experience little social input may inadvertently compensate by generating complex social stimuli in the form of positive symptoms (Hoffman, 2007).

Less research has focussed on loneliness and psychotic disorders to date, and findings have been mixed, partly due to heterogeneity in conceptualisation, recruitment processes and design across studies (Lim et al., 2018). Several studies have reported high levels of loneliness and a desire for improved social relationships among people with psychotic disorders (Meltzer et al., 2013; Michalska Da Rocha, Rhodes, Vasilopoulou, & Hutton, 2018; Morgan et al., 2012; Stain et al., 2012; Sündermann, Onwumere, Kane, Morgan, & Kuipers, 2014), with some evidence that this association may be mediated by depression symptoms (Jaya et al., 2016). However, most previous studies in this area have been cross-sectional with relatively small samples (Lim et al., 2018). Reverse causation is a concern in previous studies in this area, particularly in cross-sectional studies where the temporal relationship between loneliness and psychotic disorders is unknown.

As part of a systematic review, Lim et al., (2018) proposed a five-factor conceptual model of the association between loneliness and psychotic disorders, whereby the association operates in both directions. The model emphasised the importance of the following factors: 1) mental health symptoms, such as depression, psychosis and anxiety, 2) social support, 3) well-being, including quality of life, 4) societal perceptions, including discrimination and internalised stigma, and 5) self-constructs, such as self-esteem and self-efficacy.

There is some evidence that the psychological processes underlying loneliness in psychotic disorders may differ from those found in the general population (Trémeau, Antonius, Malaspina, Goff, & Javitt, 2016), in that reported feelings of loneliness may be less strongly associated with social isolation in those with psychotic disorders, relative to in the general population. Correspondingly, not all previous studies have found a straightforward association between loneliness and psychotic disorders (Lim et al., 2018). For instance, a recent study reported significantly reduced levels of loneliness among participants with psychotic disorders compared to participants with depression, despite those with psychotic disorders reporting higher levels of social isolation (Giacco, Palumbo, Strappelli, Catapano, & Priebe, 2016). Another study found that those with psychotic disorders did not report significantly more dissatisfaction with their relationships relative to the comparison group, despite the group with psychotic disorders reporting significantly fewer and less helpful relationships in their social network (Lim, Gleeson, Jackson, & Fernandez, 2014). This lack of dissatisfaction may relate to reduced insight or social anhedonia (Lim et al., 2018).

1.7.3 Social isolation, loneliness and VLOSLP

In comparison, little is known about social isolation or loneliness in relation to VLOSLP. Broadly, the literature suggests that individuals with VLOSLP may experience high levels of social isolation throughout the life course, including before symptoms emerge (Fuchs, 1999; Kay & Roth, 1961; Pearlson et al., 1989; Rodriguez-Ferrera, Vassilas, & Haque, 2004). However, previous studies in this area are small-scale involving clinical samples, without validated measures of social isolation, and are cross-sectional, providing little insight into whether social isolation is a risk factor for or a consequence of VLOSLP.

Additionally, although the literature tentatively suggests that people with VLOSLP may experience high levels of social isolation, even less is known about how lonely those with VLOSLP actually feel. At face value, one might expect people with VLOSLP to feel lonely, assuming that they experience high levels of social isolation. However, it is also conceivable that hallucinations and delusions in VLOSLP serve as a form of social input that alleviates feelings of loneliness. In line with this, positive symptoms in schizophrenia are notably social in nature and generally represent interactive social agents (Bell, Mills, Modinos, & Wilkinson, 2017). By contrast, non-social hallucinations, such as geometric shapes and

meaningless sounds, are less frequent in schizophrenia, despite being relatively common in psychosis as part of other health conditions (Hoffman, 2007).

Further, research suggests that most voice hearers engage with their voices, often in interactive conversations (Bell et al., 2017), and that relationships with voices often feel intimate and highly personal despite the frequently unpleasant and intrusive content of positive symptoms (Nayani & David, 1996). This may be particularly applicable to those with VLOSLP, who tend to present with a highly delusional form of psychosis, largely presenting with positive rather than negative symptoms (Howard et al., 1993). Given the social nature of positive symptoms, in Chapter 6, I hypothesise that individuals with VLOSLP may feel less lonely than would be expected in light of the high levels of isolation that they experience. Additionally, given that those with VLOSLP are likely to have smaller social networks, they may also be more likely to engage with their auditory hallucinations, thereby potentially leading to lower levels of loneliness.

1.8 Introduction to social cognition and psychotic disorders

1.8.1 Social cognition and psychotic disorders

Impairments in social cognition have been observed in those with younger, more typical age-at-onset psychotic disorders (Bora, Yucel, & Pantelis, 2009), and have been found to be an important predictor of functional outcomes in the domains of vocation and interpersonal relationships (Fett et al., 2011). However, despite this, few studies have examined whether those with VLOSLP show the same impairments in social cognition as those with more typical age-at-onset psychotic disorders. Social cognition broadly refers to the mental processes underlying social interactions, including how we perceive, interpret and respond to the intentions, thoughts and behaviour of others (Green, Horan, & Lee, 2008), and is considered to be related to but separable from general cognitive functioning in those with psychotic disorders (Nuechterlein et al., 2004). Impaired social cognitive processes have consistently been found in those with psychotic disorders (Bora et al., 2009), including in 'theory of mind': the ability to make inferences about the beliefs, thoughts and intentions of others (Baron-Cohen, Leslie, & Frith, 1985; Frith & Frith, 2005). Additionally, compared to the general population, research suggests that those with psychotic disorders may show a bias towards interpreting ambiguous and neutral events as threatening and towards viewing

other people as hostile, in line with the integrated sociodevelopmental-cognitive model set out in Section 1.6 (An et al., 2010; Myin-Germeys & Van Os, 2007; Reininghaus et al., 2016; Startup et al., 2016).

1.8.2 Social cognition and VLOSLP

As highlighted above, few studies have examined social cognitive impairments in VLOSLP, and findings to date have been contradictory, perhaps due to small sample sizes and variation in cognitive tasks used across studies (Moore et al., 2006; Smeets-Janssen et al., 2013). Moore et al., (2006) found that patients with VLOSLP made significantly more errors on deception mentalizing tasks, but not false belief tasks relative to a healthy comparison group, and no significant differences in attributional style were observed between groups. Conversely, Smeets-Janssen et al., (2013) found no difference between patients with VLOSLP and healthy controls on the Hinting Task, which measures theory of mind, and found that patients with VLOSLP performed significantly better than patients with a more typical age-at-onset of psychosis.

Further research on social cognition in patients with VLOSLP could help to distinguish between VLOSLP and more typical age-at-onset psychotic disorders (Van Assche et al., 2017) and in identifying potential psychosocial intervention targets to benefit those with VLOSLP. Additionally, it is possible that understanding social cognition in more typical age-at-onset psychotic disorders and VLOSLP could provide insight into the experience of social isolation and loneliness in these groups (Lim et al., 2018). For instance, difficulties in understanding the intentions and behaviour of others could contribute to difficult social interactions and subsequent social withdrawal. Additionally, a tendency to view others as hostile is associated with suspiciousness, distrust of others, interpersonal problems and social disengagement (Combs et al., 2009; Kanie et al., 2014). In Chapter 6, I describe a feasibility case-control study designed to examine levels of loneliness, social isolation and social cognition in patients with VLOSLP.

1.9 The association between VLOSLP and dementia

1.9.1 Introduction to dementia

While much of this thesis focusses on risk factors for VLOSLP, an additional component examines outcomes associated with VLOSLP, specifically the potential association with dementia. This is important given ongoing debate about the aetiology of VLOSLP and whether psychosis first emerging later in life may reflect underlying cognitive decline. In this section, I broadly overview the literature on the phenomenology and epidemiology of dementia and its association with psychotic disorders, including VLOSLP.

Dementia encompasses a range of conditions characterised by brain pathology accompanied by progressive cognitive decline which interferes with daily function, with potential for cognitive disturbance at multiple levels, including: memory, thinking, orientation, comprehension and language (World Health Organisation, 1992). All-cause dementia affects around 47 million people worldwide as of 2015. Dementia is more common in women (Mazure & Swendsen, 2016) and is usually first diagnosed after age 65 years old, with an increasing incidence with age (Corrada, Brookmeyer, Paganini-hill, Berlau, & Kawas, 2010; Lobo et al., 2000). Dementia is preceded by neuropathology which can emerge several decades before symptoms manifest (Sperling et al., 2011; Villemagne et al., 2013), and by mild cognitive impairment (MCI), an intermediary stage between healthy cognitive ageing and dementia (DeCarli, 2003). Based on 36 prevalence and 15 incidence studies, a review estimated the international prevalence of dementia to be 0.3-1.0 per 100 people aged 60-64, increasing to 42.3-68.3 by age 95+, and the incidence varied from 0.8 to 4.0 per 1000 person-years at age 60-64, increasing to 49.8 – 135.7 per 1000 person-years by age 95+, with variation between regions (Fratiglioni, Ronchi, & Agüero-torres, 1999). While the international burden of dementia is projected to increase over time due to ageing populations (Ferri et al., 2005; Prince et al., 2013), there is some evidence that dementia incidence is decreasing over time in high-income countries such as the United Kingdom, North America, Sweden and the Netherlands (Livingston et al., 2017; Matthews et al., 2016; Roehr, Pabst, Luck, & Riedel-heller, 2018).

The most commonly diagnosed dementia subtype is Alzheimer's Disease (AD), followed by vascular dementia, then Lewy Body Dementia (Lobo et al., 2000). Other less common

dementia subtypes include frontotemporal dementia, which typically onsets between age 45-60 years old (Neary, Snowden, & Mann, 2005). The underlying neuropathology of dementia is heterogeneous and is not fully understood, although symptoms are broadly related to various underlying neuropathologies including neuronal loss, amyloid plaques and neurofibrillary tangles in AD, and Lewy bodies in Lewy Body dementia. More recently, a new type of dementia neuropathology has been identified, referred to as limbic-predominant Age-related TDP-43 Encephalopathy (LATE), which is thought to largely affect those aged 80 and above and to mimic symptoms of AD (Nelson et al., 2019). There is increasing recognition that dementia cannot be neatly divided into subtypes and individuals frequently have multiple types of neuropathology (Schneider & Dagerman, 2004).

The aetiology of dementia is heterogeneous and multifactorial. In terms of genetics, familial early-onset AD has a strong genetic basis related to the presenilin 1 gene and, less commonly, the β-amyloid precursor protein gene (Sampson, Draper, & Withall, 2004), although this accounts for a relatively small proportion of AD cases. AD with a more typical age-at-onset has comparatively weaker genetic underpinnings, related to the apolipoprotein E e4 allele, which is also associated with vascular dementia (Grazina, Pratas, Silva, & Oliveira, 2006). Additionally, 40-50% of patients with frontotemporal dementia have a positive family history of the condition and various genetic causes have been identified (Mohandas & Rajmohan, 2009).

Dementia risk is also strongly related to the environment. The recent Lancet commission on dementia prevention, intervention and care identified a number of potentially modifiable environmental risk factors for dementia, including factors related to physical and mental health, education, and social engagement (Livingston et al., 2017). This is evidenced by associations between dementia and several physical health conditions and lifestyle factors, including: obesity, diabetes (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006), cardiovascular disease (Purnell, Gao, Callahan, & Hendrie, 2009), smoking (Peters et al., 2008), poor diet and lack of physical activity (Baumgart et al., 2015). Additionally, low educational attainment has been found to be associated with an increased risk of dementia, although not consistently (Sharp & Gatz, 2011). This association has been attributed to the cognitive reserve hypothesis, which posits that those with a higher IQ or educational attainment have a higher baseline level of cognitive ability, allowing a greater level of

neuropathology before symptoms of dementia manifest (Stern, 2006). There is some evidence of a slightly higher rate of Alzheimer's Disease in rural areas, particularly in relation to early rural life, and in high income countries (Russ, Batty, Hearnshaw, Fenton, & Starr, 2012). Reasons for this are unclear, although the association may reflect factors such as differential survival and different patterns of diagnosis or access to care. Additionally, in the UK, people of African and African-Caribbean ethnicity have been found to be at increased risk of dementia relative to those of white British ethnicity (Adelman, Blanchard, & Livingston, 2009), while in the US, the rate of dementia has been found to be higher in African American and Hispanic individuals, relative to white Americans (Mehta & Yeo, 2017), which may reflect factors such as socioeconomic disparities and physical health comorbitidies (Mayeda, Glymour, Quesenberry, & Whitmer, 2016). Social disengagement is also associated with an increased risk of dementia (Kuiper et al., 2015; Sommerlad, Ruegger, Singh-manoux, Lewis, & Livingston, 2018), although this could be explained by social withdrawal as part of the dementia prodrome. Similarly, psychiatric conditions, particularly depression, have been found to be associated with increased dementia risk, although the direction of association is unclear, as discussed in the following sections (Singh-Manoux et al., 2017).

1.9.2 Psychotic disorders, VLOSLP and dementia

The relationship between psychotic disorders and dementia is complex and can be understood at various levels. First, hallucinations and delusions, can be experienced as neuropsychiatric symptoms in dementia (Fischer & Agüera-ortiz, 2018; Lyketsos et al., 2002). AD with psychotic symptoms can be viewed as a distinct phenotype associated with poorer outcomes (Ropacki & Jeste, 2005; Zahodne, Ornstein, Cosentino, Devanand, & Stern, 2015). A review of 55 studies reported the median prevalence of delusions to be 23.5% in mild AD, increasing to 46% in moderate AD (Ropacki & Jeste, 2005), with persecutory delusions occurring earlier in the disease course, while misidentification delusions were associated with more advanced AD neuropathology (Reeves, Gould, Powell, & Howard, 2012). As in schizophrenia, psychotic symptoms in AD are associated with an excess of striatal dopamine D2/3 receptors and with abnormalities in brain networks involved in salience and belief evaluation (Reeves, Brown, Howard, & Grasby, 2009; Reeves et al., 2012). Psychotic symptoms have been found to be particularly common in Lewy Body

dementia and dementia related to Parkinson's Disease, and to occur earlier in the disease course (Fischer & Agüera-Ortiz, 2018).

Psychotic disorders could also be a risk factor for developing dementia (Cai & Huang, 2018), and could be part of the dementia prodrome for some individuals (Fischer & Agüera-Ortiz, 2018). Longitudinal data suggest that those with psychotic symptoms and diagnosed psychotic disorders with a more typical age-at-onset are at increased risk of subsequent dementia (Almeida et al., 2018b; Cai & Huang, 2018; Köhler et al., 2013; Ribe et al., 2015). The mechanisms underlying this association are unknown, but several potential explanations have been put forward. For instance, cognitive impairment, a core component of schizophrenia (Bora, 2015), may increase risk for dementia via reduced cognitive reserve (Barnett, Salmond, Jones, & Sahakian, 2006), in that those with a lower level of baseline cognitive functioning may require less neuropathology before meeting the clinical threshold for dementia (Stern, 2002, 2006). Second, psychotic disorders are associated with poorer physical health, including conditions such as type-II diabetes (Bushe & Holt, 2004; Osborn et al., 2008), and heart disease (Crump, Winkleby, Sundquist, & Sundquist, 2013; Hennekens, Hennekens, Hollar, Casey, & Raton, 2005; Osborn et al., 2007), which may increase risk for dementia (Biessels et al., 2006; Wolters et al., 2018).

Poorer physical health in those with psychotic disorders may also be explained by factors such as poor diet, sedentary behaviour (McCreadie, 2002), a higher prevalence of smoking and drug and alcohol use (McCreadie, 2003), antipsychotic medication use, reduced sleep quality (Davies, Haddock, Yung, Mulligan, & Kyle, 2017), and social deprivation (Hollingshead & Redlich, 1958; Silver, Mulvey, & Swanson, 2002). However, little is known about physical health in those with VLOSLP and many of these health-related risk factors seem more applicable to those with chronic schizophrenia. As mentioned above, on the other hand it is increasingly recognised that late-onset depression may be a prodromal feature of dementia rather than a risk factor (Singh-Manoux et al., 2017), and this could also be the case for some individuals with late-life psychotic symptoms (Fischer & Agüera-Ortiz, 2018).

However, little research has examined the association between VLOSLP and dementia to date, despite longstanding debate about the underlying nature of VLOSLP and its potential association with cognitive decline (Vahia et al., 2010). A recent review reported some

evidence of mild cognitive deficits and decline in those with VLOSLP above the level expected with healthy ageing (Van Assche et al., 2017). However, there was little evidence of neuropathology or neurodegeneration beyond that observed in more typical age-at-onset psychotic disorders, after accounting for age. It should be noted that most studies in this area to date are small and cross-sectional with unrepresentative samples, or longitudinal studies with short follow-up periods (Van Assche et al., 2017). This is problematic given that dementia neuropathology emerges over several decades (Villemagne et al., 2013). Epidemiological evidence on the association between VLOSLP and dementia is sparse, and further large, longitudinal studies with sufficiently long follow-up periods are required to characterise the association between VLOSLP and subsequent dementia.

1.10 Overall aims and hypotheses

In this Chapter, I broadly overviewed the literature on non-affective psychotic disorders and VLOSLP from a biopsychosocial perspective. This overview highlighted the dearth of population-based epidemiological evidence regarding the incidence of psychotic disorders in older people and risk factors and outcomes associated with VLOSLP. Further research is required to complete the life-course picture of the incidence of non-affective psychotic disorders, to gain insight into the aetiology and possible outcomes of VLOSLP, and to identify potential environmental and psychological targets for the development of interventions and preventative strategies to benefit those with VLOSLP.

Aims

The overall aim of this thesis is to address these gaps in the literature, in particular:

1. To characterise the incidence of non-affective psychotic disorders in people aged 60 years old and above.
2. To investigate potential risk and protective factors associated with VLOSLP.
3. To examine the rate of subsequent dementia in those with VLOSLP.
4. To investigate levels of social isolation, loneliness and impairments in social cognition in individuals with VLOSLP.

Structure

In order to address these aims, this thesis is structured as follows:

Chapter 1: Introduction and broad overview of the literature
Chapter 2: The incidence of very late-onset psychotic disorders: a systematic review and meta-analysis, 1960-2014
Chapter 3: Overview of Swedish population register data and cohort study methods
Chapter 4: The incidence of non-affective, non-organic psychotic disorders in older people: a population-based cohort study of 3 million people in Sweden
Chapter 5: Dementia in very late-onset schizophrenia-like psychosis: a matched Swedish population-based cohort study
Chapter 6: Social isolation and loneliness in very late-onset schizophrenia-like psychosis: a feasibility study
Chapter 7: Discussion

Information about methods

Given the varied methodological approaches taken in this thesis, methods for each study are described in the following Chapters:

In Chapter 2, I set out methods for the systematic review and meta-analysis.
Chapter 3 presents methods and describes the data source for two cohort studies using Swedish population register data (Chapters 4 and 5).
Chapter 6 describes the methods for a feasibility case-control study involving primary data collection, which focusses on social isolation, loneliness and social cognition in VLOSLP.

Hypotheses

Hypotheses for each study were as follows:

Chapter 2. The incidence of very late-onset psychotic disorders: a systematic review and meta-analysis, 1960-2014
In this systematic review, I hypothesised that the rate of VLOSLP would increase with age and would be higher among women. Where data were available, I sought to test the

hypotheses that the rate of VLOSLP would be higher among migrants, those with a family history of non-affective psychotic disorder, lower socio-economic status, sensory impairment, and those exposed to traumatic life events.

Chapter 4. The incidence of non-affective, non-organic psychotic disorders in older people: a population-based cohort study of 3 million people in Sweden

In a cohort study using Swedish population register data, I hypothesised that the rate of VLOSLP would increase with age and would be higher among: women, migrants to Sweden, those whose offspring had a recorded non-affective psychotic disorder diagnosis, with hearing or visual impairments, with gestational exposure to World War II, exposure to social isolation as indexed by having no partner or children, and those who had experienced the death of a child, or the recent death of a partner.

Chapter 5. Dementia in very late-onset schizophrenia-like psychosis (VLOSLP): a matched Swedish population-based cohort study

In a matched cohort study using Swedish population register data, I hypothesised that the rate of dementia would be higher among those with VLOSLP relative to the age and calendar period matched comparison group. I expected the rate of dementia associated with VLOSLP to be similar across subgroups, such as sex, educational attainment and family history of non-affective psychotic disorder. I hypothesised that the association between VLOSLP and dementia would remain after considering possible bias introduced by differences in survival and detection between those with and without VLOSLP.

Chapter 6. Social isolation and loneliness in very late-onset schizophrenia-like psychosis: a feasibility case-control study

In a feasibility study involving primary data collection from National Health Service (NHS) sites, I hypothesised that participants with VLOSLP would be more socially isolated than control participants with mixed mental health difficulties, but that those with VLOSLP would be less lonely than control participants after accounting for levels of social isolation. I also hypothesised that those with VLOSLP would have higher levels of theory of mind impairments and hostile attribution bias relative to the control group.

Chapter 2 The incidence of very late-onset psychotic disorders: a systematic review and meta-analysis, 1960-2014

A modified version of this Chapter was published in Psychological Medicine:
Stafford, J., Howard, R., & Kirkbride, J. B. (2018). The incidence of very late-onset psychotic disorders: a systematic review and meta-analysis, 1960–2016. *Psychological Medicine*, *48*(11), 1775-1786.

2.1 Introduction

As highlighted in the general review of the literature presented in Chapter 1, people aged 65 years old and above are consistently excluded from research on the epidemiology of psychotic disorders, hence little is known about the incidence of very late-onset schizophrenia-like psychosis (VLOSLP). Most previous studies focussed on risk factors for VLOSLP have been cross-sectional, involving small, unrepresentative samples. As discussed in Chapter 1, these studies have identified several potential risk factors for VLOSLP. One of the more replicated findings in the literature is of a higher preponderance of VLOSLP among females relative to males (Howard et al., 2000). Other potential risk factors include hearing impairment (Cooper & Curry, 1976; Cooper, Curry, Kay, Garside, & Roth, 1974), visual impairment (Cooper & Porter, 1976), adverse life events (Fuchs, 1994, 1999; Gurian, Wexler, & Baker, 1992; Reulbach, Bleich, Biermann, Pfahlberg, & Sperling, 2007), social isolation, and premorbid schizotypal traits (Kay & Roth, 1961; Pearlson et al., 1989). However, these findings have not been consistently replicated and epidemiological support is lacking (Brunelle, Cole, & Elie, 2012).

To address these gaps in the literature, I conducted a systematic review and meta-analysis of the literature on the incidence of very late-onset affective and non-affective psychotic disorders, and how this varied by age and sex. I hypothesised that the incidence of very late-onset psychotic disorders would increase with age and would be higher among women than men. Additionally, where data were available, I sought to examine variation in incidence by

family history of psychopathology, socioeconomic status (SES), ethnicity, migrant status, sensory impairment, social isolation, marital status, education, employment history, and traumatic life events. I expected higher incidence rates among migrant groups, given similar findings in younger adults (Kirkbride et al., 2012), and among those with: a family history of psychotic disorders, lower SES, the experience of traumatic life events, and sensory impairment. Synthesising evidence on the incidence of VLOSLP may highlight consistent themes which could help to provide insight into the aetiology of late-life psychotic disorders, or gaps in the literature requiring examination.

2.2 Methods for systematic review

I conducted this systematic review following PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009), including pre-registering the study protocol (http://www.crd.york.ac.uk/PROSPERO, registration number: CRD42016035720).

2.2.1 Search strategy

I systematically searched PubMed, PsychInfo and Web of Science databases using terms covering three main areas: “late-onset”, “incidence” and “psychosis” (see Table 2.1). I adapted search terms for each database using database-specific MeSH headings.

I searched bibliographies of included citations and directly contacted authors to request data, where appropriate. I restricted the review to English language papers published between January 1960 and March 2016.

2.2.2 Eligibility criteria

Although VLOSLP usually refers to those aged over 60 years old, I restricted my search to those aged 65 years and older because this is typically the upper age cut-off in epidemiological studies of “adult-onset” psychotic disorders, which have been widely reviewed (Kirkbride et al., 2012; McGrath et al., 2004; Van der Werf, Hanssen, Köhler, et al., 2014).

Other eligibility criteria were as follows:

- Contained incidence data, or data from which incidence rates could be derived (numerator and denominator).
- Attempted to conduct a population-based epidemiological study, irrespective of quality (see below).
- Cases first diagnosed with psychotic disorders after age 65 years old (incident cases).
- Excluded those with dementia, organic or drug-induced psychoses.

Table 2.1 Search terms

Late-onset:	Incidence terms:	Psychosis:
1. MeSH: Geriatrics	1. MeSH: Onset (disorders)	1. MeSH: Psychosis
2. 'Late-onset'	2. MeSH: Epidemiology	2. Psychos*
3. LOP	3. 'First episode'	3. Psychotic
4. VLOSLP	4. 'First contact'	4. Schizoaffective
5. 'Very late-onset'	5. 'First contact admission'	5. Schizophreniform
6. 'Late life'	6. 'First admission'	6. Delusion*
7. 'Later life'	7. 'First hospitalization'	7. Hallucinat*
8. Aging	8. 'First hospitalisation'	8. 'Affective psychos*'
9. Ageing	9. Incepted	9. 'Schizophrenia-like psycho*'
10. Geriatric	10. 'First treatment'	10. Paranoi*
11. 'Old age'	11. 'First treated'	11. 'Bipolar affective psycho*'
12. 'Older age'	12. Epidemiol*	12. 'Bipolar psycho*'
13. 'Older adult'	13. Incidence	13. 'Bipolar disorder'
	14. Cohort	14. 'Psychotic depression'
	15. 'Attack rate'	15. 'Depressive psycho*'
	16. 'Inception rate'	16. 'Manic depressive psychos*'
		17. 'Severe depression with psycho*'
		18. Paraphrenia

2.2.3 Screening

I screened citation titles to assess whether they met eligibility criteria, with definite or possible citations forwarded to abstract, and subsequently, full text review. I initially screened studies and extracted data, and a second researcher (JBK) independently screened a randomly selected 10% sample (99.8% inter-rater agreement, Cohen's k=0.88, p=<.001).

2.2.4 Database management and data extraction

I stored extracted data in a spreadsheet, adapted from a previous systematic review (Kirkbride et al., 2012). Data were divided into study-level data about study characteristics,

rate-level data about incidence rates, and meta-level data on time period and study quality (see below).

2.2.5 Exposures and outcomes

The primary outcome was the incidence rate per 100,000 person-years at-risk of a non-organic psychotic disorder in those aged 65 years old and above. Included studies used a range of diagnostic classifications, including ICD-8 to ICD-10, DSM-III-R, and DSM-IV. Although the classification of psychotic disorders varies between diagnostic classifications and editions, it was assumed that there were sufficient commonalities to pool citations according to the following diagnostic outcomes: i) non-affective psychotic disorders (ICD-10 F20-F29 or equivalent, including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, and brief and unspecified psychoses), ii) schizophrenia (ICD-10 F20 or equivalent), iii) affective psychoses (ICD-10 F30-39 or equivalent, excluding depression without psychosis).

Where available, I extracted incidence data in relation to the following exposures: age, sex, ethnicity, SES, migrant status, marital status, education, employment, sensory impairment such as deafness or blindness, traumatic life events (childhood or adulthood), and family history of psychopathology. Where incidence rates were not explicitly reported, I derived them from ancillary information where possible (i.e. numerator, denominator, standard errors). Where citations reported overlapping data from the same study, the rate or citation providing the most pertinent information for each specific analysis was considered primary.

2.2.6 Study quality

Study quality was rated by two independent raters (JS, JBK) based on 5 criteria, with 87% inter-rater agreement, Cohen's k=0.61, p=<.001. Discrepancies were dealt with via consensus. I used a quality scale adapted from a previous review (Kirkbride et al., 2012) to assess five key indicators of epidemiological quality: defined catchment area, accurate denominator, population-based case ascertainment, standardised research diagnoses, and well-defined inclusion and exclusion criteria (Table 2.2).

Table 2.2 Quality criteria

	Criterion	Description
1.	*Defined catchment*	Did the study have a well-defined catchment area to ensure that the numerator (case) and denominator populations came from the same source? Evidence of a defined catchment was needed to meet this criterion.
2.	*Accurate denominator*	Did the study report how it estimated the denominator population from which the cases came? Was the source known to be accurate, reliable and valid? Evidence of an accurate denominator was needed to meet this criterion.
3.	*Population-based case finding*	Did the study employ a population-based case finding approach? This includes identifying cases from community-based settings and service contact points, including primary, secondary and tertiary facilities. Studies which only considered hospital-based admissions, for example, would not meet this quality criterion as they would be likely to underestimate the true rate of disorder in the community. Evidence of a broad case-finding approach was needed to meet this criterion.
4.	*Standardised research diagnoses*	Did the study use standardised research diagnoses to ensure that the cases met comparable diagnostic criteria for psychotic disorder? Studies reliant on clinician-led chart diagnoses may introduce bias into diagnoses given inter-clinician variation in making diagnoses. Applying standardised criteria, by using a method such as the Schedule for the Clinical Assessment in Neuropsychology [SCAN] or using OPCRIT-generated diagnoses would reduce such problems. Evidence of attempts to standardise diagnoses was needed to meet this criterion.
5.	*Inclusion criteria*	Did the study use inclusion criteria to accurately define their study population (numerator and denominator)? Were these criteria sufficient? Standard criteria in epidemiological research include age limits, residency within catchment area at time of disorder, absence of an organic basis to the disorder and no previous episode of disorder (incidence studies only). Inclusion criteria needed to be present *and* of sufficient relevance/quality to meet this criterion.

Adapted from Kirkbride et al., (2012) systematic review.

2.2.7 Data analysis

First, I conducted a narrative synthesis of published incidence data on very-late-onset psychotic disorders, particularly important given the substantial heterogeneity observed between incidence estimates (generally, $I^2 = \geq .90$). Where three or more citations provided incidence data which could be pooled, I conducted random effects meta-analyses using the Dersimonian and Laird (1986) method to obtain pooled estimates. Incidence rates were transformed to their natural logarithm and entered into meta-analyses with corresponding

standard errors. Where possible, to allow the pooling of incidence rates for those aged 65 and above, estimates reported from the same citation for different age bands were aggregated into an overall age 65+ rate. I also conducted random-effects meta-regressions to explore whether variation in incidence was associated with sex, study quality, or case ascertainment period. I examined evidence of publication bias via visual inspection of funnel plots and formal testing using Egger's test of bias. I conducted meta-analyses in Stata version 13 using the metan command. Funnel plots and Egger's bias test were conducted using metafunnel and metabias packages. Random effects meta-regressions were conducted using the metareg package.

In this systematic review, I chose to examine incidence rates, given that I was specifically interested in new cases of psychotic disorder developed after age 65 years old, excluding older adults who were diagnosed with psychotic disorders when they were younger. I also chose to conduct a meta-analysis where possible, despite the high levels of heterogeneity that have been observed in schizophrenia incidence in younger adults (e.g. Kirkbride et al., 2012). I chose to pool rates alongside narrative synthesis, given that this has been done for younger adults with psychotic disorders, to promote comparison of incidence rates between older and younger people. I pooled rates using random-effects, rather than fixed-effects, meta-analyses. Fixed effects meta-analysis assumes that there is one 'true effect' across studies, and that any variation observed is due to error, whereas random effects allows for variation across studies due to other factors. I also chose to examine incidence in relation to psychosocial factors and sex differences given the previous literature in this area and research on psychotic disorders in younger adults.

2.3 Results

I retrieved 5687 citations, of which 41 – published between 1967 and 2014 – met eligibility criteria (Figure 2.1; Table 2.3; Figure 2.2). Four authors provided original data (Baldwin et al., 2005; Bogren, Mattisson, Isberg, Munk-Jørgensen, & Nettelbladt, 2010; Pedersen et al., 2014; Van Os, Howard, Takei, & Murray, 1995) and Van der Werf et al. (2014) provided further unpublished data from studies ascertained as part of a previous systematic review.

Included studies covered case ascertainment periods ranging from 1926 to 2010 (Andersen & Hynnekleiv, 2007; Baldwin et al., 2005 [including unpublished supplemental data]). Most citations reported incidence across the lifespan, whereas only eight focussed specifically on older people (Castle & Murray, 1993; Copeland et al., 1998; Holden, 1987; Mitford, Reay, McCabe, Paxton, & Turkington, 2010; Mitter, Krishnan, Bell, Stewart, & Howard, 2004; Mitter et al., 2005; Reeves, Sauer, Stewart, Granger, & Howard, 2001; Van Os et al., 1995). 22% of citations were rated as high quality (rated 4-5), 71% as average quality (rated 2-3), and 7% as poor quality (rated 0-1) (see Table 2.3).

Figure 2.1 Frequency of citations by year of publication

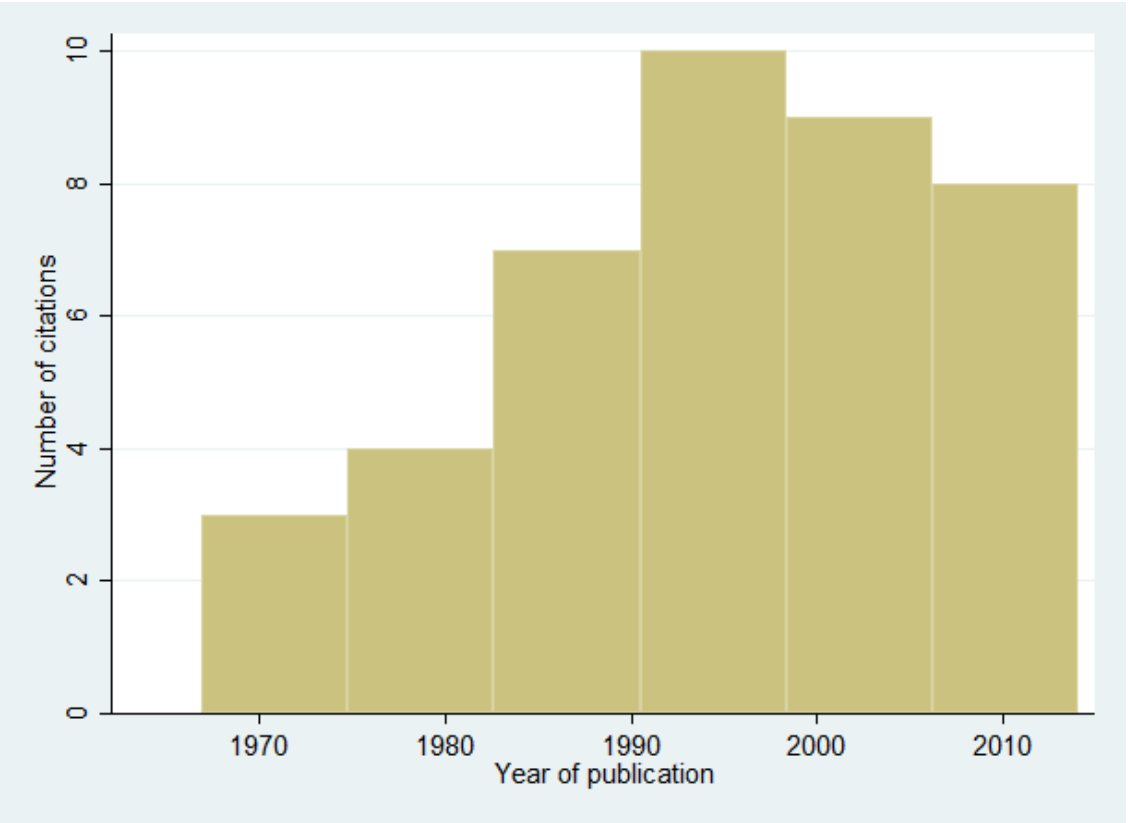


Figure 2.2 PRISMA flow diagram

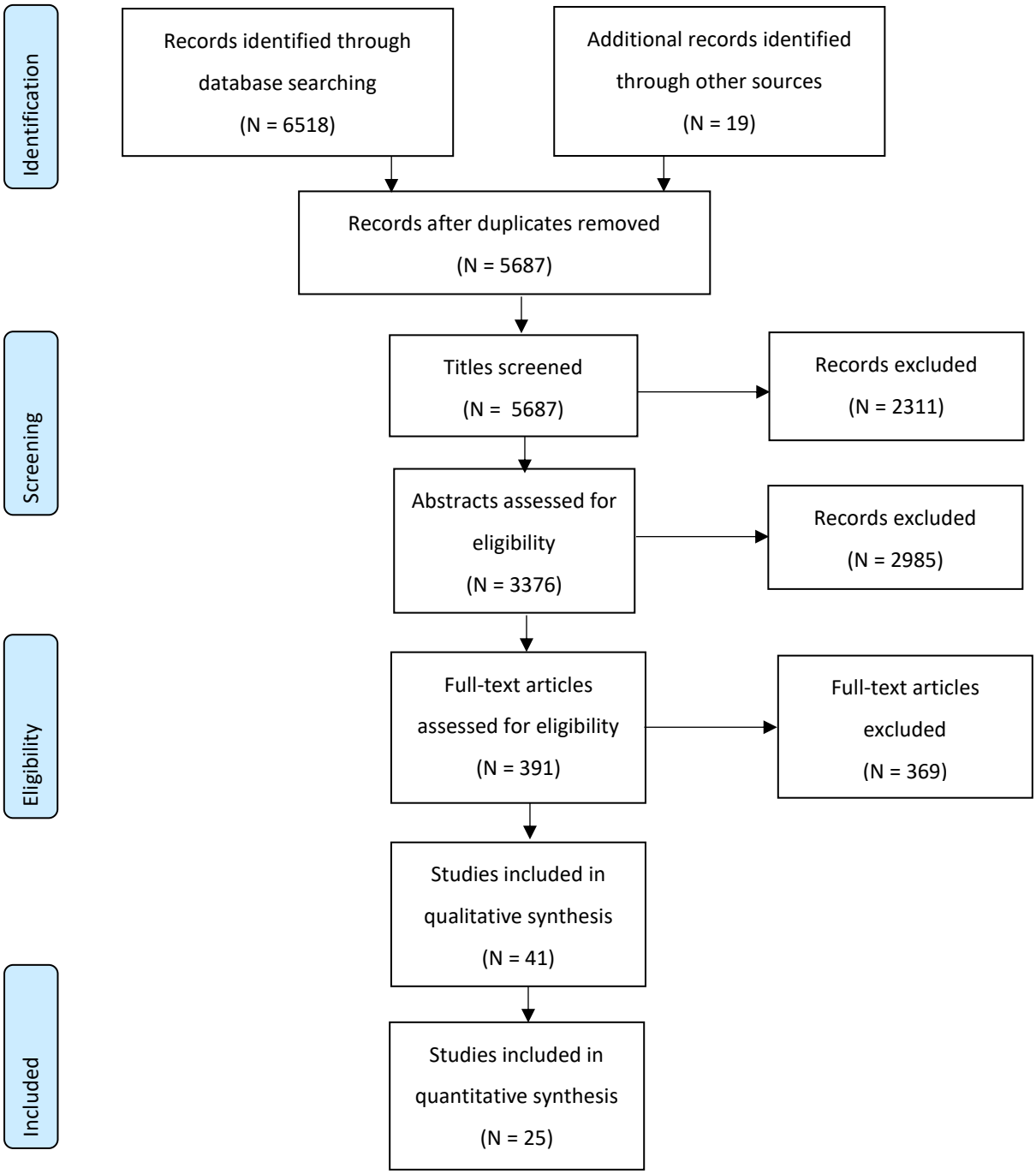


Table 2.3 Citation characteristics

Citation	Setting	Period	Case ascertainment	Sample[1]	Dx[2,3]	Diagnostic classification	Outcomes	N[4]	Quality
Adelstein (1968)	Salford	1959-1963	Case register	FC	Sz, PD	DSM-I	Age 60+, age & sex	Sz N=19	2
Ajdacic-Gross (2007)*	Canton of Zurich	1977-2005	Case register	FA	Sz	ICD-8, 9 & 10 295	Age 60+, age & sex	N=298	3
Allardyce (2000)*	Dumfries & Galloway	1979-1998	Case record, administrative	FC	Sz	ICD-9 295, ICD-10 F20	Age 60+, age & sex	N=25	4
Andersen (2007)	Hedmark, Norway	1926-1935	Case record review	FA	Sz	ICD-10 F20-20.9	Age & sex	N=1	2
Baldwin et al. (2005)*	Cavan & Monaghan	1995-2010	Interview (SCID)	FC	Sz, aff	DSM-III-R & DSM-IV	Age 65+, age & sex	Sz N=8, aff N=35	5
Bamrah (1991)	Salford	1984	Case register	FC	Sz	ICD-9 295, excluding 295.9	Age	Not specified.	4
Bland (1977)	Canada	1972	Administrative	FA	Sz, aff	ICD-8 295, 296	Age 60+, age & sex	Sz N=192, aff N=882	2
Bogren (2007)	Lundby	1947-1997	Interview, case register	FC	NAPD	DSM-IV	Age 60+, age & sex	N= 44	3
Bogren (2010)*	Lundby	1947-1997	Interviews, case register	FC	Sz, PD	DSM-IV 295.1-295.3, 295.9	Age 65+, age & sex	Sz N=1, Pd N=4	3
Boydell (2003)*	South East London	1965-1997	Case register	FC	Sz	DSM-III-R, ICD-9 & RDC 295	Age 65+, age & sex	N=78	4
Castle (1993)(a)	Camberwell	1965-1984	Case register	FC	Sz, NAPD	ICD-9 295, 297.2, 298	Age & sex	Not specified	4
Castle (1993)(b)	Camberwell	1965-1984	Case register	FC	Sz, NAPD	ICD-9 295, 297.2, 298	Age & sex	Not specified	4
Cochrane (1987)	England	1981	Administrative	FA	Sz	ICD-8	Age 65+, ethnicity	Not specified	2
Cochrane (1989)	England	1981	Administrative	FA	Sz	ICD-8 & 9	Age 65+, ethnicity	Not specified	2

Copeland (1998)	Liverpool	Not clear	GP lists, interview	FA	Sz	DSM-III	Age 65+	N=1	3
De Alarcon (1993)	Oxfordshire	1975-1986	Case register	FC	Sz, aff	ICD-8 & 9	Age 65+	Sz N=47, aff N= 198	2
De Salvia (1993)	Portogruaro	1982-1989	Case Register	FC	Sz	ICD-9 295	Age 65+ by sex	N=10	3
Eagles (1985)	Scotland	1969-1978	Administrative	FA	Aff	ICD-8 296	Age & sex	Not specified	2
Gater (1995)*	South Verona & South Manchester	1990	Case register	FC	Sz	ICD-9 295, ICD-10 F20	Age 65+	N=2	3
Geddes (1993)	Scotland	1969-1988	Administrative	FA	Sz	ICD-9 295	Age 65+, age & sex	N= 270	2
Goldacre (1994)	Oxfordshire	1975-1986	Case register	FA	Sz	ICD 7, 8 & 9 295	Age 60+ by sex	N=286	2
Helgason (1977)	Iceland	1966-1967	Case register	FC	Sz, aff	ICD-8 295, 296	Age 65+, age & sex	Sz N=7, Aff, N=90	3
Holden (1987)	Camberwell	1971-1975	Case Register	FC	LP	Clinical	Age 60+	N=24	3
Malzberg (1967)	New York	1960-1961	Administrative	FA	Sz	Not specified	Age 65+, age & migrant status	N=46	2
McCabe (1975)	Denmark	1967-1968	Administrative	FA	Sz	ICD-8	Age 65+, age & sex	N=23	1
Mitford (2010)	Northumberland	1998-2005	Case register	FC	NAPD, aff	ICD-10 F20-F29	Age 65+	NAPD=54, aff=38	3
Mitter (2005)	Camberwell & Tower Hamlets	1995-2003	Case note review	FC	SLP	Clinical	Age 65+, age, sex & migrant status	N=84	4
Mitter (2004)	Tower Hamlets	1997-2002	Case note review	FC	SLP	Clinical, ICD-10	Age 65+ by sex & ethnicity	N=40	4
Munk-Jorgensen (1986)(a)	Denmark	1972-1983	Case register	FA	Sz	ICD-8 295.0-.9	Age 65+ by sex	Not specified	2

Munk-Jorgensen (1986)(b)	Denmark	1970-1984	Case register	FA	Sz	ICD-8 295.0-.9	Age 65+ by sex	Not specified	2
Omer (2014)	Cavan & Monaghan	1995-2007	Interview (SCID)	FC	Sz, aff	DSM-IV	Age 65+, age & sex	Sz N=18, aff N=16	3
Pedersen (2014)*	Denmark	2000-2012	Case register	FA	NAPD, sz	ICD-8 to 10 F20, F25, F20-F29	Age & sex	Not specified	3
Proctor (2004)*	Northumberland	1998-2005	Case register	FC	Sz	ICD-10 F20	Age 60+, age & sex	N=13	1
Reeves (2001)	Camberwell	1995-2000	Case notes, in-patient data	FC	SLP	Clinical	Age 60+, by ethnicity	N=61	2
Salokangas (1979)	Turku	1949-1950 1959-1960 1969-1970	Case register	FA	Sz, aff	ICD-7 & ICD-8	Age 60+	Sz N=9	2
Spicer (1973)	England & Wales	1965 & 1966	Administrative	FA	Pd	ICD-7 301.1, 301.2, 302	Age 65+, age & sex	N=3161	2
Thornicroft (1993)*	South Verona & Portogruaro	1983-1989	Case register	FC	Sz	ICD-8 & 9 295	Age 65+	N=3	4
Thorup (2007)	Denmark	1970-2005	Case register	FA	Sz	ICD-8 & ICD-9 295 (not 295.79), ICD-10 F20	Age 60+, age & sex	N=391	3
Van Os (1993)	England & France	1973-1982	Administrative	FA	Sz	ICD-9 295	Age & sex	Not specified	1
Van Os (1995)*	England, Wales, The Netherlands	1976-1992	Case register	FA	NAPD	ICD-9 295.1-295.9, 297.0, 298.2-298.9	Age & sex	Sz N=11026	3
Welham (2004)	Queensland	1979-1991	Case register	FA	Sz, aff	ICD-9 295.x., 296.x (not 296.1)	Age 65+, age & sex	N=253	2

*Supplementary data obtained. [1]FA, FC: First admission, first contact, [2]Dx: Diagnoses (only those included in this review), [3]Sz, aff, NAPD, PD, SLP, LP: Schizophrenia, affective psychotic disorder, non-affective psychotic disorder, psychotic depression, schizophrenia-like psychosis, late paraphrenia, [4]N: Number of cases aged 60 or 65 and above

2.3.1 Incidence by age and sex

Non-affective psychotic disorders

Seven citations reported the incidence of non-affective psychotic disorders in older people (Bogren et al., 2010; Mitford et al., 2010; Mitter et al., 2004; Mitter et al., 2005; Pedersen et al., 2014; Reeves et al., 2001; Van Os et al., 1995). Studies were conducted in Sweden, England, Wales and Denmark, and were rated as high (29%) or average (71%) quality. Three non-overlapping studies provided overall incidence rates of non-affective psychotic disorders in those aged 65 and above (Mitford et al., 2010; Mitter et al., 2004; Reeves et al., 2001). The reported incidence rate of non-affective psychotic disorders in Northumberland was 14.3 per 100,000 person-years at-risk (kpy) (95%CI: 10.5-18.1) in those aged 65 years old and above, compared with 17.8 (95%CI: 15.5-20.0) in those aged below 65 years old (Mitford et al., 2010). A study conducted in Tower Hamlets, London, provided a rate of 31.4 per 100kpy (95%CI: 25.4–38.8) (Mitter et al., 2004), and in Camberwell, London, a rate of 39.9 per 100kpy (95%CI: 31.1–51.3) was reported in those aged 60 and above (Reeves et al., 2001).

Incidence was higher among older women than men in five studies reporting rates of non-affective psychotic disorders by sex (Bogren et al., 2010; Mitter et al., 2004; Pedersen et al., 2014; Reeves et al., 2001; Van Os et al., 1995). Three studies reporting incidence by age provided evidence of increasing rates with older age (Mitter et al., 2005; Pedersen et al., 2014; Van Os et al., 1995). In a study conducted in Denmark, incidence peaked in younger adulthood, followed by an additional increase after age 65 (Pedersen et al., 2014). Another study reported increasing rates from age 60 in both sexes in England, Wales and the Netherlands (Van Os et al., 1995), while Mitter et al. (2005) reported a slight decrease in incidence with age among older men, but substantial increases for women.

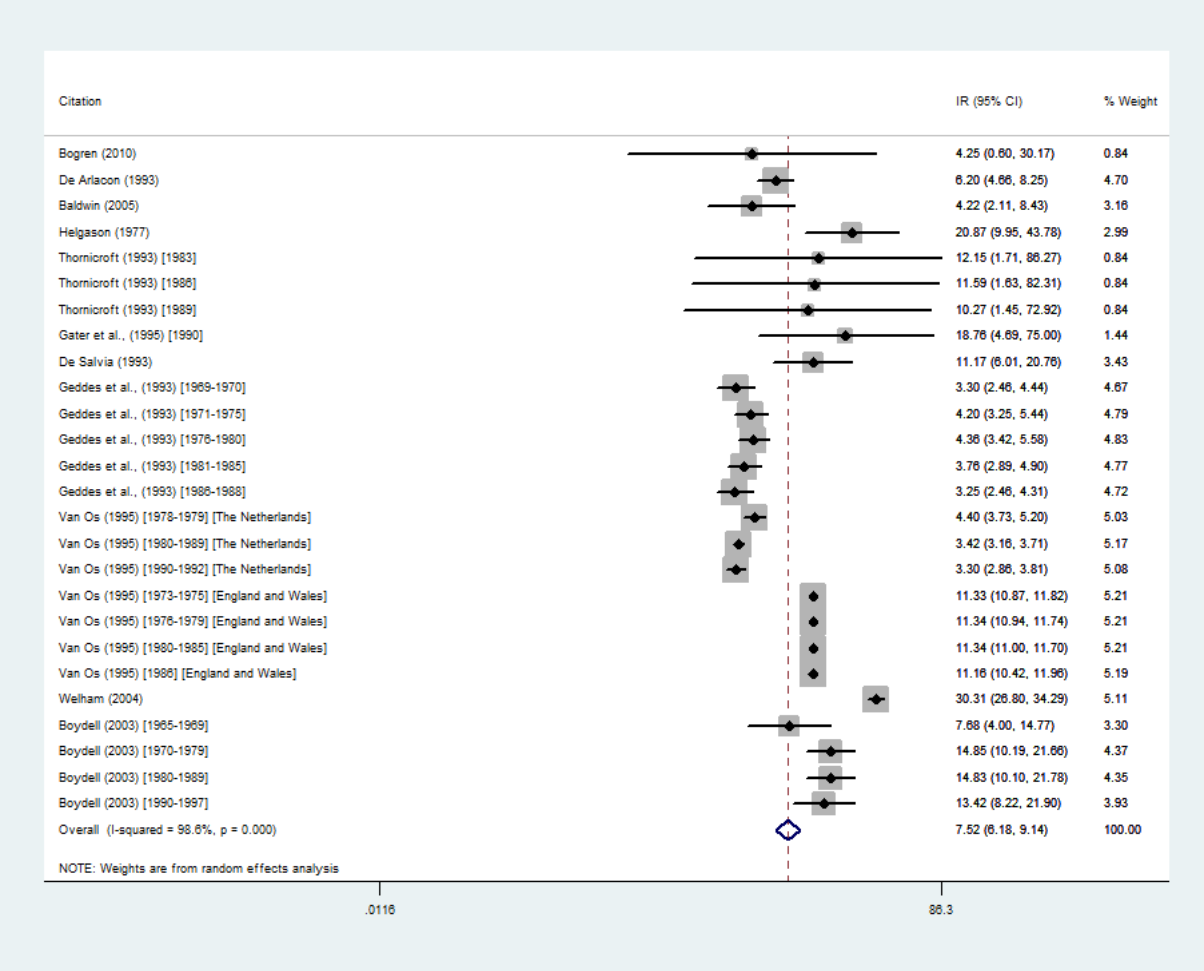
Schizophrenia

I identified 23 non-overlapping citations conducted between 1926 and 2010 providing data on the incidence of schizophrenia among older adults (Adelstein et al., 1968; Ajdacic-Gross et al., 2007; Allardyce et al., 2000; Andersen & Hynnekleiv, 2007; Baldwin et al., 2005; Bamrah et al., 1991; Bland, 1977; Bogren et al., 2010; Boydell et al., 2003; Copeland et al.,

1998; De Alarcon et al., 1993; De Salvia et al., 1993; Gater et al., 1995; Geddes et al., 1993; Helgason, 1977; Malzberg, 1967; Pedersen et al., 2014; Proctor et al., 2004; Salokangas, 1979; Thornicroft et al., 1993; Thorup et al., 2007; Van Os et al., 1995; Welham et al., 2004). Quality ranged from low (4%), to average (74%) or high (22%). Eight citations were excluded from the meta-analysis as they provided data on overall incidence aged 60+, rather than aged 65+ (Adelstein et al., 1968; Ajdacic-Gross et al., 2007; Allardyce et al., 2000; Andersen & Hynnekleiv, 2007; Bland, 1977; Proctor et al., 2004; Salokangas, 1979; Thorup et al., 2007). Another citation was excluded due to including a provisional case who did not meet full DSM-III-R criteria (Copeland et al., 1998). This citation reported a rate of 3 per 100kpy (95%CI: 0-110.7) in Liverpool. Three citations could not provide an age 65+ rate due to lack of corresponding standard errors and/or sample size data, although findings on incidence by age and sex are reported in the following sections (Bamrah et al., 1991; Malzberg, 1967; Pedersen et al., 2014).

The remaining 11 citations provided 26 estimates (due to several citations reporting separate estimates for different time periods) of schizophrenia incidence in those aged 65 years old and above, which could be pooled in a meta-analysis (Baldwin et al., 2005; Bogren et al., 2010; Boydell et al., 2003; De Alarcon et al., 1993; De Salvia et al., 1993; Gater et al., 1995; Geddes et al., 1993; Helgason, 1977; Thornicroft et al., 1993; Van Os et al., 1995; Welham et al., 2004). Quality was average (73%) or high (27%). The pooled incidence of schizophrenia was 7.5 per 100kpy (95%CI: 6.2-9.1; I^2= 0.98) (Figure 2.3). Estimates ranged from 3.3 per 100kpy (95%CI: 2.5–4.4) in Scotland (Geddes et al., 1993) to 30.3 per 100kpy (95%CI: 26.8–34.3) in Australia (Welham et al., 2004).

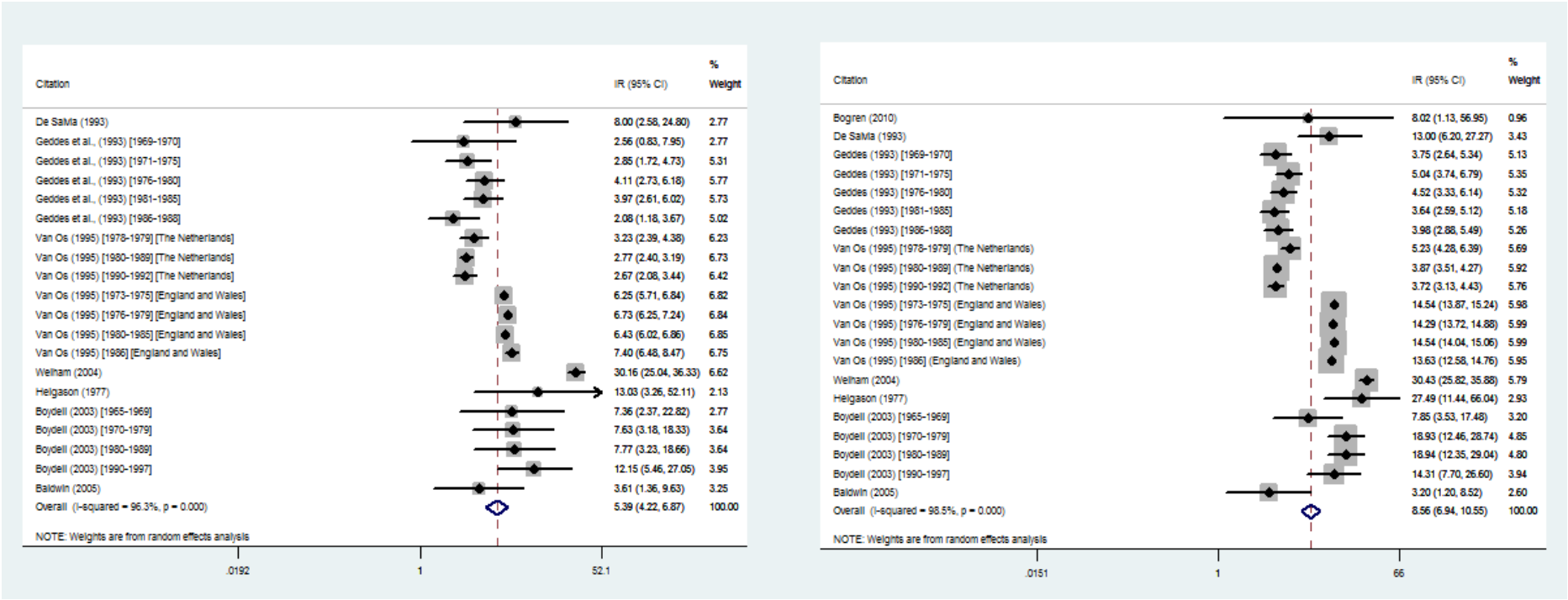
Figure 2.3 Forest plot of incidence rates of schizophrenia in those aged 65 years old and above



Incidence rate per 100,000 person-years at risk

Pooled rates were higher in women than men, based on 41 estimates from 8 suitable citations (women: 8.6 per 100kpy; 95%CI: 6.9-10.6; I^2= 0.98, men: 5.4 per 100kpy; 95%CI: 4.2–6.9, I^2= 0.96) (Figure 2.4) (Baldwin et al., 2005; Bogren et al., 2010; Boydell et al., 2003; De Salvia et al., 1993; Geddes et al., 1993; Helgason, 1977; Van Os et al., 1995; Welham et al., 2004). A meta-regression indicated that this sex difference approached statistical significance (OR= 1.6, 95%CI: 1.0-2.5, p=.052). Visual inspection of funnel plots of standard error against log incidence rates and formal testing via Egger's test did not provide evidence of publication bias (p=0.9) (Figure 2.5).

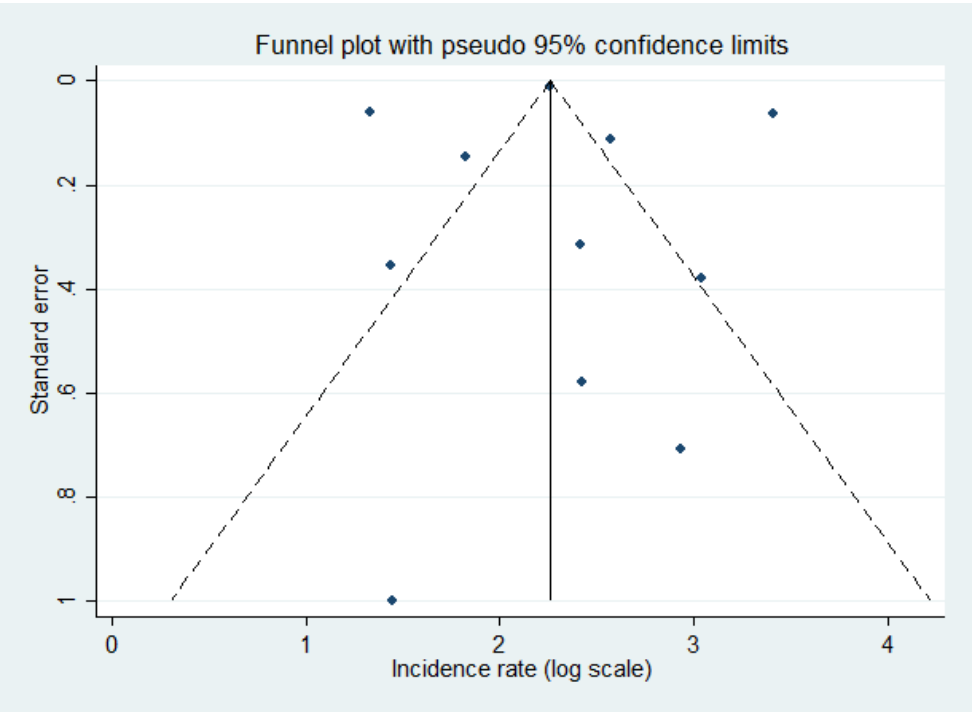
Figure 2.4 Forest plots of schizophrenia incidence aged 65 years old and above by sex, male (L), female (R)



Incidence rate per 100,000 person-years at risk

Fifteen citations reported the incidence of schizophrenia by age and sex (Adelstein et al., 1968; Ajdacic-Gross et al., 2007; Allardyce et al., 2000; Andersen & Hynnekleiv, 2007; Baldwin et al., 2005; Bamrah et al., 1991; Bland, 1977; Bogren et al., 2010; Boydell et al., 2003; Geddes et al., 1993; Helgason, 1977; Pedersen et al., 2014; Proctor et al., 2004; Van Os et al., 1995; Welham et al., 2004). While incidence mostly peaked among younger adults, (e.g. Helgason, 1977; Pedersen et al., 2014; Proctor et al., 2004) the pattern among older adults varied considerably across studies. Three citations broadly found increasing rates with age for men and women after age 65 years (Allardyce et al., 2000; Boydell et al., 2003; Proctor et al., 2004), whereas three citations reported decreases with age (Andersen & Hynnekleiv, 2007; Bland, 1977; Pedersen et al., 2014). One paper reported relatively stable rates with age, although few cases were identified (Bogren et al., 2010). In a study conducted in Salford (UK), incidence increased up to age 80 in both sexes, followed by a decline (Adelstein et al., 1968), whereas in a study in Queensland (Australia), incidence decreased from age 65 to 75 years old, followed by an increase in both sexes (Welham et al., 2004). In several studies no consistent pattern emerged by age (Baldwin et al., 2005; Helgason, 1977), or mixed findings were observed over time (Ajdacic-Gross et al., 2007; Bamrah et al., 1991; Geddes et al., 1993; Van Os et al., 1995).

Figure 2.5 Funnel plot of log schizophrenia incidence rates in those aged 65 years old and above by standard error



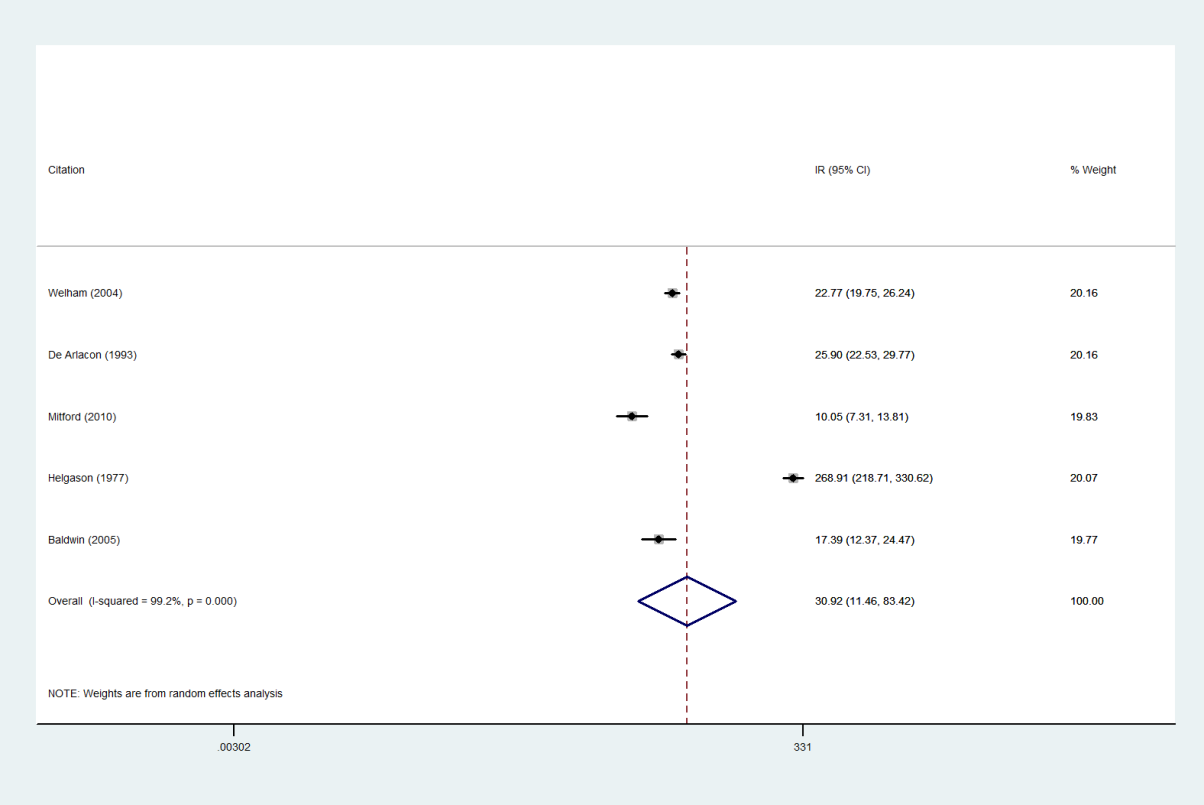
Affective psychoses

11 non-overlapping citations provided data on the incidence of affective psychoses in older adults (Adelstein et al., 1968; Baldwin et al., 2005; Bland, 1977; Bogren et al., 2010; De Alarcon, Seagroatt, Sellar, & Goldacre, 1993; Eagles & Whalley, 1985; Helgason, 1977; Mitford et al., 2010; Salokangas, 1979; Spicer, Hare, & Slater, 1973; Welham et al., 2004). Studies were conducted between 1951 and 2010 and quality was average (91%) or high (9%). Studies were conducted in England, Wales, Scotland, Ireland, Finland, Iceland, Canada, Australia and Costa Rica.

Five citations provided sufficient data to estimate an overall pooled rate of affective psychotic disorder in those aged 65 years old and above (pooled incidence rate: 30.9 per 100kpy, 95%CI: 11.5–83.4; I^2= 0.99; Figure 2.6) (Baldwin et al., 2005; De Alarcon et al., 1993; Helgason, 1977; Mitford et al., 2010; Welham et al., 2004). Four of these citations used ICD-8 and -9 diagnostic codes 296 and one used ICD-10 codes F30-F32.3. Four estimates lay between 10.1 per 100kpy (95%CI: 7.3–13.8) (Mitford et al., 2010) to 25.9 per 100kpy (95%CI: 22.5–29.8) (De Alarcon et al., 1993), with one study in Iceland reporting a substantially higher rate (268.9 per 100kpy; 95%CI: 218.7–330.6) (Helgason, 1977). Two further citations could not be included in the meta-analysis (Bland, 1977; Bogren et al., 2010). Bogren et al., (2010) only provided incidence data on more narrowly defined psychotic depression (excluding transient affective psychoses and bipolar disorder with psychosis): no cases of psychotic depression were identified in older males, whereas the rate for females was 16 per 100kpy (95%CI: 4.0–64.2). Bland (1977) reported an estimated incidence of affective psychoses in those aged 60 years old and above (rather than age 65) of 34.6 per 100kpy (95%CI: 32.4–36.9).

Three citations provided six estimates of the incidence of affective psychoses by sex (Baldwin et al., 2005; Helgason, 1977; Welham et al., 2004). Pooled incidence was higher among women (50.3 per 100kpy; 95%CI: 6.4–396.9; I^2= 0.99) than men (35.1; 95%CI: 9.8–125.5; I^2= 0.97), although confidence intervals around these estimates were wide, partially driven by the Icelandic study (Helgason, 1977) (Figure 2.7). There was no evidence from meta-regression that the incidence of affective psychosis differed between older men and women (OR= 1.22, 95%CI: 0.03–49.35).

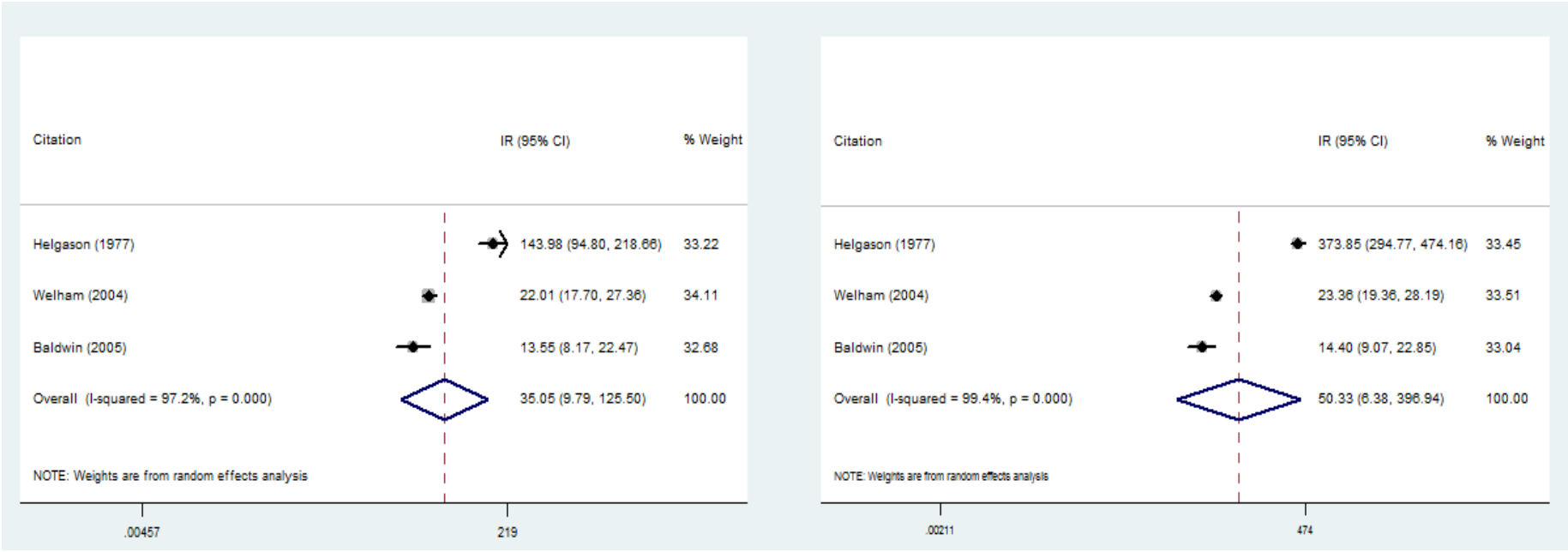
Figure 2.6 Forest plot of incidence rates of affective psychosis in those aged 65 years old and above



Incidence rate per 100,000 person-years at risk

Eleven citations reported rates of affective psychoses among both younger and older adults (Adelstein et al., 1968; Baldwin et al., 2005; Bland, 1977; Bogren et al., 2010; De Alarcon et al., 1993; Eagles & Whalley, 1985; Helgason, 1977; Mitford et al., 2010; Salokangas, 1979; Spicer et al., 1973; Welham et al., 2004). Interestingly, five citations reported the highest rates in older adults compared with among younger adults (De Alarcon et al., 1993; Eagles & Whalley, 1985; Helgason, 1977; Mitford et al., 2010; Salokangas, 1979). Two further studies reported the highest rates of more narrowly defined psychotic depression after age 65 (Adelstein et al., 1968; Bogren et al., 2010). Conversely, three studies reported the highest rates of affective psychoses among young or middle-aged adults (Baldwin et al., 2005; Bland, 1977; Welham et al., 2004).

Figure 2.7 Forest plot of affective psychosis incidence in those aged 65 years old and above by sex, male (L), female (R)



Incidence rate per 100,000 person-years at risk

After age 65, four citations reported a decrease in incidence with age (Adelstein et al., 1968; Bland, 1977; Helgason, 1977; Spicer et al., 1973), which was more substantial among women in two studies (Adelstein et al., 1968; Helgason, 1977). One study broadly reported increased incidence in older men, but a slight decrease with age in women (Eagles & Whalley, 1985). No consistent pattern by age emerged in two further studies (Baldwin et al., 2005; Welham et al., 2004).

2.3.2 Incidence by migrant status

Only five non-overlapping studies reported incidence by migrant status (Cochrane & Bal, 1987; Malzberg, 1967; Mitter et al., 2004; Mitter et al., 2005; Reeves et al., 2001). These studies related to non-affective psychotic disorders (Mitter et al., 2004; Mitter et al., 2005; Reeves et al., 2001), or schizophrenia (Cochrane & Bal, 1987; Malzberg, 1967). Studies were conducted between 1960 and 2003 and were of average (60%) or high quality (40%). The incidence of non-affective psychotic disorders in older adults was generally substantially higher for those of black ethnicities compared with baseline populations (those of white British ethnicity) (Cochrane & Bal, 1987; Mitter et al., 2004; Reeves et al., 2001), whereas the pattern was less consistent among Asian migrants. For example, Mitter et al., (2004) reported a higher incidence among black elders in Tower Hamlets, 260 per 100kpy (95%CI: 55–750), compared with an incidence rate of 32 per 100kpy among white elders (95%CI: 20–45). Conversely, incidence was lower among Bangladeshi elders (25 per 100kpy; 95%CI: 4-89). A higher incidence of schizophrenia was reported among white migrants to New York State from other regions of the USA compared with those born in New York State between ages 65-74 years old, although this was not observed in those aged 75 years old and above (Malzberg, 1967).

2.3.3 Incidence by time period and study quality

Given the substantial heterogeneity observed between estimates, I examined whether the incidence of any outcomes varied by time period of case ascertainment or study quality. It was only possible to carry out meta-regressions on overall incidence rates of schizophrenia (N=11) and affective psychoses (N=5), due to insufficient data in other categories. Variation in study quality among these citations was slightly narrower than variation across citations included in the entire study [Study quality: Schizophrenia [N=11]: average (73%), high (27%).

Affective psychosis [N=5]: average (80%), high (20%). All citations [N=41]: poor (7%), average (71%) or high (22%)] (see Table 2.3).

Using random-effects meta-regressions, I found no evidence that study quality or time of case ascertainment (using mid-year) influenced incidence rates of schizophrenia or affective psychosis in those aged 65 and above [Study quality: Schizophrenia OR= 1.37 (95%CI: 0.32-6.78), Affective psychosis OR= 1.04 (95%CI: 0.74–1.49)], [Case ascertainment period: Schizophrenia OR= 0.92 (95%CI: 0.83–1.02), Affective psychosis OR= 1.00 (95%CI: 0.95-1.05)].

2.4 Discussion of findings from systematic review and meta-analysis

2.4.1 Summary of principal findings

In the largest systematic review of the incidence of very-late onset schizophrenia-like psychosis to date, there was evidence of a substantial burden of disorder which increased with age after 65 years old. This review revealed substantial heterogeneity in estimates of incidence, which may have been driven by the relative absence of robust epidemiological studies in this field compared with psychotic disorders with a more typical age-at-onset. Where the evidence was most consistent, there were higher rates of non-affective psychotic disorders, including schizophrenia in older women than men, and higher rates of non-affective psychotic disorders among migrants. The overall pooled incidence of affective psychosis reported in those over 65 years old was high. No epidemiological studies were identified which had investigated the incidence of VLOSLP by several putative risk factors, including socioeconomic status, social isolation or sensory impairments. Taken together, these findings point towards a lack of a robust epidemiological evidence base important in informing aetiology and public mental health about variation in the incidence of VLOSLP.

2.4.2 Strengths and weaknesses

To my knowledge this is the first study to systematically review the literature on the incidence of affective and non-affective psychotic disorders specifically among older adults. Strengths of this review include pre-registration and a thorough literature search involving comprehensive search terms, bibliography searches and contacting authors directly to

request additional data. Further, I used strict eligibility criteria, including only epidemiological studies focussed on new cases of psychotic disorders in old age.

There were several limitations inherent to the studies included in this review. First, many citations did not provide standard errors or confidence intervals around estimates, limiting insight into the precision of estimates and preventing the pooling of incidence rates. Second, variation in age bands across studies hindered my ability to pool some estimates. Third, although few studies were rated as poor, certain quality criteria were consistently lacking across studies. For example, only 30% of included studies attempted to validate diagnoses against operationalised research criteria, which may have affected their validity and contributed to the high levels of between-study heterogeneity observed here. Additionally, only 5% of studies took a population-based approach to case ascertainment, with reliance on hospital admissions common across studies, which may have led to underestimates of incidence.

Several limitations of the review should also be considered. First, pooled incidence rates should be interpreted cautiously, and alongside the narrative review, given high levels of heterogeneity between estimates. Second, due to the inclusion of only published English language papers, there was a possibility of missing relevant unpublished papers and those published in other languages, although findings from the funnel plot and Egger's test did not indicate publication bias. Third, although incidence was examined in relation to study quality, there was a high tendency to the mean among quality ratings, which may have influenced findings about the lack of association between incidence and study quality.

2.4.3 Meaning of findings

The lack of epidemiological research focussed on VLOSLP incidence highlights the need for further high quality, primary research examining incidence variation in relation to a range of potential risk factors for VLOSLP, including socio-economic status, sensory impairment, social isolation and traumatic life events. This could have important implications for our understanding of the aetiology of VLOSLP and could help to inform public mental health and service commissioning and planning.

The relatively low incidence of schizophrenia observed among older adults in this review (vis-à-vis younger adults) could reflect 'true' rates in this group. Overall rates of non-affective psychotic disorders identified in this review were substantially higher than those for schizophrenia alone, suggesting that older adults are more likely to be diagnosed with other non-affective psychotic disorders, perhaps due to atypical clinical presentation; such patients often present as highly delusional, but lacking negative symptoms and thought disorder (Pearlson et al., 1989). Alternatively, given that many included citations did not attempt to ascertain cases from the community and often relied on hospital admissions, it is possible that some studies underestimated the true incidence of very late-onset schizophrenia-like psychosis. This bias could be particularly problematic in older people experiencing psychotic phenomena, given that they may be less likely to contact services due to higher levels of functioning (Kay & Roth, 1961), and a lack of social contact (Castle & Murray, 1993). This study found relatively high rates of affective psychoses after age 65 years old, which again may reflect differing symptomatic presentation of psychotic disorders in later life.

The finding of higher incidence rates of non-affective psychotic disorders among older women compared with men distinguishes psychotic disorders with late-onset from those with a younger, more typical age-at-onset. Data from this review suggest that the previously identified peak in incidence among women in middle age (Coid et al., 2008; Häfner et al., 1993) may be maintained into older age. The mechanisms underlying the higher rates of psychotic disorder observed in middle aged and older women are unclear. It is possible that changing social roles and demands experienced by women in middle age and later in life could be implicated. Additionally, the anti-dopaminergic properties of oestrogen may operate as a protective factor against the development of psychotic disorders in younger women, and the drop in oestrogen in middle-age could lead to an increased risk of psychotic disorder (Häfner, 2003; Riecher-Rössler & Hafner, 1993).

VLOSLP incidence was generally higher among migrant groups than baseline populations, which corresponds with the literature on psychotic disorders in adults under age 65 (Kirkbride et al., 2012). Various potential explanations for this association have been put forward, including stressors experienced prior to, during, and post-migration (Cantor-Graae, Pedersen, McNeil, & Mortensen, 2003; Kirkbride et al., 2012; Morgan & Hutchinson, 2017;

Veling et al., 2007). Further research is needed to examine the association between migration and psychotic disorder incidence in older people and to explore whether migration imparts the same social stressors on older adults as at other ages.

2.4.4 Conclusion

This review highlighted a substantial and increasing incidence of disorder after 65 years old, with some evidence of higher rates in women and migrants. The dearth of research on other putative risk factors for VLOSLP, such as sensory impairments, socioeconomic status or social adversities highlight the need for further high-quality research designed to precisely delineate the descriptive epidemiology of different psychotic disorders in older adults using large population-based cohorts. Only via robust, evidence-based research will it be possible to provide appropriate mental health services for those who experience a first episode of psychosis later in life; this study provides some quantification of this burden, but suggests more research is urgently required given the ageing population profiles of many countries.

Chapter 3 Overview of Swedish population register data and cohort study methods

In order to address the gaps in the literature described in the introductory Chapter and the systematic review (Chapters 1 and 2), I conducted two cohort studies using Swedish population register data, presented in Chapters 4 and 5. Chapter 4 examines the incidence of and risk factors associated with very late-onset schizophrenia-like psychosis (VLOSLP), while Chapter 5 focusses on the association between VLOSLP and subsequent dementia (Chapter 5). In this Chapter, I overview the methods of the two cohort studies, including information about the Swedish population register data and the Psychiatry Sweden linkage, a description of the cohorts and study designs, and a general discussion around the use of population register data in epidemiological research. More detailed methods specific to each study, including information about exposure definition and statistical analyses, are presented in Chapters 4 and 5, respectively. Methods for the case-control study involving primary data collection, rather than the Swedish registers, are set out in Chapter 6.

3.1 Introduction to the Swedish population register data

Routinely collected register data, where available, plays a crucial role in evaluating and planning health care provision (Ludvigsson et al., 2016) and has become a core component of medical research (Olsen, 2011), with Sweden and other Nordic countries considered to be at the forefront (Nelson et al., 2016). For research purposes, administrative registers can provide longitudinal data on populations or particular subgroups, with the potential for a large number of observations and long follow-up periods, generally at lower cost than other forms of cohort study (Gissler, Marjo-Ritta, & Hemminki, 2000; Hemkens, Contopoulos-Ioannidis, & Ioannidis, 2016; Kane, Wellings, Free, & Goodrich, 2000).

The national registries in Sweden consist of highly complete data spanning several generations and totalling over 15 million people (Ludvigsson et al., 2016). These data have been utilised over several decades to estimate the incidence and prevalence of a range of medical conditions and to gain insight into the aetiology of various health outcomes by examining potential biological and social risk factors. The registers originated from the

Church of Sweden, which began keeping local parish registers in the 17th Century in order to collect tax and enrol soldiers, and later became the responsibility of the Swedish Tax Agency (Ludvigsson et al., 2016). Local population registers were digitalised in 1967, through which the Total Population Register was established (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekbom, 2009). Individuals can be linked across registers via a unique Personal Identification Number assigned at birth or at entry to Sweden, which was introduced in 1947. Register data is anonymised for research purposes and, importantly, the Swedish health care system is tax-funded, with the aim of providing health care accessed by the entire population. The Swedish registers contain detailed and comprehensive routinely collected socio-demographic data, including information about births, deaths, migration, civil status, education, occupation, income, geographic location and health outcomes across generations.

In the cohort studies set out in Chapters 4 and 5, I used data from Psychiatry Sweden, led by Professor Christina Dalman at the Karolinska Institute, which includes a group of linked registers specifically intended for mental health research. The linkage consists of all people born in 1932-2011 and their 1st and 2nd degree relatives. Those not included in this criterion, but who participated in the 1960 and 1965 censuses, and/or the Stockholm Public Health Survey were also included along with their 1st and 2nd degree relatives. In Table 3.1, I have described the registers used to create outcomes, exposures, and covariates in Chapters 4 and 5, including a description of each register and its coverage.

Table 3.1 Databases used in cohort studies (Chapters 4 and 5)

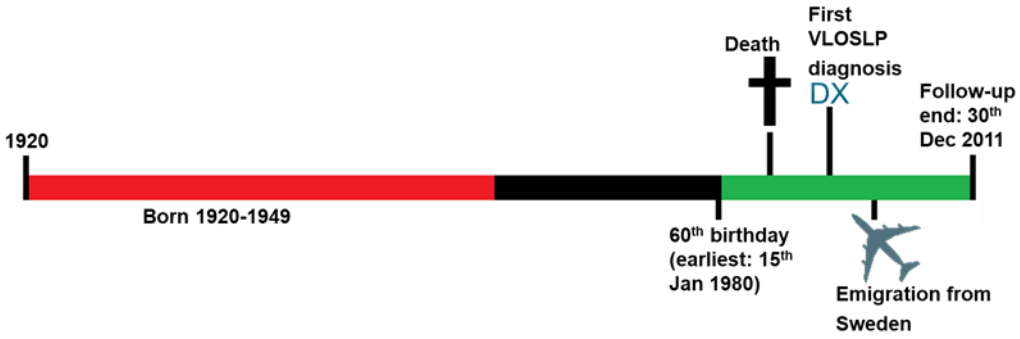
Databases used in this thesis	Description of register coverage and contents	Variables in Chapters 4 and 5
Register of Total Population (RTP)	The RTP is the base register for the total population of Sweden. It was established following the introduction of the Personal Identification Number in 1947 and is currently maintained by Statistics Sweden. The RTP has coverage from 1968-2011 and contains information about residency in Sweden, immigration, emigration, and region of birth.	In Chapters 4 and 5, the RTP was used to obtain demographic information on age, sex, birth date, region of birth and information about immigration and emigration.

Multi-Generation Register	The Multi-Generation Register contains information about the connection between people, for example: son, daughter, father, grandmother. Those registered in Sweden at any time since 1961 and who were born in 1932 or later have a link both to his/her parents and forward to their own children. For those born before 1932, data on parents are unavailable. By 2005, the register contained maternal information for 97% of the population and paternal information on 95% of individuals.	The Multi-Generation Register was used to link the cohort with their children to create the offspring psychotic disorder variable, and to create the death of a child variable in Chapter 4.
Population and Housing Census	The Population and Housing Census recorded information on employment and household every five years between the years 1960-1990, including individual and household information such as residency, housing, civil status, socioeconomic status and education. From 1990, this information was collected via the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA), see below.	I obtained data on partners of cohort members to create the death of a partner variable in Chapter 4.
Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA)	The LISA contains yearly recorded information on the labour market, education and social services for the total Swedish population aged 16 years and older, obtained via administrative registers (from 1990 to 2011). This includes work-related information such as employment, education, health insurance and income (from sources including welfare receipts, employers, savings and investments).	From the LISA, I obtained data on disposable income for both Chapters, the death of a partner for Chapter 4, and educational attainment for Chapter 5.
National Patient Register (NPR)	The National Patient Register began recording data on inpatient somatic diagnoses in 1964 and inpatient psychiatric diagnoses were recorded from 1974, with complete coverage from 1987. Recording of outpatient visits began in 1997, although coverage was not complete until 2007. The NPR contains information about the admission or visit, including diagnosis and admission date.	I used the NPR in both studies to obtain data on ICD diagnoses of non-affective psychotic disorders and dementia.
Cause of Death Register	The Cause of Death Register records causes and dates of death in Sweden since 1952, including those who have died in Sweden or abroad, although coverage is poorer for those who died abroad.	The Cause of Death Register was used to obtain data on dates of death for censoring in both studies and to examine mortality rates in Chapter 5.
Integration Register (STATIV)	In addition to the Total Population Register, the STATIV Register contains further information on integration, segregation and migration. Data became available in 1997 and are updated annually by Statistics Sweden. STATIV records around 95% of immigrations and 91% of emigrations within 30 days of the migration event, which is improving over time (Ludvigsson et al., 2016).	The STATIV was used to obtain data on immigration and emigration for censoring purposes and to define the region of birth variable in both studies.

3.2 Overview of cohorts and study designs

In both Chapters 4 and 5, I identified a cohort of individuals who were born between 1920 and 1949, although the outcomes and follow-up periods differed between Chapters, as described below. In Chapter 4, I aimed to characterise the incidence of non-affective psychotic disorders in individuals aged 60 years old and above and to examine variation in VLOSLP incidence in relation to potential social and environmental risk factors.

Figure 3.1 Cohort and follow-up period (Chapter 4)

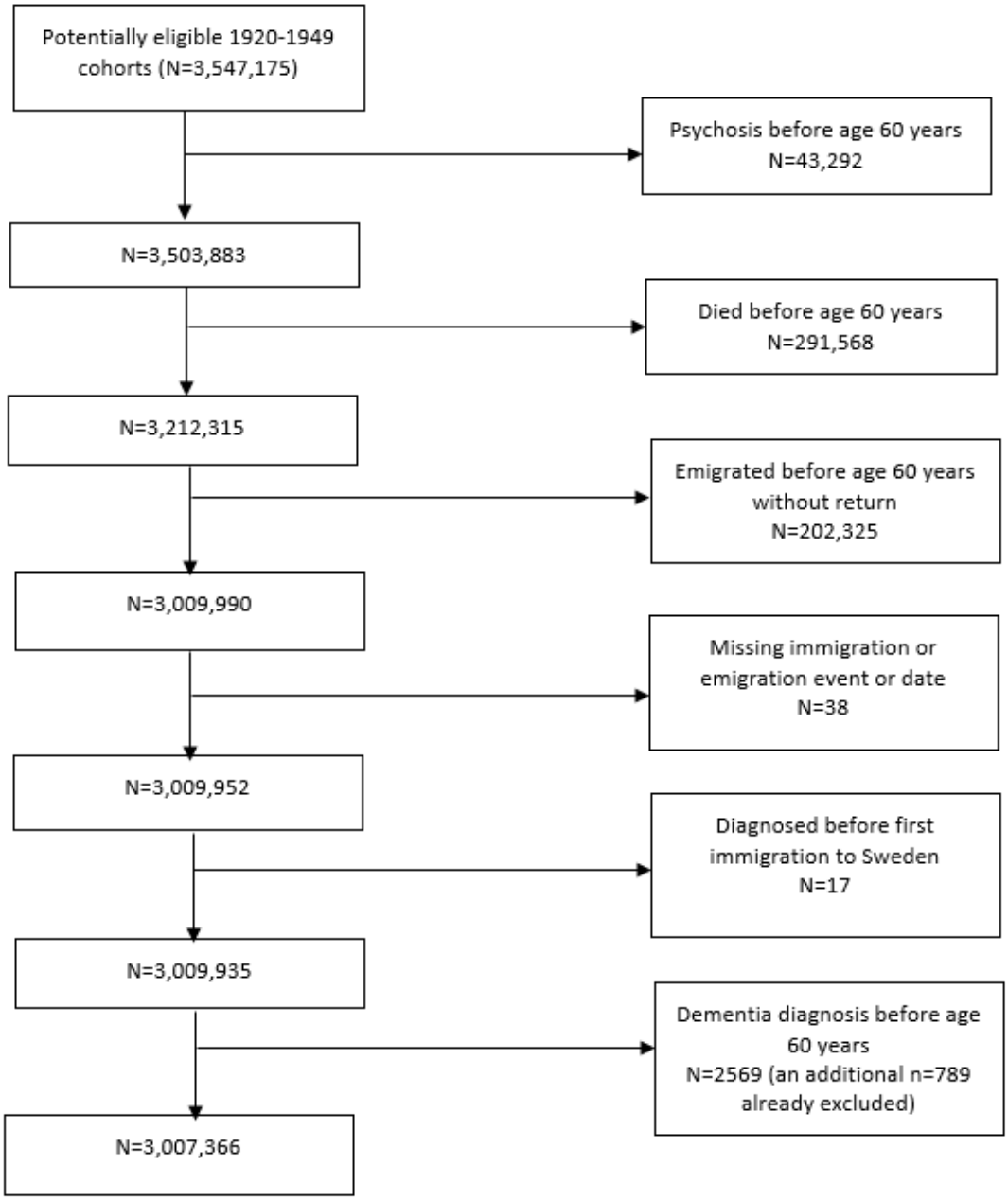


The follow-up period began from each participant's 60th birthday (earliest possible date: 15th January 1980). The cohort were followed up until the outcome (first recorded diagnosis of a non-affective psychotic disorder after age 60 years old; Table 3.2), or until death, emigration from Sweden without return, or until the end of the follow-up period on the 30th of December 2011, depending on which event occurred first (Figure 3.1). I excluded those who, before the age of 60 years: died, were diagnosed with a non-affective psychotic disorder or dementia, or those who emigrated from Sweden without returning (Figure 3.2).

In the second cohort study, described in Chapter 5, I investigated the rate of subsequent dementia in those with VLOSLP relative to an age- and calendar-period matched comparison group. In the same initial cohort of individuals born between 1920-1949, as set out above, I matched each individual with VLOSLP (first recorded non-affective psychotic disorder diagnosis after age 60 years old) to ten individuals without a recorded non-affective psychotic disorder diagnosis at any point in their life by age and calendar period (within the same year of birth). Matches for a given individual with VLOSLP were required to be alive, living in Sweden and free from dementia on the date of VLOSLP diagnosis for the individual

to whom they were matched. Individuals who did not meet these criteria for one individual with VLOSLP could still be considered as a match for other individuals with VLOSLP.

Figure 3.2 Exclusion process for cohort studies



Matching enabled me to assign an appropriate index date from which to follow up the comparison group (those without VLOSLP), while adjusting for age and calendar period. The follow-up period for the VLOSLP group began from the date of first recorded diagnosis with

a non-affective psychotic disorder after age 60 years old (earliest possible date: 15th January 1980), and the same date of entry was assigned to the age- and calendar-period matched comparisons (Figure 3.3). Both groups were followed up until the outcome (first recorded dementia diagnosis), or until death, emigration from Sweden or the end of the follow-up period (31st December 2011), whichever came first. Further information about study design and statistical analyses for the two cohort studies is presented in Chapters 4 and 5, respectively.

Figure 3.3 Cohort and follow-up period (Chapter 5)

3.3 Outcome definition

As described above, in Chapter 4, the outcome was time to first recorded diagnosis with a non-affective psychotic disorder after age 60 years old, while in Chapter 5, the outcome was time to first recorded dementia diagnosis (see Table 3.2 and Table 3.3 for a complete list of ICD codes). Outcome data were obtained from the Swedish National Patient Register (NPR) and included both inpatient and outpatient diagnoses. The NPR was established in 1964 for somatic diagnoses and included psychiatric diagnoses from 1973. The NPR contains records of approximately 70% of all psychiatric admissions in the healthcare system (excluding primary care) from 1970, 83% by 1973, 97% from 1974 to 1983, 80-95% from 1984 to 1986, and has been close to complete since 1987 (Zammit, Lewis, Dalman, & Allebeck, 2010). Recording of outpatient data began in 1997, although the outpatient registers were not considered to have full national coverage until 2007.

The Swedish registers have been used widely to investigate the incidence of non-affective psychotic disorders with a younger, more typical age-at-onset (e.g. Blomström et al., 2014;

Dykxhoorn, Hollander, Lewis, Dalman, & Kirkbride, 2019; Dykxhoorn, Hollander, Lewis, Magnusson, et al., 2019; Harlow et al., 2007; Price, Dalman, Zammit, & Kirkbride, 2018).

Table 3.2 VLOSLP ICD codes

	Diagnostic classification system	
ICD-10 codes 1997 onwards	**ICD-9 codes 1987-1996**	**ICD-8 codes 1969-1986**
F20.0: Paranoid schizophrenia	295A: Schizophrenia, simple type	295.0: Schizophrenia, simple type
F20.1: Disorganised schizophrenia	295B: Schizophrenia, disorganised type	295.1: Schizophrenia, hebephrenic type
F20.2: Catatonic schizophrenia	295C: Schizophrenia, catatonic type	295.2: Schizophrenia, catatonic type
F20.3: Undifferentiated schizophrenia	295D: Schizophrenia, paranoid type	295.3: Schizophrenia, paranoid type
F20.5: Residual schizophrenia	295E: Acute schizophrenic episode	295.4: Acute schizophrenic episode
F20.8: Other schizophrenia	295F: Borderline schizophrenic condition	295.5: Latent schizophrenia
F20.9: Schizophrenia, unspecified	295G: Chronic undifferentiated schizophrenia	295.6: Residual schizophrenia
F21: Schizotypal disorder	295H: Schizoaffective type	295.7: Schizoaffective type
F23: Brief psychotic disorder	295W: Other specified form of schizophrenia	295.8: Other specified type of schizophrenia
F24: Shared psychotic disorder	295X: Schizophrenia, unspecified	295.9: Unspecified schizophrenia
F25: Schizoaffective disorder	297A: Paranoid state, simple	297.0: Paranoid state, simple
F28: Other psychotic disorder not due to a substance or known physiological condition	297B: Delusional disorder	297.1: Paranoia
F29: Unspecified psychosis not due to a substance or known physiological condition	297C: Paraphrenia	297.2: Paraphrenia
	297D: Induced psychosis	297.3: Induced psychosis
	297W: Other specified paranoid conditions	297.8: Other specified paranoid state
	297X: Paranoid condition, unspecified	297.9: Unspecified paranoid state
	298C: Reactive state of confusion	298.2: Reactive confusion
	298E: Reactive paranoid psychosis	298.3: Acute paranoid reaction
	298W: Other specified reactive psychosis	298.4: Psychogenic paranoid psychosis
	298X: Reactive psychosis, unspecified	298.8: Other unspecified reactive psychosis
		298.9: Unspecified psychosis

Further, several studies have demonstrated high validity for schizophrenia and broader non-affective psychotic disorder diagnoses within the Swedish registers (Dalman & Cullberg, 2002; Ekholm et al., 2009; Jörgensen, Ahlbom, Allebeck, & Dalman, 2010; Ludvigsson et al., 2011). In a review examining the validity of diagnoses within the Swedish National Inpatient Register, non-affective psychotic disorder diagnoses were found to have high validity, although positive predictive values ranged from 56% to 95.5% between studies (Ludvigsson et al., 2011). However, it is important to note that the validity of non-affective psychotic disorder diagnoses first recorded in older people has not been assessed and requires investigation in future research.

As proposed in an international consensus on late-onset schizophrenia and VLOSLP, I defined VLOSLP using an age cut-off of after age 60 years old, whereas age 40 years old and above refers to late-onset schizophrenia (Howard et al., 2000). I took a broad definition of non-affective psychotic disorders, including all ICD-10 F20-F29 diagnoses (or earlier ICD equivalents) rather than only focusing on schizophrenia (F20) (Table 3.2). This broader approach is considered more valid than focussing solely on more narrowly defined diagnoses, such as schizophrenia, in those with a later age-at-onset (Hanssen et al., 2015; Riecher-Rössler, Hafner, Hafner-Ranabauer, Loffler, & Reinhard, 2003). It was only possible to include diagnosed psychotic disorders, as data on subthreshold psychotic symptoms were not available. Affective psychoses were not included as an outcome, given that VLOSLP specifically refers to non-affective psychotic disorders, whereas late-life affective disorders are considered to be separate conditions.

In Chapter 5, I examined the rate of subsequent dementia in those with VLOSLP (Table 3.3). I focussed on all-cause dementia, as previous studies suggest that misclassification between dementia subtypes is relatively common in the Swedish registers and that the positive predictive value is lower for diagnoses such as vascular dementia (Rizzuto et al., 2018).

Table 3.3 Dementia ICD codes

	Classification system	
ICD-10 codes **1997 onwards**	**ICD-9** **1987-1996**	**ICD-8** **1969-1986**
F00.1: Late onset Alzheimer's disease F00.2: Atypical/mixed Alzheimer's disease F00.9: Unspecified Alzheimer's disease F01: Vascular dementia F02: Dementia in other diseases classified elsewhere F03: Unspecified dementia G30: Alzheimer's disease G31.1: Senile degeneration of brain, not elsewhere classified G31.8: Lewy body dementia	290A: Senile dementia 290B: Presenile dementia 290E: Multi-infarct dementia 290W: Other specified senile dementia 290X: Dementia associated with aging, unspecified 291C: Alcohol-related dementia 294B: Dementia in somatic disease classified elsewhere 331A: Presenile and senile Alzheimer's degeneration 331B: Pick's disease	290.0: Senile dementia, simple type 290.1: Presenile dementia 290.2: Senile dementia, depressed or paranoid type 290.3: Senile dementia with acute confusional state 290.4: Arteriosclerotic dementia 290.8: Other senile and presenile organic psychotic conditions 290.9: Unspecified senile and presenile organic psychotic conditions

Nonetheless, for descriptive purposes, I also categorised dementia diagnoses into the following subtypes: Alzheimer's disease, vascular dementia, dementia due to a medical comorbidity, dementia related to alcohol use, frontotemporal dementia, Lewy body dementia and dementia unspecified.

The most recent validation study to date in this area examined the ascertainment of dementia cases within the Swedish registers in comparison to population-based cohorts in Sweden, including the following: Dementia in Swedish Twins (HARMONY), The Kungsholmen Project (KP), The Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) Care System Study, The Swedish Adoption/Twin Study of Aging (SATSA), Origin of Variances in the Oldest-Old: Octogenarian Twins (OCTO-twin) and Gender Differences in Health Behaviour and Health among Elderly (GENDER) (Rizzuto et al., 2018). The specificity of dementia diagnoses in the National Patient Register was found to be high at around 99%, suggesting that cases of dementia identified in the registers are likely to be true cases (Rizzuto et al., 2018). By contrast, the sensitivity was low, with only around half of true dementia cases detected by the registers. This corresponds with previous validation studies of dementia in the Swedish registers which reported high specificity but low sensitivity (Dahl, Berg, & Nilsson, 2007; Jin, Gatz, Johansson, & Pedersen, 2004). These findings are also in line with many other diagnoses within the registers, where sensitivity tends to be lower than specificity (Ludvigsson et al., 2011). The finding of low sensitivity of dementia diagnosis within the registers is perhaps unsurprising given that dementia tends to be diagnosed clinically and is unlikely to be the primary cause of hospitalisation (Rizzuto et al., 2018). Additionally, the same validation study reported that dementia diagnoses appear in the National Patient Register on average 5.5 years after the diagnosis is first received, although this gap appears to be reducing over time (Rizzuto et al., 2018).

3.4 Broad strengths and limitations of data source

In this section, I discuss general strengths and limitations of register-based studies which are relevant to the two Swedish cohort studies described above, while study-specific strengths and limitations are described in detail in Chapters 4 and 5. Population register data has several clear benefits for epidemiological research. First, administrative data can be hugely

time- and cost-saving, given that data are routinely collected, rather than being collected by individual research teams. Additionally, administrative data are less likely to be compromised by selection and attrition bias, or bias associated with self-report, such as recall bias (Thygesen & Ersbøll, 2014).

Importantly, register data often allows for a large number of observations, potentially including data on an entire population, and across a range of domains. This allows for large sample sizes, providing good statistical power and the opportunity to study rare outcomes, including VLOSLP. Using the Swedish population register data, I obtained data on a cohort of over three million individuals, and I was able to identify over 17,000 incident cases with VLOSLP over the follow-up period. Data on this scale is almost unprecedented within the VLOSLP literature, particularly given the comprehensiveness and completeness of the Swedish register data, and the opportunity for linkage with registers containing demographic, social and environmental data. This allowed examination of the overall incidence of VLOSLP and investigation of variation in incidence in relation to a range of potentially important risk factors. However, it should be noted that in register studies involving very large sample sizes, it is likely that many of the comparisons of interest tested will be statistically significant and researchers must therefore consider whether these associations are likely to be meaningful clinically or at policy-level (Simon, 2019).

Research involving register data can also support longitudinal data analysis with long follow-up periods, which provides insight into the temporal relationship between exposure and outcome and is particularly important when there is a long latency period between exposure and disease expression. As described in Chapter 5, this allowed examination of the relationship between VLOSLP and subsequent dementia, which is important given the long preclinical phase preceding dementia (Villemagne et al., 2013). Long follow-up periods and linkage between family members using register data also allows the study of health across generations. In the cohort studies, although I was not able to link the cohort with their parents, it was possible to link individuals with their children, providing some insight into familial risk of psychotic disorder.

On the other hand, studies involving population register data are subject to many of the same limitations as other observational epidemiology studies, and correspondingly, they require carefully considered designs to minimise the potential for bias and confounding. As with other observational studies, there are significant challenges around inferring causality (Rothman & Greenland, 2005). It is also important to note that, although register data may allow large sample sizes, this does not necessarily mean that findings will generalise across settings. There may be substantial differences depending on region, time period and diagnostic trends (Simon, 2019).

Importantly, the quality of register-based studies depends heavily on data availability, and the quality, completeness and validity of recording in the registers (Weiss, 2011). For instance, in the two cohort studies described in this Chapter, it was only possible to ascertain cases with VLOSLP after the date that hospital diagnoses were first routinely recorded in the registers. Hence, in the cohort studies, those diagnosed with a non-affective psychotic disorder before the registers began recording psychiatric diagnoses will be classified as healthy, and therefore any re-admission for psychotic disorder will be wrongly categorised as incident psychosis. This may have led to overestimates of VLOSLP incidence, especially in the first few years after registration began. I also lacked data on previous histories of psychotic disorder for those who migrated to Sweden, thus potentially over-estimating incidence among immigrants to Sweden. I conducted sensitivity analyses to try to mitigate against these potential sources of bias, which are discussed in Chapters 4 and 5.

In terms of completeness, data on important exposures or confounders are often not routinely recorded and are therefore not available within register data. In some cases, these can be indexed by proxy variables, although these may only crudely capture the variable of interest, leading to residual confounding (Weiss, 2011). Misclassification is another potential issue within register data. For instance, in Chapters 4 and 5, it was not possible to rule out the possibility of misclassification of VLOSLP as dementia, and the reverse. Additionally, there may be underreporting or recording of some health conditions in the register data. This may have influenced the prevalence of sensory impairment detected in Chapter 4, for example. More generally, there may be issues around relying on diagnosed psychotic disorders in older adults, given that those with those with VLOSLP may be less likely to

contact services than those with younger, more typical age-at-onset psychotic disorders (Castle & Murray, 1993). The ways in which these limitations may have influenced results, along with more specific strengths and limitations of each study, are discussed in detail in Chapters 4 and 5, and in the discussion section (Chapter 7).

In this Chapter, I overviewed the methods for two cohort studies involving Swedish population register data, which focus on the incidence of VLOSLP, potential risk factors for VLOSLP (Chapter 4), and the association with subsequent dementia (Chapter 5). In the following Chapters (Chapters 4 and 5), I present and discuss the findings of these studies, in addition to providing more detailed information about methods specific to each study.

Chapter 4 The incidence of non-affective, non-organic psychotic disorders in older people: a population-based cohort study of 3 million people in Sweden

A modified version of this Chapter was published in Schizophrenia Bulletin:
Stafford, J., Howard, R., Dalman, C., & Kirkbride, J. B. (2018). The Incidence of Nonaffective, Nonorganic Psychotic Disorders in Older People: A Population-based Cohort Study of 3 Million People in Sweden. *Schizophrenia Bulletin*, *45*(5), 1152-1160.

4.1 Introduction

As demonstrated in the systematic review presented in Chapter 2, the epidemiology of very late-onset schizophrenia-like psychosis (VLOSLP) has been less well-characterised than psychotic disorders with a younger, more typical age-at-onset (Stafford, Howard, & Kirkbride, 2018). While there is consistent evidence that VLOSLP is more common in women than men (Howard, Almeida, & Levy, 1994), whether rates vary by age, migration, or other potential social determinants of risk, such as traumatic life events or social isolation, remains largely unexamined.

Previous findings with respect to age have been mixed, showing both increased (Van Os et al., 1995) and decreased rates of VLOSLP with advancing age (Andersen & Hynnekleiv, 2007; Bland, 1977; Pedersen et al., 2014). It is also unclear whether these patterns differ between men and women. In line with the literature on psychotic disorder incidence in younger adults (Kirkbride et al., 2012; McGrath et al., 2004), several studies have also reported higher risk among migrants (Mitter et al., 2004; Reeves et al., 2001), but this literature remains sparse, particularly outside of the UK. Indeed, in general, the VLOSLP literature has predominantly consisted of small-scale, cross-sectional studies. While these have led to the identification of several potential risk factors, including sensory impairments (Cooper et al., 1974), social isolation, premorbid schizotypal traits (Kay & Roth, 1961; Pearlson et al., 1989), and traumatic life events (Fuchs, 1994, 1999; Gurian et al., 1992; Reulbach et al., 2007),

results have not been consistently replicated (Brunelle et al., 2012). Epidemiological investigation in large, population-based longitudinal studies is largely lacking, with limited exceptions (Pedersen et al., 2014). Older people have consistently been excluded from studies which have elucidated a robust set of risk indicators for psychotic disorders at younger ages (Hollander et al., 2016; Mortensen et al., 1999; Richardson, Hameed, Perez, Jones, & Kirkbride, 2018; Zammit, Lewis, Rasbach, et al., 2010).

The principal aim of this study was to delineate the epidemiology of VLOSLP in a national, population-based cohort of people living in Sweden since 1920. I examined variation in incidence rates by potential risk factors for VLOSLP, as discussed in Chapters 1 and 2, hypothesising that advanced age, female sex, migrant status, lower socio-economic status (SES), family history of psychotic disorders, sensory impairment, gestational exposure to World War II (WWII) (which could confer risk, *in utero*, via nutritional deficiencies or maternal trauma), social isolation and experiencing the death of a partner or child would be associated with a higher rate of VLOSLP.

4.2 Methods

4.2.1 Study design and setting

Using the Psychiatry Sweden linkage described in Chapter 3, I established a longitudinal cohort of individuals born between 1920 and 1949, and living in, or who immigrated to, Sweden on or after their 60th birthday. Participants were followed from their 60th birthday (earliest: January 15th 1980) until the end of follow-up (30th December 2011), emigration from Sweden, dementia diagnosis, death or first recorded non-affective psychotic disorder diagnosis, whichever came first. As detailed in Chapter 3, I excluded those who: died before age 60 years old, emigrated from Sweden before age 60 years old without return, or were diagnosed with dementia before diagnosis with a psychotic disorder.

4.2.2 Outcome

I identified all participants recorded in the Swedish National Patient Register diagnosed with a non-affective psychotic disorder according to the International Classification of Diseases,

Revisions 8-10 (ICD-8, -9, -10) since 1980. In Chapter 3, I provided a full list of ICD codes and further detail about the Swedish National Patient Register.

4.2.3 Exposures

Exposures included age, sex, region of birth, birth period, disposable income at age 60 years old, family history of psychotic disorder, death of a partner in the two years before study entry, death of a child and hearing and visual impairments. Data on age, sex, birth period and region of birth were obtained from the Swedish Register of the Total Population. I categorised region of birth into the following groups: Sweden, Africa, Asia, North America, Europe, Finland, South America, Oceania, Middle East, Russia-Baltic and 'Other'. To investigate the possible role of gestational exposure to maternal stressors experienced during World War II (WWII: 1st Sep 1939-2nd Sep 1945), a typical gestation of 40 weeks was assumed (280 days). All participants born from the first day of WWII (1st Sep 1939), up until 279 days after the end of the war (2nd Sep 1945 + 279 days = 8th June 1946) were classified as having had some gestational exposure to WWII. Date of birth in the Register of the Total Population is only available for research purposes for the month and year of birth, with all participants given a birthday of the 15th of their birth month. For this reason, the gestational exposure definition excluded all people born in June 1946, making the gestational exposure window effectively Sep 1945 – May 1946. Remaining participants were coded to the following birth periods, based on their date of birth: 1920-1924, 1925-1929, 1930-1933, 1934-Aug 1939, June 1946-1949.

The disposable income variable grouped individuals into quartiles, based on all cohort members with disposable income from all sources (employment, welfare receipts, savings, investments) at age 60 years old recorded in the same calendar year, using data from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA). Using administrative registers, the LISA collects information annually on work-related information such as income, employment, education and insurance for the total Swedish population aged 16 years old and above. Participants were linked to their children via the Multigenerational Register to derive a measure of psychotic disorder family history, based on whether their biological children had ever received a psychotic disorder diagnosis. This register was linked to the Cause of Death Register to obtain data on death of a child

(biological and adopted) prior to cohort exit, before child age 12 months or age 18 years old. These exposures were grouped as follows: “Had children, no child death” (reference exposure), “Had no children”, and “Death of at least one child”.

I also created a variable on the death of a partner in the two years preceding cohort exit, using Census data (before 1990) or the LISA database thereafter, linked to the Cause of Death Register. Two assumptions were made to allow definition of partner deaths in the two years prior to cohort exit. First, prior to the LISA, information on partner status was only available from quinquennial census data (i.e. 1985, 1980, 1975). I therefore assumed that for participants who exited the cohort prior to 1990, their partner status was consistent with their last census entry (i.e. someone who left the cohort between the years 1986-1989 would be coded according to their partner status in the 1985 census). Second, the exact date at which partner status was recorded (via Census or the LISA) was not given, therefore partner status recorded in a given year was assumed to apply for the whole year. This variable was grouped as follows: “Had a partner, but did not experience partner death (reference exposure)”; “Death of one or more partners”, and “Had no partner”. Binary hearing and visual impairment variables were created using diagnoses from the National Patient Register recorded before cohort exit (ICD codes: Table 4.1).

Table 4.1 Hearing and visual impairment ICD codes

Classification system	Years	Codes
ICD-10	1997 - 2011	**Hearing impairment:** H90, H91, H80, Z46.1, Z82.2, Z96.2 **Visual impairment:** H25, H31.1, H33, H34, H35.3, H35.4, H36, H40, H42, H44.5, H54, Z44.2, Z82.1, Z90.01, Z97.0
ICD-9	1987 – 1996	**Hearing impairment:** 389, 387, 95.48, V19C, V53.2, Z97.4 **Visual impairment:** 360.41, 361, 362.0, 362.3, 362.5, 362.6, 363.4, 365, 366, 368, 369, V19A, V41A, V42F, V43A, V45.G, V52C, V53B

4.2.4 Missing data

Missing data was limited to income. Where possible, I included income data at age 55-59 for those missing data at age 60 years old (N=21,325, 0.72%). I conducted complete-case

analyses, dropping those with remaining missing data on income from analyses (1.7%) (Table 4.2).

Table 4.2 Missing data (disposable income at age 60 years old)

	Missing, N (%), Cohort N=3,007,366	**χ^2 p-value**
Sex:		P≤.001
Men	26,779 (1.79)	
Women	24,796 (1.64)	
Region of birth:		P≤.001
Africa	1,580 (23.75)	
Asia	5,546 (23.68)	
North America	719 (11.41)	
Europe	16,733 (9.38)	
Sweden	22,213 (0.84)	
South America	733 (8.28)	
Middle East	1,302 (11.42)	
Russia-Baltic	766 (5.38)	
Finland	1,983 (1.69)	
Birth period:		P≤.001
1920-4	3,079 (0.60)	
1925-9	7,650 (1.73)	
1930-4	8,791 (2.11)	
1934-August 1939	8,033 (1.94)	
WW2-May 1946	13,135 (1.71)	
Post WW2-1949	10,887 (2.40)	
Child with a psychotic disorder:		P≤.001
Yes	51,228 (1.74)	
No	347 (0.49)	
Death of a child in infancy:		P≤.001
Had no children	40,313 (8.41)	
No children died	11,158 (0.45)	
1+ child died	104 (0.30)	
Death of a child aged 12m-18 years		P≤.001
Had no children	40,313 (8.41)	
No children died	11,187 (0.45)	
1+ child died	75 (0.30)	
Death of a partner two years before date of exit:		P≤.001
Had no partner	38,324 (2.84)	
Had partner, no partner died	12,734 (0.80)	
1 or more partners died	517 (0.70)	
Visual impairment		P≤.001
No	51,378 (1.72)	
Yes	197 (1.14)	
Hearing impairment		P≤.001
No	50,416 (1.78)	
Yes	1,159 (0.65)	

4.2.5 Statistical analysis

I analysed the data using survival analysis, a group of methods for analysing data when the outcome is time to a given event. A survival analysis approach was considered appropriate to allow for censoring, in which people come into and out of the study at different times, all contributing to person-years at-risk. Specifically, I analysed the data using Cox Proportional Hazards regression (Cox, 1972), a semi-parametric method in which rates are measured instantaneously over time. This allowed me to model survival in the context of time to VLOSLP diagnosis in relation to exposures of interest, reported using hazard ratios (HR) with 95% confidence intervals (95%CI). Initially, I examined univariable associations between each exposure and the outcome, recording the overall fit of each model using Akaike's Information Criterion (AIC), where low scores indicated better fit. Using a forward-fitting modelling strategy, I added variables with the lowest AIC scores to a multivariable model with age, sex and their interaction included as *a priori* confounders. Model building was tested via likelihood ratio test (LRT). Age was modelled as a time-varying covariate using Lexis expansion to examine age at-risk during follow-up, which was grouped into five-year age bands between ages 60-90 years old and above. In sensitivity analyses I excluded migrants diagnosed with a psychotic disorder within two years of immigration to Sweden to mitigate the possibility of including prevalent cases in the sample. Additionally, I conducted a sensitivity analysis to examine any differences in results after excluding those diagnosed with dementia within two years of diagnosis with VLOSLP, given that these individuals may be more likely to be experiencing VLOSLP as part of the dementia prodrome. A major assumption of Cox regression is that hazards are constant over time, referred to as the proportional hazards assumption. I examined this assumption first by visually inspecting survival curves and Schoenfeld residuals plots and then by formally testing the assumption via Schoenfeld residuals tests (Schoenfeld, 1982). Where there was evidence of violation of the proportional hazards assumption for a given exposure, I reported the hazard ratios stratified by time. Analyses were conducted using STATA version 14.

4.3 Results

From 3,007,366 people, contributing 39,301,407 person-years of follow-up time, I identified 17,538 cases diagnosed with VLOSLP during the follow-up period, corresponding to a crude

incidence rate of 44.61 per 100,000 person-years at-risk (95%CI: 43.95–45.27). After excluding participants with missing income data (1.7%), 2,955,791 cohort members were retained, including 17,378 cases. Median age-at-first diagnosis of VLOSLP was 68 for men (interquartile range (IQR)=64-74) and 70 for women (IQR=65-77; Mann-Whitney p≤0.001). Compared with the remainder of the population, individuals with VLOSLP were more likely to be women (60% vs. 50%), from the lowest income quartile (38% vs. 22%), have no children (32% vs. 15%), have children with a psychotic disorder (5% vs. 2%), have no partner in the two years before cohort exit (65% vs. 44%), be born outside of Sweden (15% vs. 11%) and be born in the oldest birth period (Table 4.3; all p≤0.001).

Table 4.3 Participant characteristics

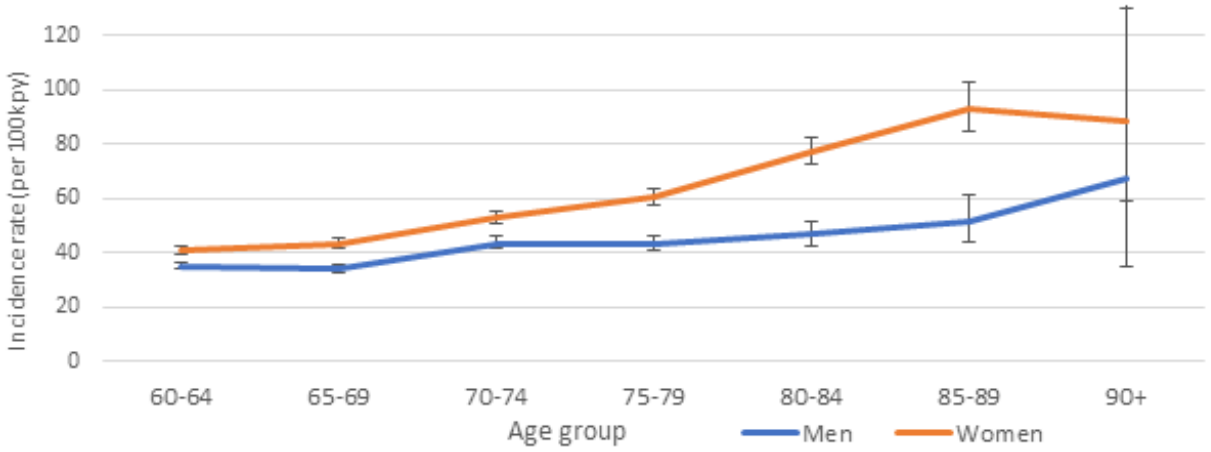
	All participants born in Sweden between 1920-1949 (N= 2,955,791)		
	Population at-risk (N= 2,938,413, 99.5%) N (%)	**Cases (N= 17,378, 0.5%), N (%)**	**χ^2 test**
Sex:			
Men	1,459,136 (49.66)	7,036 (40.49)	$\chi^2(1)=581.03$, P≤.001
Women	1,479,277 (50.34)	10,342 (59.51)	
Region of birth:			
Sweden	2,604,005 (88.62)	14,777 (85.03)	$\chi^2(8)=338.07$, P≤.001
Africa	5,031 (0.17)	41 (0.24)	
Asia, Oceania and other	17,781 (0.61)	91 (0.52)	
North America	5,536 (0.19)	44 (0.25)	
Europe	160,345 (5.46)	1,244 (7.16)	
South America	8,074 (0.27)	42 (0.24)	
Middle East	10,060 (0.34)	37 (0.21)	
Russia-Baltic	13,312 (0.45)	171 (0.98)	
Finnish	114,269 (3.89)	931 (5.36)	
Birth period:			
1920-4	502,893 (17.11)	6,421 (36.95)	$\chi^2(5)=7600$, P≤.001
1925-9	431,322 (14.68)	3,834 (22.06)	
1930-4	405,530 (13.80)	2,660 (15.31)	
1934-August 1939	404,006 (13.75)	1,833 (10.55)	
WW2-May 1946	752,605 (25.61)	2,071 (11.92)	
Post WW2-1949	442,057 (15.04)	559 (3.22)	
Disposable income at age 60:			
Lowest quarter	645,286 (21.96)	6,633 (38.17)	$\chi^2(3)=5100$, P≤.001
Second quarter	638,310 (21.72)	5,492 (31.60)	
Third quarter	817,553 (27.82)	3,268 (18.81)	
Highest quarter	837,264 (28.49)	1,985 (11.42)	

Child with a psychotic disorder:			
Yes	69,013 (2.35)	901 (5.18)	$\chi^2(1)=601.70$, P≤.001
No	2,869,400 (97.65)	16,477 (94.82)	
Death of child under 12 months:			
No children died aged under 12 months	2,471,308 (84.10)	11,620 (66.87)	$\chi^2(2)= 4300$, P≤.001
Had no children	433,145 (14.74)	5,628 (32.39)	
1 or more children died	33,960 (1.16)	130 (0.75)	
Death of child aged 12 months-18 years:			
No children died aged 12m–18 years	2,480,332 (84.41)	11,628 (66.91)	$\chi^2(2)= 4300$, P≤.001
Had no children	433,145 (14.74)	5,628 (32.39)	
1 or more children died aged 12m–18 years	24,936 (0.85)	122 (0.70)	
Partner death two years before date of exit:			
Had no partner	1,301,027 (44.28)	11,235 (64.65)	$\chi^2(2)=3100$, P≤.001
Had partner, no partner died	1,564,647 (53.25)	5,624 (32.36)	
1 or more partners died	72,739 (2.48)	519 (2.99)	
Visual impairment			
Visual impairment	16,945 (0.58)	77 (0.44)	$\chi^2(1)=5.38$, P=0.20
No visual impairment	2,921,468 (99.42)	17,301 (99.56)	
Hearing impairment			
Hearing impairment	176,146 (5.99)	474 (2.73)	$\chi^2(1)=328.20$, P≤.001
No hearing impairment	2,762,267 (94.01)	16,904 (97.27)	

4.3.1 Incidence by age and sex

I observed a significant interaction between age and sex in crude and fully adjusted analyses (adjusted model LRT: $\chi^2(6)=49.31$, p<.001), suggesting that VLOSLP incidence increased with age for men and women, but at a quicker rate for women after age 80 years old (Figure 4.1).

Figure 4.1 Incidence rates of very late-onset schizophrenia-like psychosis by age and sex



[a]Crude incidence rates of VLOSLP per 100,000 person-years at-risk (100kpy) by age and sex

4.3.2 Proportional hazards modelling

After adjustment for age and sex, I observed associations between almost all variables of interest and risk (hazard) of being diagnosed with VLOSLP (Adjustment 1, Table 4.4). Full adjustment following multivariable model building led to some attenuation in observed associations (Table 4.4), but most risk factors remained associated with VLOSLP.

Table 4.4 Association between potential risk factors and VLOSLP hazard ratios

	Adjustment 1 HR (95%CI)[a]	**Adjustment 2 HR (95%CI)[b]**
Offspring with non-affective psychotic disorder (NAPD) (ref: no offspring with NAPD)	2.06 (1.92 – 2.20)	2.45 (2.29 – 2.62)
Region of birth (ref: Sweden)		
Africa	2.63 (1.94 – 3.58)	1.96 (1.44 – 2.66)
Asia, Oceania and other	1.48 (1.20 – 1.82)	0.99 (0.80 – 1.22)
North America	1.36 (1.01 – 1.83)	1.25 (0.93 – 1.68)
Europe	1.53 (1.44 – 1.62)	1.33 (1.25 – 1.41)
South America	1.54 (1.14 – 2.08)	1.09 (0.80 – 1.47)
Middle East	0.89 (0.65 – 1.23)	0.67 (0.49 – 0.93)
Russia-Baltic	1.93 (1.66 – 2.24)	1.77 (1.52 – 2.05)
Finland	1.69 (1.58 – 1.81)	1.61 (1.51 – 1.72)
Birth period (ref: 1920-1924)		
1925 - 1929	0.76 (0.73 – 0.80)	0.79 (0.76 – 0.82)
1930 - 1934	0.67 (0.64 – 0.70)	0.77 (0.73 – 0.80)
1934 - August 1939	0.60 (0.57 – 0.64)	0.73 (0.70 – 0.78)
Sep 1939 - May 1946 (gestational exposure to WWII)	0.62 (0.58 – 0.65)	0.84 (0.80 – 0.89)
Jun 1946 - 1949	0.62 (0.57 – 0.68)	0.89 (0.81 – 0.98)
Disposable income at age 60 (ref: highest quartile (4)		
Income quartile 1 (lowest)	3.30 (3.13 – 3.48)	2.82 (2.67 – 2.97)
Income quartile 2	2.93 (2.78 – 3.08)	2.51 (2.38 – 2.65)
Income quartile 3	1.56 (1.47 – 1.65)	1.43 (1.35 – 1.51)
Death of child (ref: had children, none died):		
Had no children	2.87 (2.78 – 2.96)	2.55 (2.47 – 2.64)
1 or more children died aged under 12 months	1.08 (0.91 – 1.28)	1.17 (0.99 – 1.39)
1 or more children died aged 12 months – 18 years	1.02 (0.86 – 1.22)	1.00 (0.84 – 1.20)
Death of partner 2 years before date of exit (ref: no partner died)		
Had no partner	1.77 (1.72 – 1.83)	1.32 (1.28 – 1.37)
1 or more partners died	1.23 (1.12 – 1.35)	1.03 (0.94 – 1.13)
Visual impairment (ref: no visual impairment)	0.52 (0.42 – 0.65)	0.51 (0.41 – 0.64)
Hearing impairment (ref: no hearing impairment)	0.38 (0.35 – 0.42)	0.43 (0.39 – 0.47)

[a]Adjustment 1 Adjusted for age, sex and their interaction
[b]Adjustment 2 Adjusted for age, sex, their interaction, and all exposures included in this table

For example, migrants from Africa (HR: 1.96; 95%CI: 1.44-2.66), Europe (HR: 1.33, 95%CI: 1.25-1.41), Russian-Baltic regions (HR: 1.77, 95%CI: 1.52-2.05) and Finland (HR: 1.61, 95%CI:

1.51-1.72) were at elevated VLOSLP risk after adjusting for all other covariates, including disposable income at age 60. Those born in later birth periods were less likely to receive a diagnosis of VLOSLP compared with those born in 1920-1924. Lower disposable income at age 60 was strongly associated with future risk of VLOSLP, with the highest rates in those in the lowest income quartile (HR: 2.82, 95%CI: 2.67-2.97). Participants whose children had a history of psychotic disorder were over twice as likely to be diagnosed with VLOSLP than those without such a family history (HR: 2.45; 95%CI: 2.29-2.62), as were those without children (HR: 2.55, 95%CI: 2.47-2.64), and the rate of VLOSLP was also higher among participants without a partner two years prior to cohort exit (HR: 1.32, 95%CI: 1.28-1.37).

Death of a partner was weakly associated with increased risk of VLOSLP in partially adjusted analyses, but this was attenuated after adjusting for confounders (HR: 1.03, 95%CI: 0.94-1.13). There was weak evidence that those who lost a child in infancy were more likely to be diagnosed with VLOSLP than those with children who did not die in infancy (HR: 1.17, 95%CI: 0.99-1.39), although death of a child before age 18 years old was not associated with VLOSLP risk. Contrary to hypotheses, those with a history of sensory impairment were less likely to receive a diagnosis of VLOSLP (visual impairment HR: 0.51; 95%CI: 0.41-0.64, hearing impairment HR: 0.43, 95%CI: 0.39-0.47); this finding was independently present in the domains of visual impairment and hearing loss.

4.3.3 Sensitivity analysis

Results from a sensitivity analysis excluding migrants who were diagnosed with a non-affective psychotic disorder within two years of arrival to Sweden, and who may have been prevalent cases with psychotic disorder, led to slight attenuations in the rate of VLOSLP among migrants relative to those born in Sweden, most notably in migrants from Africa (fully adjusted sensitivity analysis HR: 1.42, 95%CI: 0.98-2.04) (Table 4.5). The rate of VLOSLP remained higher in migrants from Finland, Russian-Baltic regions, Europe, and North America.

Table 4.5 Migration sensitivity analysis

	Adjustment 2 HR (95%CI)[b]	Sensitivity analysis HR (95%CI)[a,b]
Offspring non-affective psychotic disorder (NAPD) (ref: no offspring with NAPD))	2.45 (2.29 – 2.62)	2.45 (2.29 – 2.62)
Region of birth (ref: Sweden)		
Africa	1.96 (1.44 – 2.66)	1.42 (0.98 – 2.04)
Asia, Oceania and other	0.99 (0.80 – 1.22)	0.81 (0.64 – 1.02)
North America	1.25 (0.93 – 1.68)	1.14 (0.83 – 1.55)
Europe	1.33 (1.25 – 1.41)	1.15 (1.08 – 1.22)
South America	1.09 (0.80 – 1.47)	0.89 (0.64 – 1.25)
Middle East	0.67 (0.49 – 0.93)	0.55 (0.39 – 0.80)
Russia-Baltic	1.77 (1.52 – 2.05)	1.53 (1.31 – 1.80)
Finland	1.61 (1.51 – 1.72)	1.39 (1.29 – 1.50)
Birth period (ref: 1920-1924)		
1925 - 1929	0.79 (0.76 – 0.82)	0.79 (0.76 – 0.83)
1930 - 1934	0.77 (0.73 – 0.80)	0.77 (0.73 – 0.80)
1934 - August 1939	0.73 (0.70 – 0.78)	0.74 (0.70 – 0.78)
Sep 1939 - May 1946 (gestational exposure to WWII)	0.84 (0.80 – 0.89)	0.83 (0.79 – 0.88)
Jun 1946 - 1949	0.89 (0.81 – 0.98)	0.85 (0.77 – 0.93)
Disposable income at age 60 (ref: highest quartile (4))		
Income quartile 1 (lowest)	2.82 (2.67 – 2.97)	2.78 (2.63 – 2.93)
Income quartile 2	2.51 (2.38 – 2.65)	2.47 (2.34 – 2.60)
Income quartile 3	1.43 (1.35 – 1.51)	1.41 (1.34 – 1.50)
Death of child (ref: had children, none died):		
Had no children	2.55 (2.47 – 2.64)	2.56 (2.47 – 2.65)
1 or more children died aged under 12 months	1.17 (0.99 – 1.39)	1.19 (1.00 – 1.41)
1 or more children died aged 12 months – 18 years	1.00 (0.84 – 1.20)	1.01 (0.85 – 1.21)
Death of partner 2 years before date of exit (ref: no partner died)		
Had no partner	1.32 (1.28 – 1.37)	1.32 (1.28 – 1.37)
1 or more partners died	1.03 (0.94 – 1.13)	1.04 (0.95 – 1.14)
Visual impairment (ref: no visual impairment)	0.51 (0.41 – 0.64)	0.52 (0.41 – 0.64)
Hearing impairment (ref: no hearing impairment)	0.43 (0.39 – 0.47)	0.43 (0.39 – 0.47)

[a]Excluding migrants diagnosed with VLOSLP within two years of arrival to Sweden
[b]Adjusted for age, sex, their interaction, and all exposures included in this table

Results from an additional sensitivity analysis excluding those diagnosed with dementia within two years of diagnosis with VLOSLP were very similar to results involving the full sample (Table 4.6), with some slight differences, including a stronger association between disposable income and VLOSLP (lowest income quartile HR: 3.06, 95%CI: 2.89-3.24).

Table 4.6 Dementia sensitivity analysis

	Adjustment 2 HR (95%CI)[b]	**Sensitivity analysis HR (95%CI)[a,b]**
Offspring with non-affective psychotic disorder (NAPD) (ref: no offspring with NAPD))	2.45 (2.29 – 2.62)	2.52 (2.35 – 2.71)
Region of birth (ref: Sweden)		
Africa	1.96 (1.44 – 2.66)	1.87 (1.35 – 2.58)
Asia, Oceania and other	0.99 (0.80 – 1.22)	0.96 (0.77 – 1.19)
North America	1.25 (0.93 – 1.68)	1.34 (0.99 – 1.81)
Europe	1.33 (1.25 – 1.41)	1.29 (1.22 – 1.38)
South America	1.09 (0.80 – 1.47)	1.02 (0.74 – 1.42)
Middle East	0.67 (0.49 – 0.93)	0.61 (0.43 – 0.87)
Russia-Baltic	1.77 (1.52 – 2.05)	1.70 (1.45 – 2.01)
Finland	1.61 (1.51 – 1.72)	1.60 (1.49 – 1.71)
Birth period (ref: 1920-1924)		
1925 - 1929	0.79 (0.76 – 0.82)	0.78 (0.75 – 0.82)
1930 - 1934	0.77 (0.73 – 0.80)	0.77 (0.74 – 0.81)
1934 - August 1939	0.73 (0.70 – 0.78)	0.76 (0.72 – 0.80)
Sep 1939 - May 1946 (gestational exposure to WWII)	0.84 (0.80 – 0.89)	0.87 (0.83 – 0.92)
Jun 1946 - 1949	0.89 (0.81 – 0.98)	0.91 (0.83 – 1.00)
Disposable income at age 60 (ref: highest quartile (4))		
Income quartile 1 (lowest)	2.82 (2.67 – 2.97)	3.06 (2.89 – 3.24)
Income quartile 2	2.51 (2.38 – 2.65)	2.68 (2.53 – 2.84)
Income quartile 3	1.43 (1.35 – 1.51)	1.47 (1.38 – 1.56)
Death of child (ref: had children, none died):		
Had no children	2.55 (2.47 – 2.64)	2.61 (2.52 – 2.71)
1 or more children died aged under 12 months	1.17 (0.99 – 1.39)	1.13 (0.94 – 1.37)
1 or more children died aged 12 months – 18 years	1.00 (0.84 – 1.20)	1.06 (0.88 – 1.27)
Death of partner 2 years before date of exit (ref: no partner died)		
Had no partner	1.32 (1.28 – 1.37)	1.37 (1.32 – 1.43)
1 or more partners died	1.03 (0.94 – 1.13)	1.02 (0.93 – 1.13)
Visual impairment (ref: no visual impairment)	0.51 (0.41 – 0.64)	0.49 (0.38 – 0.63)
Hearing impairment (ref: no hearing impairment)	0.43 (0.39 – 0.47)	0.41 (0.37 – 0.45)

[a]Adjusted for age, sex and their interaction, and all variables included in this table

[b]Sensitivity analysis excluding those diagnosed with dementia in the two years after VLOSLP diagnosis (n=2,035, (11.71%))

4.3.4 Proportional hazards assumption

There was some evidence that the proportional hazard assumption was violated for several variables (Table 4.7).

Table 4.7 Assessment of proportional hazards assumption

Variable	Schoenfeld residuals test[a]
Offspring with a non-affective psychotic disorder	$\chi^2(1)=1.47$, P=0.23
Region of birth	$\chi^2(8)=11.35$, P=0.18
Disposable income at age 60	**$\chi^2(3)=430.65$, P=<.001**
Birth period	**$\chi^2(5)=37.41$, P=<.001**
Death of a partner	**$\chi^2(2)=90.35$ P=<.001**
Death of a child aged under 12 months	**$\chi^2(2)=160.38$, P=<.001**
Death of a child aged 12 months to 18 years	**$\chi^2(2)=160.12$, P=<.001**
Visual impairment	**$\chi^2(1)=20.50$, P=<.001**
Hearing impairment	**$\chi^2(1)=178.56$, P=<.001**

[a]Schoenfeld residuals test. Bold denotes possible violation of proportional hazards assumption (see Table 4.8).

Inspection of the data, stratified by time (Table 4.8), suggested that the effects of income and sensory impairments on VLOSLP risk weakened over time.

Table 4.8 Hazard ratios stratified by time

Variable	Time 1[a,b,c]	Time 2[a,b,d]	Time 3[a,b,e]
Disposable income at age 60 (ref: highest income quartile)			
Income quartile 1 (lowest)	4.78 (4.34 – 5.26)	2.85 (2.60 – 3.13)	1.61 (1.48 – 1.76)
Income quartile 2	3.96 (3.59 – 4.36)	2.50 (2.28 – 2.74)	1.57 (1.44 – 1.71)
Income quartile 3	1.60 (1.44 – 1.78)	1.51 (1.37 – 1.66)	1.20 (1.09 – 1.31)
Death of a partner			
Had no partner	1.41 (1.33 – 1.50)	1.35 (1.28 – 1.44)	1.16 (1.09 – 1.23)
1 or more partners died	0.81 (0.66 – 0.99)	1.00 (0.84 – 1.17)	1.13 (0.99 – 1.29)
Death of a child (ref: had children, none died)			
Had no children	2.92 (2.75 – 3.09)	2.50 (2.36 – 2.66)	2.20 (2.07 – 2.33)
1 or more children died aged under 12 months	1.11 (0.83 – 1.47)	1.41 (1.08 – 1.83)	0.97 (0.65 – 1.43)
1 or more children died aged 12 months – 18 years	0.93 (0.70 – 1.30)	1.16 (0.87 – 1.54)	0.91 (0.66 – 1.25)
Birth period (ref: 1920-1924)			
1925 - 1929	0.72 (0.66 – 0.78)	0.77 (0.72 – 0.83)	0.85 (0.79 – 0.90)
1930 - 1934	0.71 (0.65 – 0.78)	0.70 (0.65 – 0.76)	0.86 (0.80 – 0.93)
1934 - August 1939	0.65 (0.59 – 0.71)	0.80 (0.74 – 0.86)	0.70 (0.58 – 0.77)
Sep 1939 - May 1946 (gestational exposure to WWII)	0.92 (0.85 – 0.99)	0.76 (0.69 – 0.83)	-
Jun 1946 - 1949	0.95 (0.86 – 1.05)	-	-
Visual impairment (ref: no visual impairment)	0.21 (0.11 – 0.42)	0.38 (0.23 – 0.60)	0.75 (0.57 – 0.99)
Hearing impairment (ref: no hearing impairment)	0.23 (0.18 – 0.29)	0.32 (0.27 – 0.39)	0.66 (0.58 – 0.74)

[a]Adjusted for age, sex and their interaction, and all variables included in this table
[b]Time split into centiles based on failure rates
[c]Time 1: January 1980–May 1985. [d]Time 2: May 1985–October 1992. [e]Time 3: October 1992–December 2011

4.4 Discussion

4.4.1 Summary of findings

In this nationwide cohort study investigating the epidemiology of VLOSLP, I found substantial incidence of the condition after the age of 60. The overall incidence rate of 44.61 per 100,000 person-years at-risk (95%CI: 43.95-45.27) was towards the higher end of previously reported rates of VLOSLP. In the systematic review reported in Chapter 2 (Stafford, Howard, & Kirkbride, 2018), the overall rate of non-affective psychotic disorders in those aged 60 years old and above was found to vary substantially across studies, ranging from 14.3 per 100kpy in Northumberland (Mitford et al., 2010) to 39.9 per 100kpy (95%CI: 10.5-18.1) in Camberwell (95%CI: 31.1-51.3) (Reeves et al., 2001). In the present study, rates increased with age beyond 80 years old, and were generally higher in women than men, a disparity that widened with increased age. This corresponds with previous data indicating a higher preponderance of VLOSLP in women, whereas previous findings regarding variation in VLOSLP incidence with age were mixed (Stafford et al., 2018). Consistent with epidemiological research in younger adult-onset samples, I found raised rates among some migrant groups, particularly from Africa and Europe. There was little evidence that these findings were fully explained by prevalent cases among migrants, or by income, itself a strong predictor of VLOSLP. Unexpectedly, rates were lower in those with sensory impairments. Rates were higher for those born earlier, with no evidence of a higher rate in those with gestational exposure to WWII. I also found higher rates among those without a partner or children and those whose children had a history of psychotic disorder, with weaker evidence of a higher rate in those who experienced the death of a child in infancy.

4.4.2 Strengths and limitations

This is the largest population-based cohort study to date to examine the incidence of VLOSLP. I used Swedish register data, which are highly complete and reliable for research purposes (Dalman & Cullberg, 2002; Ludvigsson et al., 2011). This enabled me to include a relatively high number of cases and to obtain precise estimates for potential risk factors.

I note several study limitations, including the need to consider whether reliance on register-based diagnoses could have biased results. On the one hand, I may have underestimated

true incidence, as those with VLOSLP may be less likely to contact services due to higher levels of functioning (Kay & Roth, 1961), and limited social contact (Castle & Murray, 1993). By contrast, given that recording of psychiatric diagnoses in Swedish registers only began in 1973, I may have included some prevalent cases, which would have overestimated incidence. Nonetheless, the follow-up period began in 1980 and I excluded those with a recorded psychotic disorder in the seven years prior. Register coverage improved over this washout period, during which most prevalent cases would be expected to present to services.

To mitigate the possibility of VLOSLP representing misclassified dementia with psychotic symptoms, I excluded those diagnosed with dementia before psychotic disorder. In general, when an older patient presents to services with psychotic symptoms, one would expect dementia to be assessed and ruled out before a psychotic disorder diagnosis was given. However, I cannot exclude the possibility of psychosis representing misdiagnosed dementia in some cases, or the reverse. It is also possible that, in some patients, VLOSLP represents a prodrome for future dementia (Brodaty, Sachdev, Koschera, Monk, & Cullen, 2003). Correspondingly, a Danish register-based study identified higher rates of subsequent dementia in those with VLOSLP compared with the general population and osteoarthritis patients (Kørner, Lopez, Lauritzen, Andersen, & Kessing, 2009). To examine whether findings were influenced by including those who may be experiencing the dementia prodrome, I conducted a sensitivity analysis excluding individuals diagnosed with dementia in the two years following diagnosis with VLOSLP. Results were very similar to those involving the full sample, suggesting that these findings are unlikely to be explained by the inclusion of this group. I have investigated the association between VLOSLP and dementia in greater detail in Chapter 5.

In this study, I could not link the cohort with their parents, hence I could not delineate second-generation migrants from the Swedish-born population. However, I would not expect a large number of second-generation migrants in this cohort given the birth periods covered. I was also, therefore, unable to investigate parental history of psychotic disorder; instead I used offspring psychotic illness as an indirect proxy. This will have overestimated the prevalence of psychotic disorder family history, and the strong estimates for this

variable may therefore be conservative. I also had to make some assumptions about coding death of a partner in the two years before cohort exit, as discussed in the methods section. I do not consider this will have introduced any substantial biases in this data. Additionally, I did not examine other mental health diagnoses such as depression, substance abuse or bipolar disorder in this study. Future studies examining premorbid mental health conditions in those with VLOSLP could provide valuable insights into the mental health trajectories of this group throughout adult life, prior to the emergence of late-life psychotic disorder. Finally, the proportional hazards assumption was violated for several exposures, warranting further exploration of potential reasons for variation in these effects over time in future studies. For example, the attenuation of a protective effect over time in those diagnosed with sensory impairments (Table 4.7) may be attributable to better clinical awareness of physical health comorbidities in people with psychotic disorders.

4.4.3 Meaning of findings

In this study I have precisely delineated a substantial incidence of non-affective psychosis occurring in later life. There is already evidence that individuals with VLOSLP have greater preserved functioning compared to those with more typical age-at-onset psychotic disorders (Kay & Roth, 1961; Pearlson et al., 1989), but may be more socially isolated (Castle & Murray, 1993). This is consistent with observations of greater risk with older age, particularly for women (Almeida et al., 1995; Howard et al., 1994; Castle & Murray, 1991; Castle, Wessely & Murray, 1993), and given that this population were less likely to have children, or a partner in the two years prior to diagnosis. Together, these findings suggest that this group may harbour unrecognised psychiatric morbidity requiring clinical attention. These findings also raise questions about the biological and/or social mechanisms underlying increased psychotic disorder risk in older women, which may begin from the well-documented secondary peak in incidence in their late 40s (Kirkbride et al., 2006; Jackson et al., 2013).

Psychotic disorder incidence was higher among migrants to Sweden from Africa, Finland, Russian-Baltic regions, and Europe, corresponding with previous VLOSLP findings (Mitter et al., 2004; Mitter et al., 2005; Reeves et al., 2001), and findings from the younger adult-onset literature (Kirkbride et al., 2012; McGrath et al., 2004; Cantor-Graae & Selten, 2005). Several

potential explanations have been proposed, including stressors experienced pre- and post-migration and during migration itself (Kirkbride et al., 2012). In this study I found a higher rate of VLOSLP in earlier birth cohorts, independent of age; contrary to hypotheses, the rate of VLOSLP was not found to be associated with gestational exposure to WWII. This contrasts with several previous cohort studies which found a higher rate of schizophrenia in offspring of mothers who, during pregnancy, were exposed to war (Malaspina et al., 2008), famine (Susser et al., 1996), or other severe adverse life events (Khashan et al., 2019). However, a previous study did not find evidence of a higher rate of schizophrenia in those exposed to war in utero, and the authors concluded that further research is needed in order to draw conclusions about the association between psychotic disorders and maternal stress (Selten, Cantor-graae, Nahon, & Levav, 2003). It should be noted that Sweden remained neutral during WWII, although nonetheless, it was subject to naval blockades, food and fuel shortages, rationing (until 1951), accidental bombings and threats of invasion throughout this period. In light of this, other regions more directly involved in WWII may provide more suitable contexts in which to test this hypothesis in future research.

I found lower rates of VLOSLP in those with hearing and visual impairments, in contrast to several previous small-scale studies (Cooper et al., 1974; Moore, 1981). One possibility is that this population-based (rather than clinical) sample reflects under-detection and treatment of sensory impairments in older adults with psychotic disorders at a national-level, as observed for other physical health problems, such as cardiovascular disease, in those with serious mental illness (Roberts, Roalfe, Wilson, & Lester, 2006; Smith et al., 2013). Such disparities may reflect reduced-help seeking behaviour, or provider-level factors, such as the separation of specialist physical and mental health services (Smith, Langan, Mclean, Guthrie, & Mercer, 2013), clinical uncertainty in providing suitable health care for patients with psychotic disorders, or ‘diagnostic overshadowing’, where physical symptoms are misattributed to mental illness (Viron & Stern, 2010).

Participants with VLOSLP were more likely to experience a range of social disadvantages than the population at-risk, including lower income, greater social isolation and adverse life events. One interpretation of these findings is that exposure to structural inequalities and social stressors may have long-lasting effects on psychotic disorder risk into later life. In the

younger adult onset literature, low socio-economic status has consistently been associated with psychotic disorder risk (Hollingshead & Redlich, 1958; Silver et al., 2002; Wicks, Hjern, Gunnell, Lewis, & Dalman, 2005). While findings regarding income could be attributed to social drift during the prodromal phases of psychotic disorder, this interpretation seems less readily applicable to those with VLOSLP, who would have had to maintain sufficient levels of functioning throughout their adult life (i.e. survival) (Häfner, Hambrecht, Löffler, Munk-Jorgensen, & Riecher-Rössler, 1998) to be at-risk of VLOSLP at cohort entry. Additionally, as suggested for younger adults with psychotic disorders, findings regarding social isolation could be interpreted causally (Badcock et al., 2015; Gayer-Anderson & Morgan, 2013), or may reflect premorbid impairments in social functioning, limiting one's ability to form and maintain stable intimate relationships; leading to reduced fecundity (Bundy, Stahl, & MacCabe, 2011; MacCabe, Koupil, & Leon, 2009; Power et al., 2013).

Although I found no evidence of an association between VLOSLP and the recent death of a partner after adjusting for confounders, there was weak evidence of a higher rate of VLOSLP in those who had lost a child in infancy, which corresponds with previous small-scale studies suggesting that traumatic life events could be associated with VLOSLP (Fuchs, 1994, 1999; Gurian et al., 1992; Reulbach et al., 2007), and with the wider epidemiological literature on psychotic disorders in those aged 65 years and younger (Li, Laursen, Precht, Olsen, & Mortensen, 2005; Liang et al., 2016; Morgan et al., 2007). These findings suggest that the loss of a child in infancy might convey longstanding – albeit modest – increased risk of psychotic disorder several decades later. On the other hand, this finding may be another manifestation of the association between VLOSLP and long-term social disadvantage. That I did not observe similar effects for the loss of a child at other ages, or in relation to the recent death of a partner, was somewhat surprising; further well-powered studies will be required to understand the association between VLOSLP and adverse life events. Further research is now needed to replicate these findings and to examine potential biological and psychological mechanisms underlying these associations, with the aim of identifying potential targets for intervention. In addition, further research is needed to examine outcomes associated with VLOSLP, including subsequent cognitive decline, as set out in the following Chapter.

Chapter 5 Dementia in very late-onset schizophrenia-like psychosis: a matched Swedish population-based cohort study

5.1 Introduction

As described in Chapter 1, there is ongoing debate about the aetiology of VLOSLP and its potential overlap with neurodegeneration and dementia (Brodaty et al., 2003; Vahia et al., 2010; Van Assche et al., 2017). However, epidemiological research regarding the relationship between VLOSLP and dementia is sparse. In this Chapter, I aim to address this gap in the literature by examining the association between VLOSLP and subsequent dementia in a matched Swedish population-based cohort study. Gaining insight into the association between VLOSLP and subsequent dementia may help to inform clinical practice with regard to treatment and symptom monitoring of patients with VLOSLP. Additionally, findings may provide further insight into the aetiology of VLOSLP.

To date, there is limited evidence regarding the association between VLOSLP and dementia. Although a recent review found some evidence of mild cognitive deficits and decline in those with VLOSLP, there was little evidence of neuropathology or neurodegeneration beyond that observed in more typical age-at-onset psychotic disorders, after accounting for age (Van Assche et al., 2017). However, most previous studies in this area have been limited by unrepresentative samples, cross-sectional designs, and/or short follow-up periods (e.g. Brodaty et al., 2003; Mazeh, Zemishlani, Aizenberg, & Barak, 2005).

In particular, longitudinal, population-based studies investigating VLOSLP and dementia are lacking, with limited exceptions. For instance, a study from Denmark found a higher rate of dementia among those with late-onset schizophrenia and VLOSLP compared to osteo-arthritis patients and the general population (Kørner et al., 2009). The study focussed on very late-onset schizophrenia (ICD 10: F20), whereas the present study focusses on broader non-affective psychotic disorders (ICD 10: F20-F29 or equivalent). Additionally, the study was smaller than the present study (for which characteristics are set out in Section 5.3.2), including 409 individuals with very late-onset schizophrenia who were compared with 7303 individuals with osteoarthritis. Further, the follow-up period was relatively short, with a

maximum of seven years. This is problematic given that dementia neuropathology may develop over several decades (Villemagne et al., 2013), hence longitudinal cohort designs with long follow-up periods are required to fully characterise the association between VLOSLP and subsequent dementia. Additionally, the study only adjusted for age and sex, hence several potentially important confounders were not considered, including socio-economic status (SES) and region of birth.

To summarise, although there is some evidence of an association between VLOSLP and subsequent dementia (Kørner et al., 2009), longitudinal research in this area is sparse. Further, several important aspects of this relationship remain unexamined, including the main risk period for dementia diagnosis following VLOSLP, and whether the rate of dementia in VLOSLP varies by demographic subgroup such as sex, education level, and family history of psychosis. To address these gaps in knowledge, I examined the rate of dementia diagnosis in those with VLOSLP in a Swedish population-based cohort with a sufficiently large sample size and adequate follow-up time to detect incident dementia.

My research questions were as follows:

- Research Question 1 (RQ1). Is VLOSLP associated with increased risk of subsequent dementia?
- RQ2. If so, how much quicker are individuals with VLOSLP diagnosed with dementia?
- RQ3. Does the association between VLOSLP and dementia differ by demographic subgroup?
- RQ4. Is the association between VLOSLP and dementia due to differential mortality between groups?
- RQ5. Is the association between VLOSLP and dementia due to misdiagnosis of dementia?
- RQ6. Is the association between VLOSLP and dementia due to differences in detection between groups?

I hypothesised that the rate of dementia would be higher in those with VLOSLP, and that the VLOSLP group would be diagnosed with dementia at a quicker rate than the matched comparison group. To my knowledge, previous research on the association between VLOSLP and dementia in relation to socio-demographic factors is sparse. In light of this, there was no rationale to expect variation in the rate of dementia diagnosis in those with VLOSLP by subgroup; i.e. I expected the risk of dementia associated with VLOSLP to be similar across subgroups, such as sex and educational attainment. Further, I expected the association between VLOSLP and dementia to remain present having taken into account possible biases introduced due to differences in survival and detection between those with and without VLOSLP.

5.2 Methods

5.2.1 Data source

I conducted this study using Psychiatry Sweden data, involving a Swedish population register data linkage intended for mental health research. An overview of Psychiatry Sweden and the Swedish population register data source was set out in Chapter 3.

5.2.2 Cohort

From the Swedish population register data, I established a matched cohort design. The cohort consisted of all people living in Sweden born between 1920-1949 who were diagnosed for the first time with a non-affective psychotic disorder after age 60 (ICD-10 F20-F29, or ICD-8 and -9 equivalent; full codes listed in Chapter 3), and an age and calendar period matched comparison group (matched within the same year of birth), without a recorded non-affective psychotic disorder diagnosis at any point in their lives (10 matches per person with VLOSLP). Matches for a given individual with VLOSLP were required to be alive, living in Sweden and free from dementia on the date of VLOSLP diagnosis for the individual to whom they were matched. Individuals who did not meet these criteria for one individual with VLOSLP could still be considered as a match for other individuals with VLOSLP. Although matching is relatively uncommon in cohort studies, largely due to the associated reduction in efficiency, this is less of a concern when using large-scale administrative data (Rothman, Greenland, & Lash, 2008). A matched cohort design allowed

me to assign an appropriate index date from which to follow up the matched comparison group (without VLOSLP), while adjusting for age and calendar period.

I obtained data on non-affective psychotic disorder and dementia diagnoses from the Swedish National Patient Register, described in Chapter 3. Details on date of first diagnosis with a non-affective psychotic disorder and/or dementia, death and emigration were recorded from the linked National Patient, Cause of Death, Total Population and Immigration/Emigration registers, respectively. As described in Chapter 3, the follow-up period began from the date of first diagnosis with a non-affective psychotic disorder after age 60 and from the same date for the matched comparison group. Members of the cohort were followed up until first recorded diagnosis with dementia in the Swedish registers or until death, emigration from Sweden or the end of the follow up period in December 2011.

5.2.3 Outcome

The outcome was time to first diagnosis of dementia as recorded in the Swedish inpatient and outpatient registers (ICD-10: F00, F01, F02, F03, G30, G31.0, G31.8, or ICD-8, and -9 equivalent; full codes listed in Chapter 3). For descriptive purposes, I also categorised dementia diagnoses into the following subtypes, where data were available: Alzheimer's disease, vascular dementia, frontotemporal dementia, Lewy Body dementia, dementia due to a medical comorbidity, dementia related to alcohol use, and dementia unspecified. However, in analyses, I restricted the outcome to all-cause dementia, given limited validity of examining separate dementia subtypes within the Swedish registers (Rizzuto et al., 2018).

5.2.4 Exposure

The primary exposure was whether or not someone had been diagnosed with VLOSLP (first recorded non-affective psychotic disorder after age 60 years old) or not, as identified and described above.

5.2.5 Covariates

Covariates were as follows: sex, region of birth, family history of non-affective psychotic disorder, disposable income at age 60, and educational attainment. Data on age, sex and region of birth were obtained from the Swedish Register of the Total Population. Region of

birth was broadly categorised as follows owing to a low number of migrants in several region of birth strata: Sweden, Finland, other Nordic, other European, and other. Disposable income data were obtained from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) and grouped into quartiles based on all cohort members with disposable income from all sources (employment, welfare receipts, savings, investments) at age 60 recorded in the same calendar year. I also obtained data on length of educational attainment from the LISA, which was grouped as follows: pre-high school, high school, and post-high school. A measure of family history of non-affective psychotic disorder was obtained by linking cohort participants to their children using the Multigenerational Register. This measure was based on whether participants' biological children had received a recorded psychotic disorder diagnosis in the registers.

5.2.6 Missing data

Missing data were limited to disposable income at age 60 and length of educational attainment variables. Where possible, I included data on disposable income at age 55-59 for those with missing data at age 60 years (N=21,325; 0.72%). Individuals with missing data were excluded from the cohort prior to matching (5.4%). Characteristics of those with missing data are set out in Section 5.3.1.

5.2.7 Statistical analysis

RQ1. Is VLOSLP associated with increased risk of subsequent dementia?

I used Cox regression to examine the rate of subsequent dementia diagnosis in those with VLOSLP relative to the age and calendar period matched comparison group. I assessed the proportional hazards assumption using Schoenfeld residuals plots and tests. Where this assumption was violated, I reported hazard ratios stratified by time. I used a forward-fitting modelling strategy throughout, in which I initially examined univariable associations between covariates and dementia diagnosis, assessing model fit via Akaike's Information Criterion (AIC), with lower scores indicating better fit. Next, I added variables with the lowest AIC values individually into a model including sex and the matching variable as *a priori* confounders. I retained covariates in the model if they improved model fit, assessed via likelihood ratio test.

RQ2. If so, how much quicker are individuals with VLOSLP diagnosed with dementia?

I used accelerated failure time (AFT) models to examine differences in time-to-diagnosis with dementia between those with and without VLOSLP. In particular, I sought to investigate how much more quickly (if at all) those with VLOSLP were diagnosed with dementia relative to the comparison group. AFT models provide an alternative to more widely used semi-parametric Cox proportional hazards models based on the hazard function (Cox, 1972). In AFT, the survivor function is modelled directly, and changes in absolute survival time can be estimated, which some consider to be more intuitive than the hazard ratio (Swindell, 2009). I used AFT to estimate time ratios, indicating how much quicker those with VLOSLP were diagnosed with dementia relative to the matched comparison group (if at all). I compared the fit of different distributions for the AFT error term (including exponential, Weibull, log-normal or log-logistic) via AIC, with lower scores indicating better fit.

RQ3. Does the association between VLOSLP and dementia differ by demographic subgroup?

I fitted and tested interactions (via likelihood ratio test) between VLOSLP and sex, education level and family history of non-affective psychotic disorder to examine whether the association between VLOSLP and dementia varied by socio-demographic subgroup.

RQ4. Is the association between VLOSLP and dementia due to differential mortality between groups?

I considered death to be a competing risk as it precludes observation of the outcome (dementia) and given the higher mortality rate in those with psychotic disorders (Hayes et al., 2017), including VLOSLP (Talaslahti et al., 2015). I assessed the potential impact of mortality on the association between VLOSLP and dementia using two methods: the cause-specific method (CSH) and the Fine and Gray subdistribution hazard approach (SHR) (Fine & Gray, 1999), in line with guidance from Latouche et al. (2013). In Fine and Grey competing risks regression, individuals who experience the competing event are retained in the risk set rather than being censored. Correspondingly, it should be noted that subdistribution hazard ratios are not directly comparable to hazard ratios from Cox regression. In addition, I plotted the cumulative incidence function to show the association between VLOSLP and death, and VLOSLP and dementia, each taking the other competing event into account. Cumulative incidence curves are considered more appropriate than Kaplan-Meier plots in the presence

of competing risks, where the Kaplan-Meier estimator tends to overestimate the true probability of failure (Gooley, Leisenring, Crowley, & Storer, 1999; Putter, Fiocco, & Geskus, 2007).

RQ5. Is the association between VLOSLP and dementia due to misdiagnosis of dementia?
I conducted a sensitivity analysis including a washout period in which I excluded those with VLOSLP who were diagnosed with dementia within the six months following diagnosis with VLOSLP (and their matched comparisons) to examine the potential effect of misdiagnosis of dementia as VLOSLP on findings.

RQ6. Is the association between VLOSLP and dementia due to detection differences between groups?
I conducted a second sensitivity analysis to investigate the possibility that any differences observed in the rate of dementia diagnosis in those with and without VLOSLP may be due to better detection of dementia in the VLOSLP group, given that they may have been more likely to contact health services than individuals without VLOSLP. To test this possibility, I divided the matched comparison group into two subgroups: those with and without a record of any inpatient or outpatient diagnosis (for any condition) in the year on either side of cohort entry (i.e. the time at which VLOSLP had been diagnosed). If the rate of dementia was higher in those with VLOSLP relative to those without a diagnosis, but not relative to those who had received a diagnosis during this time, this would suggest that the higher rate of dementia in the VLOSLP group could be due to better detection of dementia in those already in contact with health services.

5.3 Results

5.3.1 Missing data

As described above in Section 5.2.6, those in the full cohort (n=3,077,366) with missing data (limited to education and disposable income) were excluded prior to matching (5.4%). Missing data were more common among those without dementia (5.5% vs 2.9%), those with VLOSLP (9% vs 5.4%), men (6.2% vs 4.6%), and those with no offspring with a recorded non-affective psychotic disorder diagnosis (5.4% vs 4.8%). Missing data were substantially more

common in migrants relative to the Swedish-born group (Swedish-born: 4.1%, Finnish: 6.1%, other European 15.8%, other Nordic: 18.9% and other: 28.4%) (all Ps ≤.001) (Table 5.1).

Table 5.1 Missing data on disposable income at age 60 and educational attainment variables from full cohort, before matching (N=3,077,366)

Variable	Missing, N (%)	χ^2 p-value
Dementia	4,028 (2.94%)	p<.001
No dementia	158,318 (5.52%)	
VLOSLP	1,579 (9.00%)	p<.001
No VLOSLP	160,767 (5.38%)	
Sex		p<.001
Men	92,819 (6.22%)	
Women	69,527 (4.59%)	
Offspring non-affective psychotic disorder	3,375 (4.80%)	p<.001
No offspring non-affective psychotic disorder	158,971 (5.41%)	
Region of birth		
Sweden	106,933 (4.05%)	p<.001
Finland	7,182 (6.13%)	
Other European	21,486 (15.76%)	
Other Nordic	10,659 (18.94%)	
Other	16,086 (28.41%)	

5.3.2 Descriptive statistics

The matched cohort consisted of 169,499 individuals (15,409 participants with VLOSLP and 154,090 matched participants without VLOSLP), after excluding 3 individuals with VLOSLP due to identifying an insufficient number of matches. The 3 excluded participants were aged between 90-91 years old (female (n=2), male (n=1)). During the follow-up period, 13,610 (8%) individuals were diagnosed with dementia (VLOSLP: 17.8%; matched group: 7.1% ($X^2(1)=2200$, p=<.001)). The most common dementia subtypes were unspecified dementia (53.6%), Alzheimer's Disease (23.6%) and vascular dementia (19.9%) (Figure 5.1). The median age at first dementia diagnosis was higher in those without VLOSLP (82 years old, interquartile range (IQR): 78 – 86), relative to those with VLOSLP (76 years old, IQR: 72 – 81; Mann-Whitney p≤0.001). Compared to those without VLOSLP, those with VLOSLP were more likely to be women (60.6% vs 53.8%), to have a lower education level (pre-high school education: 59.1% vs 53.2%), a lower disposable income at age 60 years old (lowest quartile: 36.6% vs 26.1%) and to have offspring with a recorded non-affective psychotic disorder diagnosis (5.3% vs 2.5%), and less likely to be Swedish-born (85.5% vs 90.9%) (all p<.001) (Table 5.2).

Figure 5.1 Pie chart of recorded dementia diagnoses by subtype (%)

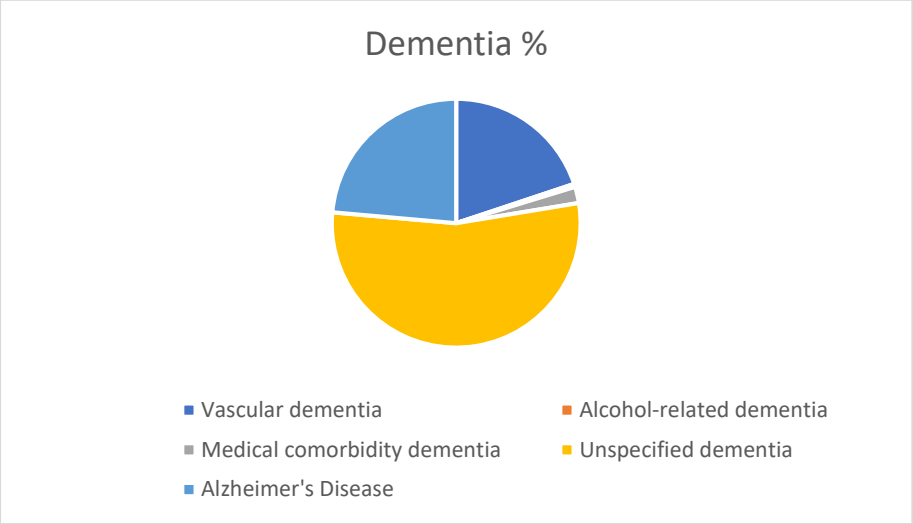


Table 5.2 Cohort characteristics in those with and without VLOSLP

Variable	**No VLOSLP (N=154,090)**	**VLOSLP (N=15,409)**	
	Median (IQR)	**Median (IQR)**	**Mann-Whitney U test**
Age-at-diagnosis with dementia (IQR)	82 (78 – 86)	76 (72 – 81)	p=<.001
	N (%)	**N (%)**	***X*² test**
Dementia status			$X^2(1)=2200.00$, p=<.001
Dementia	10,866 (7.05)	2,744 (17.81)	
No dementia	143,224 (92.95)	12,665 (82.19)	
Sex			$X^2(1)=259.41$, p=<.001
Men	71,224 (46.22)	6,078 (39.44)	
Women	82,866 (53.78)	9,331 (60.56)	
Educational attainment (ref: high school education)			$X^2(2)=239.24$, p=<.001
Pre-high school	81,994 (53.21)	9,111 (59.13)	
High school	49,827 (32.34)	4,614 (29.94)	
Post-high school	22,269 (14.45)	1,684 (10.93)	
Disposable income at age 60			$X^2(3)=2100.00$, p<.001
Lowest (1)	40,236 (26.11)	5,642 (36.61)	
2	36,892 (23.94)	4,935 (32.03)	
3	39,747 (25.79)	3,007 (19.51)	
Highest (4)	37,215 (24.15)	1,825 (11.84)	
Family history of non-affective psychotic disorder			
Family history	3,878 (2.52)	815 (5.29)	$X^2(1)=399.95$, p<.001
No family history	150,212 (97.48)	14,594 (94.71)	
Region of birth			
Sweden	139,999 (90.86)	13,173 (85.49)	$X^2(4)=497.18$, p<.001
Other Nordic	2,573 (1.67)	333 (2.16)	
Finland	4,819 (3.13)	852 (5.53)	
Other European	5,321 (3.45)	858 (5.57)	
Other	1,378 (0.89)	193 (1.25)	

5.3.3 RQ1. Is VLOSLP associated with increased risk of subsequent dementia?

In Cox proportional hazards regression, I found a higher rate of subsequent dementia in those with VLOSLP relative to those without VLOSLP after adjustment for sex, education level, disposable income at age 60, region of birth and offspring non-affective psychotic disorder diagnosis (fully adjusted hazard ratio (HR): 4.22, 95%CI: 4.05-4.41) (Table 5.3). I also found a higher mortality rate among those with VLOSLP relative to the matched comparison group (fully adjusted HR: 2.85, 95%CI: 2.78-2.91).

Table 5.3 Cause-specific hazard ratios for dementia and mortality by VLOSLP status

Variable	Dementia HR (95%CI) Adj1	Dementia HR (95%CI) Adj2	Mortality HR (95%CI) Adj1	Mortality HR (95%CI) Adj2
VLOSLP (ref: no VLOSLP)	4.21 (4.04 – 4.39)	4.22 (4.05 – 4.41)	2.83 (2.77 – 2.89)	2.85 (2.78 – 2.91)

Adj 1: Matching variable
Adj2: VLOSLP status, sex, education level, offspring non-affective psychotic disorder, disposable income at age 60, region of birth and matching variable

There was evidence of non-proportional hazards for the VLOSLP exposure, assessed via Schoenfeld residuals tests, but not for other covariates (Table 5.4).

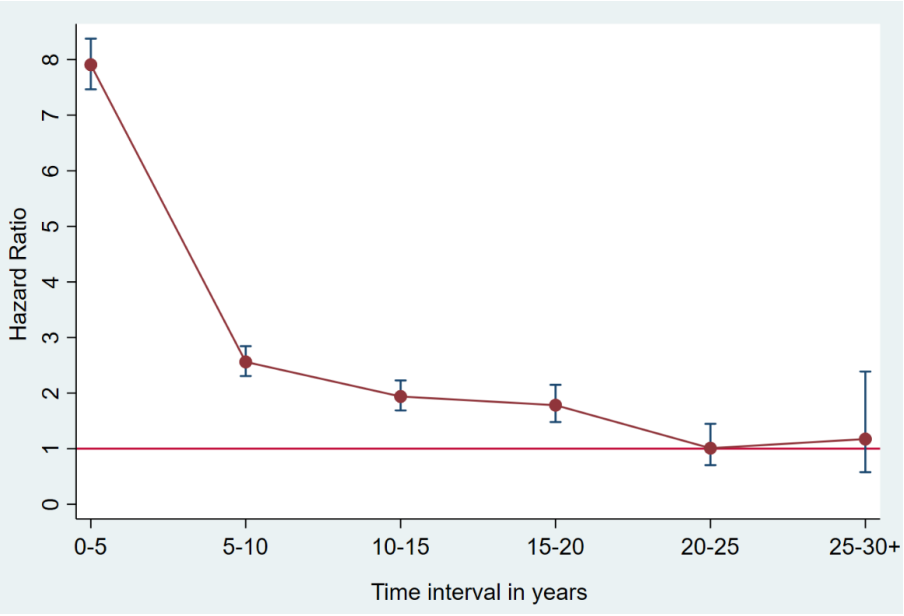
Table 5.4 Assessment of proportional hazards assumption

Variable	Schoenfeld residuals test[a]
VLOSLP (ref: no VLOSLP)	**$\chi^2(1)=774.61$, p<.001**
Sex	
Female (ref: male)	$\chi^2(1)=0.99$, p=0.57
Offspring psychotic disorder (ref: no offspring psychotic disorder)	$\chi^2(1)=0.89$, p=0.32
Educational attainment (ref: high school education)	
Pre-high school education	$\chi^2(1)=0.21$, p=0.65
Post-high school education	$\chi^2(1)=0.00$, p=0.99
Disposable income at age 60 (ref: Quartile 4 (highest)	
Income quartile 3	$\chi^2(1)=3.34$, p=0.07
Income quartile 2	$\chi^2(1)=1.37$, p=0.24
Income quartile 1 (lowest)	$\chi^2(1)=0.01$, p=0.94
Region of birth (ref: Sweden)	
Finland	$\chi^2(1)=1.18$, p=0.28
Other European	$\chi^2(1)=0.08$, p=0.78
Other Nordic	$\chi^2(1)=6.17$, p=0.01
Other	$\chi^2(1)=0.16$, p=0.69

[a]Adjusted for VLOSLP status, sex, education level, disposable income at age 60, offspring non-affective psychotic disorder, region of birth and matching variable.

Given evidence of non-proportional hazards for the VLOSLP variable, I plotted the hazard ratio for dementia over the follow-up period for those with VLOSLP relative to those without VLOSLP (Figure 5.2). I found that the hazard ratio was particularly high in the first few years of the follow-up period, followed by a decrease over time, which could reflect misdiagnosis and/or VLOSLP symptoms as part of the dementia prodrome (discussed further in the following sections). However, the rate of dementia remained higher among those with VLOSLP throughout most of the follow-up period, suggesting that these factors are unlikely to fully explain the association between VLOSLP and subsequent dementia.

Figure 5.2 Fully adjusted dementia hazard ratios for VLOSLP group relative to comparison group over follow-up period



5.3.4 RQ2. How much quicker are individuals with VLOSLP diagnosed with dementia?

Descriptively, the median time-to-dementia diagnosis in those without VLOSLP was 9.14 years (interquartile range (IQR): 4.25 – 14.70), while among those with VLOSLP, the median time-to-diagnosis with dementia was shorter at 1.93 years (IQR: 0.36 – 6.00). As described in the methods section, I used accelerated failure time models (AFT) to examine how much more quickly (if at all) those with VLOSLP were diagnosed with dementia relative to those without VLOSLP. First, I assessed the fit of different distributions for baseline survivorship to the data (including exponential, Weibull, log-normal, and log-logistic distributions) via AIC,

with lower scores indicating better model fit. As shown in Table 5.5, the Weibull distribution was found to be the best fit to the data.

Table 5.5 Comparison of distributions for baseline survivorship (model fit assessed via AIC)

Distribution	AIC[a]
Exponential	106823.9
Weibull	106817.1
Lognormal	108391.8
Loglogistic	106858.9

[a]Adjusted for: VLOSLP status, sex, education level, offspring non-affective psychotic disorder, disposable income at age 60, region of birth and matching variable. Lower AIC values indicated a better fit to the data

As shown in Table 5.6, the fully adjusted accelerated failure time model yielded a time ratio for dementia diagnosis of 0.25 (95%CI: 0.24 – 0.26). This indicated that the median time-to-diagnosis with dementia was 75% quicker for those with VLOSLP relative to the matched comparison group.

Table 5.6 Weibull accelerated failure time model (time to dementia in years)

Variable	Time ratio (95%CI) Adj1	Time ratio (95%CI) Adj2
VLOSLP (ref: no VLOSLP)	0.25 (0.24 – 0.27)	0.25 (0.24 – 0.26)

Adj 1: Matching variable
Adj2: VLOSLP status, sex, education level, offspring non-affective psychotic disorder, disposable income at age 60, region of birth and matching variable

5.3.5 RQ3. Does the association between VLOSLP and dementia differ by demographic subgroup?

I found evidence of effect modification between VLOSLP status and sex, education level, and offspring psychotic disorders in partially and fully adjusted Cox regression models. As shown in Table 5.7, in those without VLOSLP, women had a slightly higher rate of dementia diagnosis (HR: 1.10, 95%CI: 1.05–1.14), whereas in the VLOSLP group, the rate of dementia diagnosis was slightly lower in women (HR: 0.86, 95%CI: 0.79 – 0.92). Relative to those with high school education, in those without VLOSLP, the rate of dementia diagnosis was lower in those with post-high school education school (HR: 0.93, 95%CI: 0.86-0.99), while there was a weak trend towards a higher rate of dementia diagnosis in those with pre-high school education (HR: 1.03, 95%CI: 0.99-1.08).

Table 5.7 Interactions between VLOSLP and sex, offspring psychotic disorder and educational attainment

Variable	Comparison group[a] HR, 95%CI	VLOSLP group[a] HR, 95%CI	Likelihood ratio test p-value for interaction
Sex			P<.001
Men	Ref	Ref	
Women	1.10 (1.05 – 1.14)	0.86 (0.79 – 0.92)	
Offspring non-affective psychotic disorder			P=0.01
No offspring psychotic disorder	Ref	Ref	
Offspring psychotic disorder	1.21 (1.09 – 1.35)	0.94 (0.80 – 1.11)	
Educational attainment			P<.001
High school	Ref	Ref	
Pre-high school	1.03 (0.99 – 1.08)	0.80 (0.73 – 0.87)	
Post-high school	0.93 (0.86 – 0.99)	0.98 (0.85 – 1.12)	

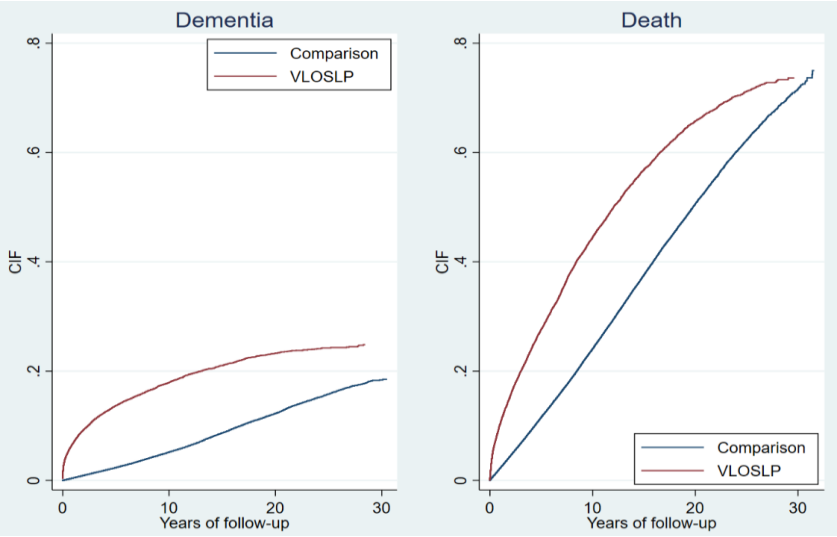
[a]VLOSLP status, sex, education level, offspring non-affective psychotic disorder, disposable income at age 60, region of birth and matching variable

By contrast, in the VLOSLP group, relative to those with high school education, the rate of dementia was lower in those with pre-high school education (HR: 0.80, 95%CI: 0.73-0.87), and no difference was found for those with post high-school education (HR: 0.98, 95%CI: 0.85-1.12). In those without VLOSLP, I found a higher rate of dementia in those who had children with a non-affective psychotic disorder (HR: 1.21, 95%CI: 1.09-1.35), but this was not observed in the VLOSLP group (HR: 0.94, 95%CI: 0.80-1.11).

5.3.6 RQ4. Is the association between VLOSLP and dementia due to differential mortality between groups?

Descriptively, 58.2% of individuals in the VLOSLP group died during the follow-up period, compared with 34.3% of individuals without VLOSLP (p=<.001). Further, as shown in Table 5.3, the mortality rate was higher in those with VLOSLP compared to those without VLOSLP (fully adjusted HR: 2.85, 95%CI: 2.78-2.91), highlighting the potential importance of taking a competing risks approach to analyses. Figure 5.3 shows the cumulative incidence of death and dementia, respectively, indicating the proportion of individuals who were diagnosed with dementia, taking into account that death is a competing risk (and vice versa). As shown, those with VLOSLP had a higher cumulative incidence of dementia across the follow-up period, and of death at most time points, although after 20 years of follow-up the cumulative incidence appeared to be similar, perhaps indicating a 'ceiling' effect in old age samples.

Figure 5.3 Cumulative incidence function for dementia and death by VLOSLP status



In addition, findings from Fine and Grey competing risks regression indicated that the rate of dementia remained significantly higher among those with VLOSLP in a model where death was included as a competing risk (fully adjusted subdistribution hazard ratio (SHR): 2.89, 95%CI: 2.77–3.03) (Table 5.8). However, it should be noted that the SHR is not directly comparable to the hazard ratio, given that in Fine and Grey competing risks regression, individuals who experience the competing event (i.e. death) are retained in the risk set rather than being censored.

Table 5.8 Fine and Grey competing risks regression

Variable	SHR (95%CI), Adj1	SHR (95%CI), Adj2
VLOSLP (ref: no VLOSLP)	2.90 (2.80 – 3.03)	2.89 (2.77 – 3.03)

Adj1: Matching variable
Adj2: VLOSLP status, sex, education level, offspring non-affective psychotic disorder, disposable income at age 60, region of birth and matching variable

5.3.7 RQ5. Is the association between VLOSLP and dementia due to misdiagnosis?

The Cox regression hazard ratio attenuated after incorporating a six-month washout period to mitigate against potential misdiagnosis of dementia as VLOSLP, although the rate of dementia remained substantially higher among the VLOSLP group (fully adjusted HR with 6-month washout: 3.12, 95%CI: 2.97-3.27) (Table 5.9). The same pattern emerged in Fine and Grey competing risks regression, which took mortality into account, where the SHR

attenuated after incorporating a six-month washout period, but the rate of dementia remained higher among the VLOSLP group (fully adjusted SHR with 6-month washout: 2.07, 95%CI: 1.97 – 2.18).

Table 5.9 Sensitivity analysis with 6-month washout period

Variable	Cox regression Dementia HR (95%CI)[a]	Cox regression Dementia with 6-month washout HR (95%CI)[a,b]	Fine and Grey Dementia SHR (competing risks) SHR (95%CI) [a]	Fine and Grey Dementia with 6-month washout (competing risks) SHR (95%CI) [a,b]
VLOSLP (ref: no VLOSLP)	4.22 (4.05 – 4.41)	3.12 (2.97 – 3.27)	2.89 (2.77 – 3.03)	2.07 (1.97 – 2.18)

[a]Adjusted for: Sex, disposable income at age 60, region of birth, respective interactions with VLOSLP, and matching variable

[b]Six month washout period: Those diagnosed with dementia within 6 months of VLOSLP diagnosis (and their matched comparisons) were excluded (VLOSLP N excluded= 796, comparison N excluded= 7960)

5.3.8 RQ6. Is the association between VLOSLP and dementia due to detection differences between groups?

I conducted a sensitivity analysis to investigate the possibility that the higher rate of dementia in those with VLOSLP could be explained by better detection of dementia in this group due to already being in contact with health services. In this analysis, I grouped those without VLOSLP into those who had and had not received any recorded diagnosis in the year on either side of cohort entry, as a proxy for contact with the healthcare system. I found that 31.7% (n=48,482) of those without VLOSLP received one or more recorded diagnoses in the year either side of cohort entry.

As shown in Table 5.10, the rate of dementia was higher in those with VLOSLP relative to both comparison groups (i.e. those without VLOSLP who did, and did not receive a hospital diagnosis in the year either side of cohort entry). However, the rate of dementia was considerably higher in those with VLOSLP relative to those without VLOSLP who had not received a diagnosis near cohort entry (fully adjusted HR: 4.90, 95%CI: 4.69 – 5.13), than compared to those who had received a diagnosis during this time (HR: 2.89, 95%CI: 2.75 - 3.04) (Table 5.10). This suggests that the association between VLOSLP and dementia may have been partly, but not fully, explained by better detection of dementia in the VLOSLP group due to already being in contact with health services. I also incorporated a six-month washout period, as described above, to examine the joint effect of these potential sources

of bias. As in Table 5.9, the hazard ratio attenuated after incorporating a 6-month washout period to take into account potential misdiagnosis, but the rate of dementia remained higher in the VLOSLP group relative to both comparison groups (Table 5.10).

Table 5.10 Sensitivity analysis to take into account differences in detection due to contact with health services

Variable	HR (95%CI) Adj1[a]	HR (95%CI) Adj2[a]	6-month washout HR (95%CI) Adj2[a,b]
VLOSLP (ref: comparison group, no diagnosis near date of entry)	4.89 (4.68 – 5.11)	4.90 (4.69 – 5.13)	3.63 (3.45 – 3.82)
VLOSLP (ref: comparison group, any diagnosis near date of entry)[a]	2.89 (2.75 – 3.04)	2.89 (2.75 – 3.04)	2.09 (1.98 – 2.21)

Adj 1: Matching variable
Adj2: VLOSLP status, sex, education level, offspring non-affective psychotic disorder, disposable income at age 60, region of birth and matching variable
[a]Any hospital diagnosis on the year either side of entry in to the study (except psychotic disorders or dementia)
[b]Six month washout period: Those diagnosed with dementia within 6 months of VLOSLP diagnosis (and their matched comparisons) were excluded (VLOSLP N excluded= 796, comparison N excluded= 7960)

The rate of dementia remained particularly high in the VLOSLP group compared to those without VLOSLP who did not have a recorded hospital diagnosis on the year either side of cohort entry (comparisons without diagnosis, fully adjusted 6-month washout HR: 3.63, 95%CI: 3.45 – 3.82; comparisons with diagnosis, fully adjusted 6-month washout HR: 2.09, 95%CI: 1.98 – 2.21).

5.4 Discussion

5.4.1 Summary of findings

In this large population-based cohort study, in line with hypotheses (RQ1), I found a substantially higher rate of subsequent dementia diagnosis among those with VLOSLP relative to those without VLOSLP, matched by age and calendar period. Further, using accelerated failure time models, I found that the median time-to-diagnosis with dementia was 75% quicker for those with VLOSLP (RQ2). These findings were robust to adjustment for a range of socio-demographic factors including sex, region of birth, disposable income and educational attainment.

Contrary to hypotheses, the association between VLOSLP and dementia varied by socio-demographic subgroup (RQ3). For instance, family history of non-affective psychotic

disorder, as indexed by offspring psychotic disorder, was associated with a higher rate of dementia in those without VLOSLP, but not in the VLOSLP group. Additionally, in those without VLOSLP, the rate of dementia was slightly higher in women and slightly lower in those with the highest education level (post-high school), in line with previous epidemiological findings (Mazure & Swendsen, 2016; Sharp & Gatz, 2011). By contrast, in the VLOSLP group, the rate of dementia was higher in men, and lower in those with the lowest educational attainment level (pre-high school). Possible reasons for differences by demographic subgroup are discussed in Section 5.4.3.

In line with hypotheses, the rate of dementia remained higher in those with VLOSLP in a Fine and Grey regression model, where death was modelled as a competing risk, indicating that the association between VLOSLP and dementia was unlikely to be an artefact of differential patterns of mortality between groups (RQ4). Contrary to hypotheses (RQ5), sensitivity analysis indicated that the higher rate of dementia in those with VLOSLP may be partly explained by misdiagnosis of dementia as VLOSLP, given the attenuation in the hazard ratio after excluding those diagnosed with dementia within six months of diagnosis with VLOSLP. However, it is also possible that the elevated rate of dementia in those with VLOSLP in the first few years of follow-up reflects a genuine co-occurrence of VLOSLP and dementia, and/or rapid cognitive decline in the VLOSLP group. A further sensitivity analysis indicated that, in contrast to hypotheses (RQ6), findings may be partly explained by better detection of dementia in the VLOSLP group due to previous contact with health services, although this bias did not appear to fully explain results. Before a more in depth discussion of the meaning of findings (Section 5.4.3), the following section sets out key strengths and limitations of this work.

5.4.2 Strengths and limitations

Several strengths should be noted. First, to my knowledge, this is the largest study to date to examine the rate of dementia in those with VLOSLP. Second, the maximum follow-up time was over 30 years, which is important given that few previous studies have had sufficiently large sample sizes or long follow-up periods to allow adequate detection of incident dementia in those with VLOSLP. Third, in accelerated failure-time models, I obtained a time ratio to quantify how much more quickly the VLOSLP group were diagnosed

with dementia relative to those without VLOSLP, which may be of particular relevance to clinicians. Fourth, I sought to examine other potential explanations for findings, including misdiagnosis, detection bias and competing risks.

It is also important to highlight several limitations, the first of which pertain to dementia diagnoses within the Swedish registers. While the specificity of dementia diagnoses is high in the registers, indicating that those diagnosed with dementia are likely to be true cases, sensitivity is relatively low, with around half of dementia cases in the population not recorded in the registers (Rizzuto et al., 2018). This means that I will have under-estimated the true rate of dementia in this cohort, reducing power to detect an association between VLOSLP and dementia. However, I would not necessarily expect this to differ in those with VLOSLP, except in relation to the potential detection bias highlighted above, which I sought to examine through sensitivity analysis involving a hospital comparison group. Further, a previous study reported an average delay of 5.5 years in recording of dementia diagnoses within the National Patient Register (Rizzuto et al., 2018), which compromises the precision of estimates of the time between VLOSLP and dementia diagnoses. Additionally, given that misclassification between different dementia subtypes is common in the registers, I was unable to examine variation in the association between VLOSLP and dementia by dementia subtype. Further, I cannot exclude the possibility of misdiagnosis of dementia as VLOSLP or vice versa, although I sought to mitigate against this potential source of bias by conducting a sensitivity analysis including a six-month washout period.

Additionally, I could not account for several potentially important confounders, such as antipsychotic medication use, as these data were not available for this older cohort. Further, it was not possible to obtain data on psychotic disorders in the parents of this cohort, therefore I indexed psychotic disorder family history via recorded non-affective psychotic disorder diagnoses in offspring. In addition, data on migrants' diagnoses before arrival in Sweden were unavailable, hence I may have overestimated the rate of dementia among migrants who arrived in Sweden in mid- to late-life. Although I was able to adjust for length of education, I could not obtain more detailed information on educational attainment, which may have provided more insight into baseline cognitive ability and cognitive reserve.

5.4.3 Meaning of findings

In this study, I found a substantially higher rate of dementia in individuals with VLOSLP relative to those without VLOSLP. This corresponds with a previous Danish cohort study, which found a higher rate of dementia in those with VLOSLP relative to osteo-arthritis patients and the general population (Kørner et al., 2009), although this study was limited by a relatively short follow-up period (maximum 7 years), and did not account for potential socio-demographic confounders and sources of bias. Findings also correspond with results from a cohort study of Australian men, in which the rate of dementia was found to be higher in older men with schizophrenia (including VLOSLP) relative to men without schizophrenia (Almeida et al., 2018b). Additionally, results align with longitudinal evidence of a higher rate of dementia in those with younger, more typical age-at-onset psychotic disorders (Cai & Huang, 2018; Ribe et al., 2015). In the present study, I was able to build on the previous literature by examining the rate of dementia in relation to VLOSLP in a larger cohort, with a long follow-up period (maximum 30 years), accounting for a range of potential confounders and sources of bias, as set out above. Further, I used an accelerated failure time modelling approach to demonstrate that those with VLOSLP were diagnosed with dementia on average 75% more quickly than the matched comparison group, providing the first quantification of this difference, which may be of particular clinical relevance.

This study was among the first to examine the association between VLOSLP and dementia in relation to socio-demographic factors. As described above, I found that, in contrast to those without VLOSLP, in the VLOSLP group, dementia diagnosis was more common in men and in those with a lower education level. While these findings could reflect true differences between subgroups, with respect to education level, this finding may be more likely to reflect diagnostic overshadowing, whereby, following VLOSLP diagnosis, those with a lower SES may be less likely to contact services or to have their symptoms of dementia detected compared to those with a higher SES. This may also be the case for women, who had a lower rate of subsequent dementia diagnosis than men in the VLOSLP group, although further research is needed to investigate these possibilities.

In this study, I found that the rate of dementia in those with VLOSLP was higher across most of the follow-up period, with a particularly elevated rate in the first few years following

diagnosis with VLOSLP. This pattern is compatible with several possible explanations. First, the particularly high hazard ratio in the first few years of the follow-up period may reflect misdiagnosis of dementia as VLOSLP. This was also evidenced by a partial attenuation in the hazard ratio in a sensitivity analysis excluding those diagnosed with dementia within the six months following diagnosis with VLOSLP. Additionally, it is possible that the frequency and speed of diagnosis with dementia were increased in the VLOSLP group due to already being in contact with health services. In support of this, I found some evidence for detection bias in a sensitivity analysis in which I grouped the non-VLOSLP comparison group based on whether they had received a hospital diagnosis near to entry into the study, as a proxy for contact with the health care system. However, I found that the rate of dementia remained higher in the VLOSLP group after jointly taking into account these potential sources of bias, and after considering mortality as a competing risk, suggesting that these biases are unlikely to fully explain the association between VLOSLP and dementia.

The finding of a particularly high rate of dementia in the VLOSLP group in the early follow-up period is also consistent with the possibility that psychotic symptoms could be part of the dementia prodrome for some individuals (Fischer & Agüera-Ortiz, 2018). Similar debates have emerged in relation to depression and anxiety (Diniz, Butters, Albert, Dew, & Reynolds, 2013; Dotson, Beydoun, & Zonderman, 2010; Gulpers et al., 2016), with evidence that late-onset depression shows a particularly strong association with cognitive decline (Ownby, Crocco, Acevedo, John, & Loewenstein, 2007), and may be an early marker of dementia neuropathology, rather than a risk factor (Singh-Manoux et al., 2017). Further research is needed to investigate this possibility given the important potential clinical implications with regard to treatment and symptom monitoring of individuals presenting with VLOSLP.

However, despite this, it is important to note that the rate of dementia remained higher among those with VLOSLP throughout most of the follow-up period, suggesting that the association is unlikely to be entirely explained by VLOSLP as part of the dementia prodrome. In light of this finding, and previous evidence of an association between dementia and more typical age-at-onset psychotic disorders (Cai & Huang, 2018; Ribe et al., 2015), it is possible that psychotic disorders, including VLOSLP, directly or indirectly increase risk for subsequent dementia. This could occur via several pathways, including poor physical health, given that

those with psychotic disorders have a higher rate of type-II diabetes (Bushe & Holt, 2004; Osborn et al., 2008), and heart disease (Crump, Winkleby, Sundquist, & Sundquist, 2013; Hennekens, Hollar, & Casey, 2005; Osborn et al., 2007), both of which are associated with an increased risk of dementia (Biessels et al., 2006; Wolters et al., 2018). Poor physical health in those with psychotic disorders may be driven by lifestyle factors such as, poor diet, sedentary behaviour (McCreadie, 2003), a higher prevalence of smoking and drug and alcohol use (McCreadie, 2002) and reduced sleep quality (Davies et al., 2017). However, little is known about physical health in those with VLOSLP and many of these health-related risk factors may be more applicable to those with longstanding schizophrenia.

Further cognitive impairment, a core component of schizophrenia (Bora, 2015), may increase risk for dementia via reduced cognitive or brain reserve (Barnett et al., 2006), in that those with a lower level of baseline cognitive functioning may require less neuropathology before meeting the clinical threshold for dementia diagnosis (Stern, 2006). Third, it is possible that the association between psychotic disorders and dementia is explained by common causes. For instance, there may be shared genetic vulnerabilities to dementia and schizophrenia, predisposing a subset of individuals with schizophrenia to neurodegeneration (Lyketsos & Peters, 2016). It is also possible that this association is explained by inflammation, which is associated with dementia (Peila & Launer, 2006) and non-affective psychotic disorders, including VLOSLP (Wium-Andersen et al., 2014).

5.4.4 Conclusion

In this matched Swedish population-based cohort study, I found that those with VLOSLP have a substantially higher rate of subsequent dementia diagnosis compared to those without VLOSLP. This may have implications for old age psychiatrists in relation to treatment planning and monitoring of cognitive decline in this patient group. A more in depth understanding of cognitive and symptom profiles in individuals with VLOSLP may allow better prediction of which subgroups are more likely to develop dementia in future. Further research is needed to understand potential pathways from psychotic disorder to dementia across the life course and whether the underlying mechanisms differ by age-at-onset of psychotic disorder.

Chapter 6 Social isolation and loneliness in very late-onset schizophrenia-like psychosis: a feasibility case-control study

6.1 Background and aims of the feasibility study

As highlighted in the introduction, although loneliness and social isolation have been found to be associated with more typical age-at-onset psychotic disorders, there has been only limited investigation of these concepts in relation to very late-onset schizophrenia-like psychosis (VLOSLP). This is important given that social isolation and loneliness are associated with a range of adverse health outcomes such as cardiovascular disease, stroke (Valtorta et al., 2016), and cognitive decline (Boss et al., 2015; Cacioppo & Hawkley, 2009). Additionally, social cognitive impairments have been observed in those with more typical age-at-onset psychotic disorders, where they have been found to predict important functional outcomes (Fett et al., 2011). However, little is known about whether the same social cognitive impairments are found in those with VLOSLP. Despite the strengths of the Swedish population register data and other large administrative datasets for investigating rare outcomes such as VLOSLP, a limitation is that these data are routinely collected and therefore do not generally contain information on psychosocial factors such as social isolation, loneliness and social cognition.

In light of this, in this Chapter, I outline and assess the feasibility of conducting a case-control study to examine levels of social isolation, loneliness and social cognitive impairments in those with VLOSLP. Feasibility and pilot studies are recommended for evaluating study procedures before conducting a full-scale study, with assessment of criteria such as: the adequacy of study measures and data collection strategies, recruitment and retention rates, and the acceptability of the study to participants (Arain, Campbell, Cooper, & Lancaster, 2010; Lancaster, 2015; Prescott & Soeken, 1989).

In this Chapter, I assess feasibility by conducting the study as set out in the protocol described in this chapter, with a smaller sample of participants. The feasibility study is therefore not powered to address the overall research questions and hypotheses of the case-control study described in the following sections. Nonetheless, assessing study

procedures with a small number of participants is likely to be informative about potential challenges in recruitment, acceptability of the study and potential logistical difficulties (Hertzog, 2008). This feasibility study may be useful for guiding future research in this area, particularly with regard to recruitment processes involving patients with VLOSLP.

In line with guidance from Orsmond and Cohn (2015), in this Chapter I assess feasibility via the following criteria:

1. Recruitment capability and resulting sample
2. Data collection procedures and measures
3. Suitability and acceptability of study procedures
4. Resources and ability to manage and implement study

6.2 Background and aims of the case-control study

Before evaluating the feasibility of the case-control study, this section presents the background and methods, including: hypotheses, eligibility criteria, recruitment targets, study measures, and planned statistical analyses. The primary aim of the case-control study was to investigate levels of loneliness and social isolation in patients with VLOSLP. As described in Chapters 1-4, social and environmental risk factors for VLOSLP are poorly understood in comparison to psychotic disorders with a younger, more typical age-at-onset, where high levels of social isolation have been observed, with less consistent evidence regarding loneliness (Lim et al., 2018). Further research is needed to examine these concepts in relation to VLOSLP. As discussed in Chapter 1, loneliness and social isolation are distinct yet over-lapping constructs which are modestly inter-correlated and often show independent associations with health (Cacioppo & Hawkley, 2009). Although there is some evidence that those with VLOSLP experience high levels of social isolation (Rodriguez-Ferrera et al., 2004), data on this topic are sparse (Stafford et al., 2018) and, in particular, little is known about how lonely those with VLOSLP feel.

At face value, one might expect those with VLOSLP to report high levels of loneliness, given that they are thought to experience high levels of social isolation (Rodriguez-Ferrera et al., 2004). However, as described in Chapter 1, there is some evidence that the psychological

processes underlying loneliness in psychotic disorders with a more typical age-at-onset may differ from the underlying mechanisms found in the general population (Trémeau et al., 2016), and correspondingly, not all previous studies have found a straightforward association between loneliness and psychotic disorders with a more typical age-at-onset (Lim et al., 2018). For instance, a recent study reported significantly lower levels of loneliness among patients with psychotic disorders compared with patients with depression, despite those with psychotic disorders reporting higher levels of social isolation (Giacco et al., 2016). Additionally, Lim et al. (2014) found that those with psychotic disorders did not report significantly more dissatisfaction with their relationships relative to the comparison group, despite the group with psychotic disorders reporting significantly fewer and less helpful relationships in their social network. This lack of dissatisfaction may relate to reduced insight or social anhedonia (Lim et al., 2018).

As discussed in Chapter 1, it is also conceivable that hallucinations and delusions in psychotic disorders serve as a form of social input that lessens feelings of loneliness, despite the presence of social isolation. In line with this, positive symptoms in schizophrenia are notably social in nature and generally represent interactive social agents (Bell et al., 2017), rather than, for example, geometric shapes and meaningless sounds (Hoffman, 2007). Further, research suggests that most voice hearers engage with their voices, often in interactive conversations (Bell et al., 2017), and that relationships with voices often feel intimate and highly personal despite the frequently unpleasant and intrusive content of positive psychotic symptoms (Nayani & David, 1996). This may be particularly applicable to those with VLOSLP, who tend to present with a highly delusional form of psychotic disorder, largely presenting with positive rather than negative symptoms (Howard, Castle, Wessely, & Murray, 1993). Given the highly social content of positive symptoms, in this study I hypothesised that those with VLOSLP may feel less lonely than the comparison group after accounting for levels of social isolation, which I would expect to be higher in the VLOSLP group (see hypotheses below).

A secondary aim of the case-control study was to investigate whether those with VLOSLP have impaired social cognition: an important predictor of functional outcomes in those with a younger, more typical age-at-onset of psychotic disorder (Fett et al., 2011). Specifically,

this study focussed on two aspects of social cognition, which have been found to be impaired in those with more typical age-at-onset of psychotic disorders: theory of mind and hostile attribution bias (An et al., 2010; Bora et al., 2009). These concepts were described in Chapter 1. Broadly, theory of mind refers to the ability to make inferences about the beliefs, thoughts and intentions of others (Frith & Frith, 2005; Stone, Baron-Cohen, & Knight, 1998), while hostile attribution bias refers to a tendency to interpret ambiguous and neutral events as threatening (An et al., 2010).

Gaining insight into social isolation and loneliness in those with VLOSLP is important given their associations with a range of adverse health outcomes, such as, stroke, coronary heart disease (Valtorta et al., 2016), cognitive decline (Cacioppo & Hawkley, 2009) and mortality (Holt-Lunstad et al., 2015). Additionally, this research may contribute to a more in depth understanding of potential risk factors for VLOSLP. Further, if high levels of social isolation, loneliness and impairments in social cognition are identified in this group, these could be considered as targets for the development of future psychosocial interventions to benefit those with VLOSLP.

Hypotheses for the full case-control study were as follows:

Primary

1. Individuals with VLOSLP will be more socially isolated than control participants
2. Those with VLOSLP will be less lonely than control participants after accounting for social isolation

Secondary

1. Relative to control participants, individuals with VLOSLP will show higher levels of:
   a. theory of mind impairments
   b. hostile attribution bias

6.3 Methods

6.3.1 Target population

The recruitment process, exposures, covariates, measures and eligibility criteria described in the following sections apply to both the full case-control study and to this feasibility study. The information sheet, consent form and measures are provided in full in Appendix 1. Participants were selected based on the presence or absence of a diagnosed non-affective psychotic disorder after age 60 years old (ICD-10: F20-F29). Cases were those with a first recorded diagnosis of a non-affective psychotic disorder after age 60 years old. Between February and December 2018, cases and controls were recruited from two Community Mental Health Teams (CMHTs) for older people within Camden and Islington NHS Foundation Trust in North London. In the 2011 UK census, the recorded population living in the Boroughs represented by these services was as follows: Camden (n=220,338) and Islington (n=206,125), with 33,232 individuals aged 60 and above in Camden, and 25,264 in Islington.

Those in the control group were individuals aged 60 years old and above recruited from the same CMHTs as cases and diagnosed with a mental health difficulty other than a psychotic disorder or dementia. The choice of control group is crucial to the validity of results in case-control studies, with the aim being to select controls free of the outcome who are representative of those at risk of becoming a case (Wacholder, Silverman, McLaughlin, & Mandel, 1992). In clinic-based case-control studies, the source population represents individuals who would be treated in a given hospital if they developed the disease in question (Rothman et al., 2008). Hence, in this case, a random sample of the general population would not necessarily represent a random sample of the source population, and hospital controls may therefore be more representative of the source population. Further, in this study, it was considered more interesting and relevant to examine whether levels of loneliness and social isolation differed in those with VLOSLP relative to those with other mental health difficulties, rather than compared with the general population. Possible benefits of hospital controls include practicality and similarities to cases in motivation to participate, and in information quality (Infante-Rivard, 2003). Additionally, in this study, the use of hospital controls means that both groups are help-seeking populations, increasing

internal validity, although this may compromise external generalisability. There are several other notable limitations to hospital controls, including that they may not be selected independently of exposure in the source population (Grimes & Schulz, 2005). To dilute this potential source of bias, I aimed to recruit controls with a variety of diagnosed mental health conditions, rather than focusing on a single diagnosis (Rothman et al., 2008).

6.3.2 Recruitment process

Clinicians or administrators within clinical teams identified potential participants by screening patient records using eligibility criteria as set out below. A member of the clinical team made first contact with potentially eligible patients, briefly described the study to patients and sought verbal consent from potential participants to be contacted by telephone, post and/or email by the research team. After potential participants were identified and verbal consent for contact was obtained by the clinical team, I sent an invitation letter and a Participant Information Sheet to potential participants by post or email. Following this, I telephoned potential participants to provide further information about the study, to answer any questions and to arrange an interview date for the research study, for those interested in participating. The study could take place in participants' homes or in a clinical setting, depending on participant preference.

6.3.3 Participant eligibility criteria

Cases

Inclusion criteria:

- Aged 60 years old and above.
- Diagnosed with an ICD-10 F20-F29 non-affective psychotic disorder diagnosis after age 60 years old.

Exclusion criteria:

- Diagnosed with a psychotic disorder before age 60 years old.
- Dementia diagnosis.
- Mild cognitive impairment diagnosis.

- Clear organic cause for psychosis.
- Does not speak English to the degree needed to engage with study materials.
- Mental health problems too severe to fully engage with the study.
- Other medical or psychosocial factor that could limit ability to fully engage with study materials, such as severe intellectual disability or imminently life-limiting illness.

Controls

Inclusion criteria:

- Aged 60 years old and above.
- Diagnosed with any mental health disorder except from a psychotic disorder, dementia, or severe depression.

Exclusion criteria:

- Diagnosed psychotic disorder, drug-induced psychosis or organic psychosis.
- Dementia diagnosis.
- Mild cognitive impairment diagnosis.
- Mental health problems too severe to fully engage with the study.
- Does not speak English to the degree needed to engage with study materials.
- Other medical or psychosocial factor that could limit ability to fully engage with study materials, such as severe intellectual disability or imminently life-limiting illness.

6.3.4 Exposures

Exposures of interest were social isolation, loneliness, hostile attribution bias, and theory of mind. I used two questionnaires to assess social isolation and loneliness, respectively, both of which have been validated for use in the elderly. I used the 20-item self-report UCLA Loneliness scale (Version 3) (Russell, 1996) to assess subjective feelings of loneliness. Each

item is scored from 0 (never) to 3 (often). Items include ‘I lack companionship’ and ‘People are around me but not with me’. The scale yields an overall loneliness score between 0-60.

I used the Lubben Social Network Scale - Revised (LSNS-R) to assess social isolation (Lubben et al., 2006; Lubben, 1988). The LSNS-R is an adaptation of the Berkman-Syme Social Network Index and has been validated for use with older adults (Berkman & Syme, 1979). The scale assesses the size, closeness and frequency of contacts within a respondent’s social network. There are two individual subscales each containing six items: one subscale for family, and another for friends and neighbours. Each subscale is scored from 0-30. The two subscales are summed to produce an overall score from 0-60. Higher scores indicate larger social networks and lower scores indicate higher levels of social isolation. Questions include ‘How many relatives do you see or hear from at least once a month?’ and 'How many friends do you feel at ease with that you can talk to about private matters?’.

In addition, I examined two aspects of social cognition: theory of mind and hostile attribution bias. I used the Ambiguous Intentions Hostility Questionnaire (AIHQ) to measure the hostile attribution bias (Combs, Penn, Wicher, & Waldheter, 2007), which has been found to have good internal consistency, test-retest reliability and has been validated for use in individuals with schizophrenia (Buck et al., 2017). However, I excluded the two interviewer derived subscales (aggression and hostility) due to the poor psychometric properties of these subscales (Combs et al., 2007). As in previous studies, I only analysed data from the ambiguous scenarios, which have been found to be most strongly indicative of the hostile attribution bias (Buck et al., 2017). In the study, I read participants each vignette and asked them to imagine that the scenario was happening to them. Participants rated whether the action was performed on purpose, with ratings from 1 (definitely no) to 6 (definitely yes), how angry it would make them feel from 1 (not at all angry) to 5 (very angry), and how much they would blame the other person from 1 (not at all) to 5 (very much). Responses to each item were averaged across scenarios and summed, with higher scores indicating greater blame.

I used The Faux Pas Test (Stone et al., 1998) to assess theory of mind, or the ability to make inferences about the thoughts, beliefs and intentions of others and to understand the

possible motivations underlying others' actions. I used a short version of the test, which has been validated for use in individuals with schizophrenia (Negrão, Akiba, Lederman, & Dias, 2016), with the aim of making the questionnaire battery more acceptable and less burdensome for participants. This test uses 5/10 faux pas stories and 5/10 control stories from the original Faux Pas Test. I read the scenarios to each participant and gave them a printed copy of each story while it was being read to avoid confounding by memory load. After reading each story, I asked participants questions to assess: detecting a faux pas, understanding the faux pas, understanding the mental state of the faux pas recipient, understanding the mental state of the person delivering the faux pas, and understanding the details of the story but without making inferences about the mental states of the characters in the story. Results can be reported separately for each subscale and can be summed to generate an overall score.

6.3.5 Covariates

I collected data on the following covariates: age, sex, ethnicity, mental health diagnosis, family history of psychotic disorder, marital status, living arrangements, number of children and grandchildren, frequency of contact with children and grandchildren, socio-economic status (education, last occupation, and last occupation of partner, if applicable), family history of psychotic disorders, major life events in the last year, depression, anxiety and IQ.

Demographic information

I used a demographic information sheet (Appendix 1) to collect data on age, sex, ethnicity, family history of psychotic disorder, living arrangements, marital status (current and previous partners), number of children and grandchildren (if any), frequency of contact with children and grandchildren, and socio-economic status.

Psychotic symptoms (administered to cases only)

I assessed psychotic symptoms using the Positive and Negative Syndrome Scale (PANSS): a scale which measures positive symptoms (7 items, example item: 'delusions'), negative symptoms (7 items, example item: 'blunted affect') and a general psychopathology scale (16 items, example item: 'depression'). Participants are rated on each item from 1 (absent) to 7

(extreme). I also used a brief measure of psychotic symptoms: the Psychosis Rating Scale (PRS) (Howard et al; see Appendix 1) with the aim of validating this shorter measure using the widely tested and well-validated PANSS (Kay, Fiszbein, & Opler, 1987). The Psychosis Rating Scale consists of four items designed to examine the symptoms of psychosis most relevant to VLOSLP, while excluding symptoms considered less common in VLOSLP, such as negative symptoms (Howard, Almeida, & Levy, 1994). The scale contains the following items: delusions, hallucinations, impact, and insight impairment. Each item is rated on a scale from 0-3 (absent, mild, moderate, or severe).

Marital status

I asked a question to ascertain whether participants were married, living with a partner but not married, divorced, widowed, separated, single and previously had a long-term partner, or single and never had a long-term partner.

Contact with children and grandchildren

I asked participants how many children and grandchildren they have (if any), and how frequently they were in contact with them.

Living arrangements

I asked participants whether they: 1) live alone, 2) live with a spouse or partner, 3) have shared living arrangements (living with another person aside from a spouse or partner, such as immediate family, other relations, or other unrelated persons), 4) or have institutional living arrangements (living on a permanent basis in a care facility).

Socio-economic status

To assess socio-economic status, I asked participants about their last occupation and/or partner's last occupation, if applicable. I also asked participants about their highest education level using the following categories: 1) no qualification, 2) clerical, commercial or trade qualification, 3) O level or equivalent, 4) A level or equivalent, 5) undergraduate university degree and 6) postgraduate degree. I decided to focus on education and last occupation to index socio-economic status rather than income or housing tenure as, after

discussion with an old age psychiatrist, these issues were deemed to be highly sensitive for this patient group.

Depression and anxiety

I used the Hospital Anxiety and Depression Scale (HADS) to measure anxiety and depression (Zigmond & Snaith, 1983), which has been widely used and is well-validated in psychiatric patients and in the general population, including in older people (Bjelland, Dahl, Tangen, & Neckelmann, 2002). The HADS is a 14-item questionnaire, with each item scored from 0-3. Participants receive a score from 0-21 for anxiety and depression, which can be categorised as 'normal' (0-7), 'borderline abnormal (borderline case)' (8-10), or 'abnormal (case)' (11-21). An example item measuring anxiety is 'I feel tense or 'wound up''. An example item measuring depression is 'I feel as if I am slowed down'.

Recent life events

I used the Geriatric Adverse Life Events Scale (GALES), a 26-item measure which has demonstrated reliability and validity in elderly participants, to assess acute adverse life events in the last year (Devanand, Kyung Kim, Paykina, & Sackeim, 2002). Adverse life events in the scale relate to financial difficulties (for example, following retirement), physical illness (such as a new major physical illness), interpersonal conflicts (such as divorce, marital difficulties, and major family problems or conflicts), interpersonal loss (for example the loss of a spouse or close family member) and disruption in living situations (including eviction or moving residence). During the interview I checked whether each reported adverse event was experienced during the last year and I asked how stressful participants perceived each event to be, ranging from not at all stressful to very stressful: 1, 2 or 3, and the impact of the events on mood (whether the event made the participant feel: 1) much better to 5) much worse).

IQ

I administered the National Adult Reading Test (NART) (Nelson, 1982), which was found to be a valid measure of IQ in the general population and in those with psychiatric conditions and other medical conditions (Bright, Jaldow, & Kopelman, 2002). This involved asking

participants to read a series of words aloud, which increased in difficulty. Results from the NART can be converted into approximate Wechsler Adult Intelligence Scale (WAIS) IQ scores (Blair & Spreen, 1989).

6.3.6 Recruitment target (n=66)

The sample size was driven by what was initially considered as a feasible target during my PhD, given that VLOSLP is a relatively rare outcome. Based on initial ideas of feasibility and a sample size calculation, I aimed to recruit 66 patients in total: 33 cases and 33 controls. I conducted a sample size calculation based on the primary outcome measure, the UCLA loneliness scale, using a previously published mean score in the elderly of 31.51 (standard deviation(SD): 6.72) in the calculation (Russell, 1996). I considered a mean difference of 15% or greater between patients with VLOSLP compared to the control group on the UCLA loneliness scale to be a clinically meaningful difference. To be able to detect a mean difference of 15% with 80% power and a significance level of 5% would require a sample size of 66 participants (33 participants per group).

6.3.7 Planned statistical analysis

In the full case-control study with a sufficient sample size, I planned to summarise binary and categorical data using frequencies and percentages, and to summarise continuous measures using means and standard deviations or medians and interquartile ranges. I planned to use logistic regression to analyse the relationship between case-control status and the following exposures of interest: 1) social isolation, 2) loneliness, 3) hostile attribution bias, and 4) theory of mind, taking into account potential confounders. I planned to handle any missing data using multiple imputation.

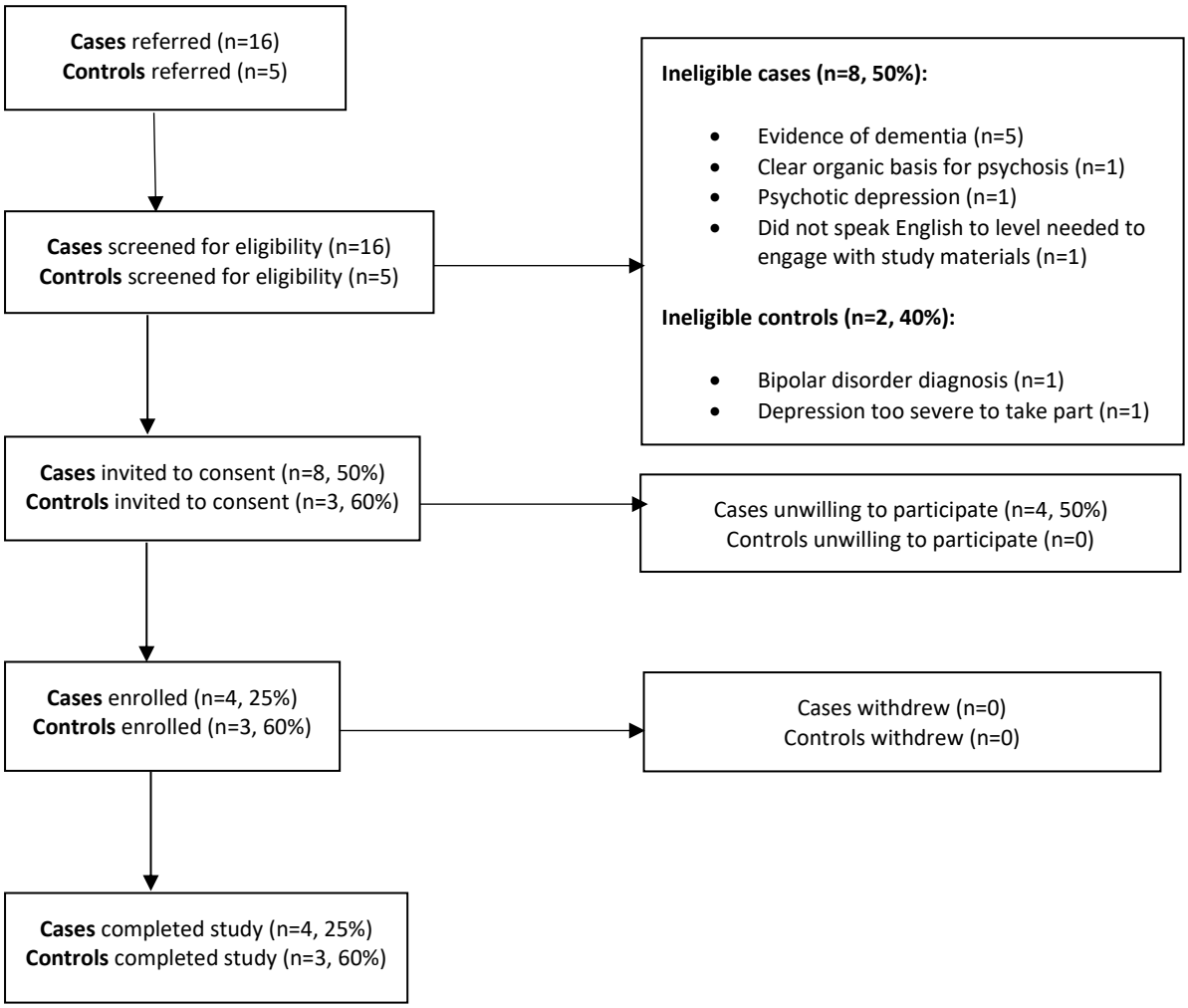
6.3.8 Ethical approval, peer review, and patient and public involvement

This study was approved by the Queens Square REC and the HRA (REC ref no. 17/LO/1393). The study protocol, information sheet and consent forms were initially peer reviewed by a reviewer independent to the study within the Division of Psychiatry at UCL. I contacted the North London Service User Research Forum (SURF) to discuss study conduct and the best way to feedback results of the study to service users. I re-drafted the Participant Information Sheet based on feedback from the SURF group.

6.4 Participant characteristics

As shown in Figure 6.1, this feasibility study did not recruit a sufficient number of participants to be powered to conduct statistical analyses as set out in the study protocol above.

Figure 6.1 Recruitment flow diagram



In Table 6.1 I have presented characteristics of the recruited sample and median scores on measures of social isolation, loneliness, social cognition and covariates as described in the previous section. Given the very small sample size these findings should not be used to draw conclusions about the outcomes of the study or to compare characteristics between cases and controls.

Table 6.1 Participant characteristics

Variable	Overall (n=7) N (%)	Controls (n=3) N (%)	VLOSLP cases (n=4) N (%)
Women	4 (57%)	2 (67%)	2 (50%)
White British or White other ethnicity	7 (100%)	3 (100%)	4 (100%)
Marital status			
Married	2 (29%)	1 (33%)	1 (25%)
Divorced	2 (29%)	0	2 (50%)
Widowed or separated	2 (29%)	2 (67%)	0
Single	1 (13%)	0	1 (25%)
Educational attainment			
No qualification	3 (43%)	1 (33%)	2 (50%)
Any qualification	4 (57%)	2 (67%)	2 (50%)
Living arrangements			
Living alone	2 (29%)	0	2 (50%)
Living with partner/family	4 (57%)	3 (100%)	1 (25%)
Institutional living	1 (14%)	0	1 (25%)
Median (interquartile range (IQR))		**Median (range)**	**Median (range)**
Age	79 (71-89)	89 (71-96)	77 (68-82)
LSNS-R social isolation	12 (11-34)	34 (12-34)	12 (7-14)
UCLA loneliness scale	25 (12-27)	25 (5-26)	23 (12-39)
Faux Pas Test[a]	0.8 (0.6-0.8)	0.8 (0.6-0.9)	0.7 (0.6-0.8)
AIHQ ambiguous items[b]	2.5 (2.5–2.7)	2.5 (2.5–2.7)	2.7 (2.5-3.7)
GALES adverse life events	2 (1-6)	2 (1-6)	3 (0-7)
HADS anxiety	14 (9-15)	15 (10-15)	12 (4-14)
HADS depression	8 (5-9)	6 (5-9)	8 (4-10)
NART IQ[c]	105 (95–115)	113 (99-115)	100 (92–123)
PANSS positive	-	-	18 (11-26)
PANSS negative	-	-	14 (12-15)
PANSS general	-	-	31 (25-39)
PRS total[d]	-	-	4 (1-9)

[a]Assesses theory of mind
[b]Assesses hostile attribution bias
[c]Scores from the NART were converted into estimates of WAIS IQ scores
[d]Overall psychotic symptoms measured by the Psychosis Rating Scale

Participants ranged in age from age 68 to age 96 years old and I recruited similar numbers of men (43%) and women (57%). Participants reported a range of living arrangements, marital statuses and educational attainment levels, as shown in Table 6.1. All participants self-reported white British or white other ethnicity.

In terms of outcome measures, cases had a median score of 12 (range: 7-14) on the LSNS-R, with lower scores indicating greater social isolation. The control group had a median score of 34 (range: 12-34). The LSNS-R ranged from 0-60 points and the mean score in older people reported by the authors was 25.1 (standard deviation(SD): 9.6) (Lubben, 1988). The median score on the UCLA Loneliness Scale was 25 (range: 5-26) in controls and 23 (range:

12-39) in cases. The scale ranged from 0-60 points, with higher scores indicating higher levels of loneliness. The authors of the UCLA Loneliness Scale previously reported a mean score of 31.51 (SD: 6.92) in older people (Russell, 1996).

The median score on the Faux Pas Test, which assesses theory of mind, was 0.8 (range: 0.6-0.9) in the control group and 0.7 (range: 0.6-0.8) in cases, with possible scores ranging from 0-1 and higher scores indicating better theory of mind. A previous study reported a mean score of 0.82 (SD: 0.11) on the Faux Pas Test in those with psychotic disorders and 0.94 (SD: 0.05) in the comparison group without psychotic disorders (Martino, Bucay, Butman, & Allegri, 2007). The median score on the AIHQ ambiguous items was 2.5 (range: 2.5-2.7) in the control group and 2.7 (range: 2.5-3.7) in cases, with higher scores indicating a higher level of hostile attribution bias. A previous study reported a mean score of 3.1 (SD: 0.6) on the AIHQ in those with persecutory delusions and a score of 2.5 (SD: 0.6) in the non-psychiatric control group (Combs et al., 2009).

In terms of covariates, the median estimated IQ was 113 (range: 99-115) in controls and 100 (range: 92–123) in those with VLOSLP. The median number of adverse life events reported was 2 in the comparison group (range: 1-6) and 3 in cases (range: 0-7). The median HADS depression score was 6 (range: 5-9) in the comparison group and 8 (range: 4-10) in cases, and the median anxiety score was 15 (range: 10-15) in the control group and 12 (range: 4-14) in cases. Scores of 11 or above on the HADS indicate cases of depression or anxiety, while scores of 8-10 indicate borderline cases.

In terms of psychotic symptoms, on the PANSS, cases had a median score of 18 (range: 11-26) for positive symptoms, 14 (range: 12-15) for negative symptoms (both subscales range from 0-49), and 31 (range: 25-39) for the general psychopathology subscale (subscale range: 0-112). This broadly corresponds with mean scores previously reported by the authors of the PANSS in adults with schizophrenia aged 20-68 years old: positive subscale: 18.20 (SD: 6.08), negative subscale: 21.01 (SD: 6.17) and general psychopathology subscale: 37.74 (SD: 9.49) (Kay et al., 1987). Cases mainly scored within the mild to moderate range of psychotic symptoms on the PRS with a median score of 4 (range: 1-9), with the scale ranging from 0-12.

6.5 Feasibility assessment

I assessed the feasibility of the study procedures in line with guidance from Orsmond and Cohn (2015). The main aim of this section was to assess the feasibility of conducting a full case-control study with the protocol described above based on appraisal of recruitment capability, data collection, measurement, and the acceptability and suitability of the study to participants.

6.5.1 Evaluation of recruitment capability and resulting sample

In this section I evaluate the recruitment capability of the study based on the number of participants recruited relative to the target, and the adequacy of the eligibility criteria. Broadly, I found recruitment to be challenging. This is likely to be, in part, because VLOSLP is a relatively rare presentation, as evidenced by findings from the Swedish cohort study described in Chapter 4, where I found an incidence rate of 44.61 per 100,000 person-years at-risk (95%CI: 43.95–45.27). In the present feasibility study, clinicians identified 8 potentially eligible cases with VLOSLP over 10 months, and I recruited 4 cases with VLOSLP to participate (Figure 6.1).

Additionally, those with VLOSLP are also known to be a hard-to-reach population (Howard et al., 2018; Sin Fai Lam, Reeves, Stewart, & Howard, 2016). Correspondingly, study uptake was low (50% of eligible patients) among those with VLOSLP identified by clinicians and approached about the study (Figure 6.1), whereas all control patients invited to consent were willing to participate. Potential reasons for this are discussed below. A second challenge in recruitment was that, under the terms of ethical approval for the study, clinicians had to make first contact with potentially eligible patients before they could be contacted by the research team. This meant that recruitment partly depended on clinicians' engagement and interest in the study, which varied considerably between clinicians and different CMHTs. This is likely to have affected recruitment of both groups.

I initially focussed on identifying patients with VLOSLP, as I anticipated that this group would be more challenging to recruit than the control group, given that VLOSLP is a rare outcome. While 16 patients were initially identified as potentially eligible VLOSLP cases, after further inspection, half of these potential referrals did not meet eligibility criteria due to: presence

of dementia or a clear organic basis for psychosis, affective psychosis, or not speaking English to the degree needed to engage with the study materials (Figure 6.1).

Although applying these exclusion criteria reduced the sample size, these exclusions were an important part of the study protocol, as affective psychosis in late life is considered to be a separate condition from VLOSLP, and this study focussed on functional psychoses rather than psychosis as part of dementia. Two control patients were ineligible as one was diagnosed with affective psychosis and another had depression which was deemed too severe to allow engagement with the study. In the study protocol, I specified that those who did not speak English to the degree needed to engage with study materials would be excluded from the study. In future studies, given the difficulty of recruiting patients with VLOSLP, involving a translator may be helpful to allow recruitment of additional patients.

6.5.2 Evaluation of data collection procedures and measures

In this section, I assess how appropriate the data collection procedures and measures were for the purpose of this study, with a focus on participants' understanding of and ability to complete the measures. This section also assesses the amount of data collection, time taken to complete the study, completeness and usability of collected data, and appropriateness of the measures.

In the study I met four participants in their homes, and three in a clinical setting, where this was preferred. Although a tablet was available to complete the study, most participants (n=5) stated a preference to have their answers recorded using pen and paper. The study took roughly between 1.5-2 hours to compete for cases and between 1-1.5 hours for controls, as cases had to complete the PANSS and PRS questionnaires regarding psychotic symptoms. In future studies in this area, it may be beneficial to administer the PANSS and PRS to both cases and controls to serve as a screener. Aside from this, both cases and controls were generally able to complete the questionnaires in a timely manner, in line with the approximate time of 2 hours which was set out in the study protocol. However, the time taken to complete questionnaires varied considerably between participants. In particular, two participants took substantially longer than anticipated to complete the questions due to a tendency to elaborate on answers, rather than due to a difficulty in understanding the

questions. It is possible that this tendency to elaborate was in itself related to levels of social isolation and loneliness. All participants completed the entire test battery, and most were able to do so in a single meeting, while one participant requested to complete the study over two separate meetings.

There was very little missing data and participants appeared to have a sufficient level of understanding and engagement to complete the questionnaires. The Faux Pas Test was perhaps the most challenging questionnaire for participants and took the longest to complete, given that it involved answering questions about a series of vignettes. I used a shortened form of this task which included 10 vignettes rather than 20, as I anticipated that the longer version might be too time consuming. This appeared to be appropriate in the present study, as even the shortened version was challenging for some participants, hence the longer version might have been overly burdensome. Although the study was underpowered, scores on the measures fell broadly within the expected ranges reported in previous studies (Table 6.1), as set out above, which provides very tentative evidence of criterion validity.

6.5.3 Evaluation of acceptability and suitability of study procedures

In this section I examine whether the study procedures were suitable for and acceptable to participants based on the level of engagement, time taken to complete the study, and the overall burden of taking part. First, it should be noted that only half of those with VLOSLP contacted about the study by clinicians were willing to be contacted by the research team. Reasons for this were not known and are discussed further below. Broadly, this could reflect attitudes towards research, severity of symptoms and/or a lack of insight into symptoms (Howard et al., 2018). Of those who took part, most participants were engaged with the study materials and were able to complete all of the questionnaires in a reasonable time with limited missing data. The study took place during a single meeting and mainly in participants' homes, which reduced the effort required to take part and appeared to be acceptable to those who participated. Two patients showed signs of mild distress when answering questions about social isolation and recent adverse life events, although these participants expressed a desire to continue with the study and were able to complete the

questionnaires. No participants reported or showed signs of significant distress or complained about the intrusiveness of the questionnaires.

6.5.4 Evaluation of resources and ability to manage and implement study

This section focusses on whether the research team had the resources and ability to manage the study, in terms of administrative capacity, expertise, skills, time and budget. In this study, I was responsible for collecting data alongside other projects conducted during my PhD. While this was feasible, as stated above, additional recruitment support from clinicians embedded in CMHTs may have improved communication with services and the overall recruitment rate. There were no issues around administration for the study. While there were no issues around budget in this feasibility study, a larger budget would have allowed for additional support with recruitment and the addition of more study sites, increasing the possibility of identifying potential cases with VLOSLP.

6.6 Discussion

6.6.1 Summary of findings from feasibility study

In this Chapter, I assessed the feasibility of a case-control study focussed on social isolation, loneliness and impairments in social cognition in individuals with VLOSLP relative to those with other mental health difficulties. This is an under-researched topic which could provide further insight into risk factors and outcomes associated with VLOSLP and could have implications for clinicians in considering the psychosocial needs of this patient group.

Although the study ran relatively smoothly once participants had consented to take part, I found that the study was not feasible in its current form based on the criteria set out above, largely due to difficulties with recruitment. Due to several barriers discussed in the previous sections, I was only able to recruit a small sample of cases and controls and therefore did not have sufficient statistical power to conduct planned statistical analyses. Difficulties in recruiting those with VLOSLP in the present study correspond with challenges described in other studies involving this patient group. For example, the ATLAS clinical trial of amisulpride in patients with VLOSLP recruited only 1/3rd of its target population, and many of the patients with VLOSLP who were approached declined to take part in the trial (Howard

et al., 2018). The authors argued that this reflects more general challenges in recruiting patients with VLOSLP. Once recruited to studies, retention and engagement rates have also been found to be low among those with VLOSLP (Howard et al., 2018).

While the recruitment targets of this study were not found to be feasible, I found that once participants were enrolled in the study, the study procedures were feasible and did not seem to be overly burdensome or time-consuming for participants. Additionally, the study measures were generally comprehended and accepted by participants. Most participants completed the study relatively quickly in a single meeting, with very little missing data.

6.6.2 Future directions and recommendations

Secondary data

The recruitment challenges described in this Chapter highlight the importance of large-scale secondary data analysis in gaining insight into the aetiology and outcomes associated with VLOSLP, as described in Chapters 2-5. However, few secondary data sources relevant to health exist on the scale of routinely collected register data in the Nordic countries, with the same level of completeness. Other secondary data sources are often not sufficiently large to detect an adequate number of cases with rare outcomes such as VLOSLP. While secondary data such as the Swedish register data described in Chapters 3-5 can be hugely valuable for studying rare conditions such as VLOSLP, routinely collected register data does not typically provide in depth information about mental health symptoms or relevant social and psychological concepts, such as social isolation, loneliness, or social cognition.

Addressing recruitment difficulties

Overall, I found that the study process as set out above is not sufficient to recruit an adequate sample of patients with VLOSLP. To facilitate recruitment of larger samples of patients with VLOSLP, future studies are likely to benefit from longer recruitment time frames and a larger number of study sites to maximise the potential of identifying cases with VLOSLP. However, this would require a larger budget to hire additional staff to help with recruitment across different sites, with a particular need for staff already embedded in clinical services, preferably with experience of recruiting hard-to-reach groups.

Before establishing further primary data collection studies involving those with VLOSLP, further research is needed to gain insight into potential barriers and facilitators of recruitment in this patient group, including attitudes towards participating in research studies. In general, factors which have been found to influence health research participation include altruism, expectations of superior care, knowledge about the study process, practical issues and commitments, and social influences, including a desire to please clinicians (Bower et al., 2009). In addition, factors found to be relevant to research participation in those with mental health difficulties include, altruism (Schafer et al., 2011), curiosity, and positive experiences with clinicians, while barriers included concerns about potential harm and views about mental health difficulties, for example, disagreement that symptoms reflect mental health difficulties (Woodall, Howard, & Morgan, 2011). Insight and views about mental health difficulties may be particularly relevant barriers to research participation in psychotic disorders, including VLOSLP, where insight into symptoms is generally low (Almeida, Levy, Howard, & David, 1996; Baier, 2010; Howard et al., 2018). Additionally, in the present study, it is possible that stigma around loneliness and social isolation may have reduced patients' desire to participate.

I found that engagement with the study varied substantially between clinicians and study sites. In line with this, there is evidence that clinicians' motivation to be involved in research and recruitment is shaped by a range of factors such as, general attitudes to research, ambivalent views about the topic under investigation, relationships with academics, and concerns about altering relationships with patients (Bower et al., 2009). Further, recruiting participants often involves extra time in addition to clinical duties, which is seen as a substantial barrier to research involvement in health care staff (Fletcher, Mant, Roalfe, & Hobbs, 2010). In mental health research, there is also evidence that clinicians may unintentionally engage in gatekeeping, with a tendency to refer patients who they deem to be suitable, rather than approaching all patients meeting eligibility criteria (Borschmann, Patterson, Poovendran, Wilson, & Weaver, 2014). Additionally, clinicians may use a cost-benefit filter in relation to service user needs vs clinical time, and they may be less likely to engage with research where they perceive the benefits to patients to be low or unclear (Bucci et al., 2015). In this study, being a non-clinical researcher added an additional barrier

to recruitment, since I was not embedded within clinical services, which made contact and communication with services more challenging.

It is important for future research in this area to examine other potential barriers to recruitment of patients with VLOSLP, to take these barriers in to account in designing study protocols, and to consider possible ways of overcoming these barriers in order to maximise recruitment. Qualitative studies involving patients and clinicians may help in identifying possible barriers to taking part in research specific to those with VLOSLP. Addressing these recruitment difficulties is important given that patients with VLOSLP are an under-researched group, and recruitment challenges may partly explain the limited number of aetiological studies and clinical trials aiming to improve outcomes for this patient group.

Future research directions

In order to gain a more in depth understanding of the VLOSLP phenotype in future, new cohorts may need to be established, potentially linked with secondary data where possible, to include measures of biological, psychosocial and environmental concepts assessed via questionnaires, cognitive tests and biological samples. There is international interest in gaining greater insight into VLOSLP and several small-scale cohorts involving patients with VLOSLP have been set up, for example in the Netherlands (e.g. Hanssen et al., 2015). A possibility would be for researchers to consider pooling data on this patient group across regions, ensuring that consistent measurement and recruitment procedures are put in place across sites. An additional possibility to promote future research in this area would be to encourage the inclusion of measures of very late-onset psychotic symptoms (or diagnoses, where possible) in relation to psychosocial concepts such as loneliness and social cognition in pre-existing cohorts which contain detailed phenotypic information about older participants, for example, the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) (Taylor et al., 2017), or UK Biobank data (Ollier, Sprosen, & Peakman, 2005). These potential strategies would allow for larger samples of patients with VLOSLP, providing sufficient statistical power to conduct analyses, and may be an important way forward given the difficulties in recruitment highlighted in this Chapter.

Chapter 7 Discussion

In this Chapter, first, I summarise the main findings from this thesis and how they contribute to the literature on the epidemiology of very late-onset schizophrenia-like psychosis (VLOSLP) (Section 7.1). Second, I discuss the broad strengths and limitations of the methods and approaches taken and how these may have influenced the results (Section 7.2). Third, I address how findings relate to previous research on the epidemiology of psychotic disorders and VLOSLP and the broader biopsychosocial psychosis literature (Section 7.3). Finally, I discuss potential implications for research, policy and clinical practice (Sections 7.4 and 7.5).

Specific aims of each part of the study were set out in Chapters 2-6. The overall aims of this thesis were as follows:

1. To systematically review evidence on the incidence of VLOSLP (**Chapter 2**).
2. To establish and characterise the incidence of VLOSLP and how this varies by age and sex in a Swedish population-based cohort study (**Chapter 4).**
3. To examine the incidence of VLOSLP in relation to potential social and environmental risk factors, including migration, socio-economic status (SES) and experiencing adverse life events (**Chapters 2 and 4).**
4. To examine the rate of dementia in relation to VLOSLP in a matched cohort study using Swedish register data (**Chapter 5).**
5. To assess the feasibility of a case-control study focussed on the association between VLOSLP, social isolation, loneliness and social cognition (**Chapter 6).**

7.1 Summary of main findings

In Chapter 2, I conducted a systematic review and meta-analysis focussed on the incidence of affective and non-affective psychotic disorders in older people. After screening 5687 citations, I identified 41 citations which met inclusion criteria. The pooled incidence rate (IR) of schizophrenia in those aged 60 years and older was 7.5 per 100,000 person-years at-risk (100kpy) (95%CI: 6.2-9.1). The rate of broader non-affective psychotic disorder was higher, ranging from 14.3 per 100kpy (95%CI: 10.5-18.1) to 39.9 per 100kpy (95%CI: 31.1–51.3). The pooled IR of affective psychosis was 30.9 per 100kpy (95%CI: 11.5–83.4). There was

substantial heterogeneity between estimates across studies. I found evidence of a higher rate of VLOSLP in women than men (meta-regression odds ratio: 1.6, 95%CI: 1.0-2.5), and some narrative evidence of a higher rate of VLOSLP among migrants, particularly in Black African and Caribbean migrants to the UK. There was little evidence that findings were explained by time period of case ascertainment or study quality. A key finding from the review was the lack of epidemiological data on VLOSLP to date, highlighting the need for further research in this area, particularly regarding social and environmental risk factors.

Building on gaps in the literature identified in the systematic review, in Chapter 4, I aimed to characterise the incidence of VLOSLP in a Swedish population-based cohort and to examine the association with potential risk factors for VLOSLP. The cohort study presented in Chapter 4 was the largest study to date to examine the incidence of VLOSLP and the first to examine VLOSLP incidence in relation to several potentially important risk factors, such as socio-economic status and adverse life events. In a cohort of 3,007,217 people, 17,532 cases were first diagnosed with a non-affective psychotic disorder after age 60 years old. The overall incidence rate of VLOSLP was 44.61 per 100kpy (95%CI: 43.95–45.27), which was higher than the rate of non-affective psychotic disorder identified in studies included in the systematic review (Chapter 2), reported above. There was an increase in the rate of VLOSLP with age, which was steeper in women from around age 80. Additionally, I found a higher rate of VLOSLP among migrants from Africa, Europe, Russian-Baltic regions, and Finland relative to those born in Sweden. This extends previous findings of a higher rate of non-affective psychotic disorders among migrants in those with a younger, more typical age-at-onset of psychotic disorder, suggesting that the association between migration and psychosis extends into late-life.

The rate of VLOSLP was higher in those with a lower disposable income at age 60 years old, providing the first epidemiological and longitudinal evidence to date of an association between VLOSLP and social disadvantage. This extends previous findings of an association between socio-economic status and more typical age-at-onset psychotic disorders (Hollingshead & Redlich, 1958), suggesting that the association between socio-economic status and psychotic disorder risk remains in later life. The rate of VLOSLP was also slightly higher in those who had a child who died in infancy, which approached significance,

although this was not found in those whose child had died between the ages of 12 months to 18 years. Those without a partner or children had a substantially higher rate of VLOSLP, which could implicate social isolation as a risk factor, although this finding may be more likely to reflect reverse causation and is consistent with evidence of reduced fecundity in individuals with a younger, more typical age-at-onset of psychotic disorder (Bundy et al., 2011). After adjustment for confounders, I found little evidence of an association between VLOSLP and experiencing the recent death of a partner. There was a higher rate of VLOSLP in those with a family history of non-affective psychotic disorder, indexed by offspring psychotic disorder. Contrary to hypotheses, the rate of VLOSLP was lower in those with hearing and visual impairment, which may reflect diagnostic overshadowing, where physical symptoms are misattributed to mental illness (Viron & Stern, 2010). Findings from Chapters 2 and 4 helped to complete the life course picture of the incidence of non-affective psychotic disorders. These findings highlighted the substantial burden of non-affective psychotic disorder in late-life and identified several potential socio-demographic risk factors associated with VLOSLP incidence. This is important given that people aged over 65 years old have frequently been excluded from epidemiological research focussed on psychotic disorders.

Additionally, there is ongoing debate about the aetiology of VLOSLP and its potential association with neurodegeneration (Vahia et al., 2010). Given the lack of data on this topic, in Chapter 5 I conducted a matched cohort study with Swedish register data to directly examine the rate of dementia in individuals with VLOSLP. The cohort study presented in Chapter 5 was the largest study to date with the longest follow-up period to investigate this topic. I found a substantially higher rate of dementia in those with VLOSLP relative to the matched comparison group, which was robust to adjustment for sex, educational attainment, disposable income at age 60 years old, and offspring psychotic disorder diagnosis. The hazard ratio (HR) attenuated somewhat in a sensitivity analysis where those diagnosed with dementia within six months of diagnosis with VLOSLP were excluded, although the rate of dementia remained considerably higher in the VLOSLP group, suggesting that misdiagnosis of dementia as VLOSLP may partly, but not fully explain this association. The rate of dementia in the comparison group was higher in women, consistent with previous research (Mazure & Swendsen, 2016), whereas in those with VLOSLP the rate

of dementia was higher in men. In the comparison group, those with offspring with a non-affective psychotic disorder had a higher rate of dementia, whereas this was not found in those with VLOSLP. The rate of dementia remained higher among those with VLOSLP in Fine and Gray competing risks regression in which death was modelled as a competing risk. The hazard ratio attenuated somewhat in a sensitivity analysis considering previous contact with health services in the comparison group, suggesting that better detection of dementia in the VLOSLP group may have partly, but not fully, explained the association found between VLOSLP and subsequent dementia.

In Chapter 6, I examined the feasibility of a case-control study investigating levels of social isolation, loneliness and impairments in social cognition in those with VLOSLP. I found that the recruitment rate from Community Mental Health Teams was substantially lower than the target rate. For a variety of documented reasons (see Chapter 6), it was challenging to identify a sufficient number of eligible cases within the time-frame of the study and the uptake of the study was low among potentially eligible cases. This study demonstrated the importance of secondary data in gaining insight into the aetiology and outcomes of VLOSLP. In this Chapter, I discussed the importance of conducting future qualitative studies involving patients with VLOSLP and clinicians to gain a better understanding of barriers to research participation in this patient group. Additionally, I argued that future studies may require multiple study sites with the potential for pooling datasets across sites, and I highlighted the need to include measures of VLOSLP and late-life psychotic symptoms in ongoing cohort studies involving older people, where possible.

7.2 Broad limitations of studies in this thesis

Before discussing the interpretation of findings, it is important to highlight potential threats to the validity of the studies described in this thesis. This section discusses broad limitations of each study in relation to chance, bias and confounding.

7.2.1 Chance

I sought to minimise the possibility of results being due to chance by defining study hypotheses *a priori*. For the systematic review, I published the study protocol online prior to

conducting analyses. Pre-registering studies and setting out *a priori* hypotheses is important for reducing practices such as p-hacking, cherry picking results, and data-dredging, all of which may have contributed to problems with replication in scientific research (Gelman, 2014). Issues with replication have also been attributed to an over-reliance on p-values in interpreting findings (Concato & Hartigan, 2016). This has led some authors to propose a redefinition of statistical significance for new discoveries to be p<.005, which remains an arbitrary cut-off point but may help to improve reproducibility (Benjamin et al., 2018), while others have called for limiting the use of p-values altogether (Amrhein & Greenland, 2018). In Chapters 4 and 5 I reported hazard ratios alongside 95% confidence intervals rather than focusing on p-values alone to interpret results. Nonetheless, cautious interpretation is needed in cases where findings were marginally significant; these findings will require replication in other large, longitudinal studies.

The studies presented in Chapters 4 and 5 used the Swedish register data, which includes data on almost the entire population, allowing good statistical power and precision in estimates. Although large sample sizes are crucial for detecting small but potentially important effects, it should be noted that this can also lead to statistically significant results which have little meaning at a clinical or policy-level (Simon, 2019). For example, this may apply to the weak evidence found in Chapter 4 of a slightly higher rate of VLOSLP in those who experienced the death of a child in infancy, which approached significance, but may be of limited public health or clinical relevance. By contrast, in Chapter 6, the proposed sample size for recruitment was relatively small, limiting statistical power and increasing the possibility of chance findings. Findings from this case-control study would need to be replicated in larger samples to allow greater confidence in the results. However, as highlighted in Chapter 6, this would be challenging given difficulties in recruiting patients with VLOSLP.

7.2.2 Bias

To mitigate against potential bias in the review (Chapter 2), I systematically searched the literature using comprehensive search terms. Non-systematic search strategies can lead to bias in that highly cited papers are more easily found and are therefore more likely to be included (Delgado-Rodrıguez & Llorca, 2004). Meta-analyses can be affected by publication

bias, where findings based on published data may not represent findings from unpublished work. Although I cannot fully exclude the possibility of publication bias in this review, I found no evidence of this based on inspection of funnel plots and via Egger's test.

A key strength of the Swedish register data used in Chapters 4 and 5 is the reduced potential for selection bias given that almost the entire Swedish population are automatically enrolled in the registers via a Personal Identification Number. This limits bias related to attrition, self-selection into studies, study withdrawal and non-response. Nonetheless, certain groups may be underrepresented in the registers, including those not registered in Sweden, such as undocumented migrants and those living in Sweden temporarily. As discussed in Chapter 5, the competing risk of death may have led to an underestimate of the rate of dementia in those with VLOSLP, given the higher mortality rate in this group. I aimed to examine and account for this potential source of bias by conducting Fine and Grey competing risks regression, incorporating both death and dementia as outcomes.

As described in Chapter 6, detection bias may have influenced findings in that dementia may be more easily detected in those with VLOSLP due to patients already being in contact with mental health services. I conducted a sensitivity analysis to examine this possibility and found that the association between VLOSLP and dementia appeared to be partly and substantially, but not fully, driven by differences in detection between groups (see Chapter 5). The fully adjusted hazard ratio for those with VLOSLP relative to the comparison group with one or more hospital diagnoses in the year on either side of study entry was 2.89 (95%CI: 2.75–3.04), whereas the hazard ratio was considerably higher in those with VLOSLP relative to those in the comparison group without a diagnosis during this time (HR: 4.90 95%CI: 4.69–5.13). Additionally, diagnostic overshadowing may have influenced findings of a lower rate of VLOSLP among those with sensory impairment in Chapter 4, given evidence that physical health problems tend to be under-detected in those with serious mental illness (Roberts et al., 2006; Smith et al., 2013).

While previous studies suggest that the schizophrenia diagnosis has high validity within the Swedish registers (Ludvigsson et al., 2011), no study has specifically evaluated the validity of non-affective psychotic disorder diagnoses in older people in the registers. Further, in

Chapters 4 and 5, I was only able to include diagnosed non-affective psychotic disorders, hence those who did not come to the attention of the broad healthcare system were excluded, which may have led to an underestimate of the incidence of VLOSLP. I cannot exclude the possibility that those with VLOSLP may be less likely to contact services than those with a younger, more typical age-at-onset of psychotic disorders, and that there may be systematic differences between those with VLOSLP who do and do not contact services. These possibilities require investigation in future research.

Another potential limitation is that I may have over-estimated VLOSLP incidence in the Swedish registers in Chapters 4 and 5, given that the registers only began recording psychiatric diagnoses in 1973. I could not obtain data on diagnosed psychotic disorders before this time, and it is therefore possible that I have misclassified some prevalent cases with psychotic disorders as incident cases of VLOSLP. However, there was a seven-year washout period between 1973 and the beginning of the follow-up period in 1980, during which new cases with psychotic disorders were excluded. Although it would be expected that most prevalent cases with a psychotic disorder would present to services during this time, it remains possible that some prevalent cases diagnosed with psychotic disorders earlier in life (e.g. before age 60 years old) have been wrongly classified as VLOSLP cases in this study, thereby overestimating VLOSLP incidence.

Additionally, as discussed in Chapter 4, it was not possible to obtain data on previous hospital diagnoses for migrants before their arrival in Sweden. In light of this, it is possible that some migrants with previously diagnosed psychotic disorders have wrongly been identified as incident cases with VLOSLP. As described in Chapter 4, I conducted a sensitivity analysis in which I excluded migrants diagnosed with a non-affective psychotic disorder within two years of their arrival in Sweden to examine the potential impact of this possible source of bias. In this sensitivity analysis, the rate of VLOSLP attenuated somewhat among migrants, suggesting that this bias may explain some of the excess risk of VLOSLP in migrants. Nonetheless, the rate of VLOSLP remained higher in most migrant groups relative to those born in Sweden, suggesting that this source of bias did not fully account for the association between migration and VLOSLP. Additionally, an alternate explanation for this

attenuation is that, given that migration can represent an acute stressor, this may bring people into contact with services for VLOSLP more quickly after arrival in Sweden.

Additionally, as discussed in Chapter 5, there were issues around detection of dementia diagnoses in the Swedish registers. While almost all cases of dementia detected in the Swedish registers have been found to be 'true cases', a validation study found that around half of cases with dementia are not picked up by the registers (Rizzuto et al., 2018). However, I would not necessarily expect this to differ between those with and without VLOSLP, except in relation to the potential differences in detection described above. There were also some limitations in the way in which I defined exposures in Chapters 4 and 5, the implications of which were discussed in each chapter. Although the Swedish register data are highly complete, with missing data limited to education and income variables in Chapter 5 (5.4%), and to income only in Chapter 4 (1.7%), I cannot rule out the possibility that this has influenced results due to different patterns of missing data related to exposure status.

Selection bias is a concern in the feasibility study described in Chapter 6, given that half of the eligible cases with VLOSLP declined to participate in the study. It is possible that those who declined to participate systematically differed from those who agreed to take part. I aimed to mitigate against measurement error in Chapter 6 by using well-validated questionnaires. While observer and self-report bias are less relevant to studies involving the Swedish register data, these are important considerations in Chapter 6 which involved primary data collection. For example, I cannot exclude the possibility of observer bias in scoring participants on the observer-rated PANSS and PRS measures. Further, given the stigma associated with concepts such as loneliness, social isolation and mental health, reporting bias is a concern in Chapter 6. It is possible that participants' answers were influenced by social desirability, although I would not expect this to differ between cases and controls. The potential for recall bias is limited in the register data, given their prospective nature. However, this remains a concern in Chapter 6 where, for example, the Geriatric Adverse Life Events Scale assessed adverse life events over the last year, although this potential source of bias would not necessarily differ between cases and controls.

As discussed in Chapter 6, the choice of control group is crucial to the validity of findings from case-control studies. In Chapter 5, I used hospital controls drawn from the same Community Mental Health Teams as cases. Benefits of hospital controls include practicality, and possible similarities in motivation to participate and quality of information, such as likelihood of recall bias (Infante-Rivard, 2003). Further, in Chapter 5, it was considered more interesting and relevant to examine social isolation and loneliness levels in those with VLOSLP relative to those with other mental health difficulties, rather than compared to the general population. However, a key limitation is that hospital controls may not be selected independently of exposure status (Grimes & Schulz, 2005). I aimed to dilute this potential source of bias (Rothman et al., 2008) by recruiting controls with mixed mental health diagnoses, rather than focusing on a single diagnosis such as depression.

7.2.3 Reverse causation

The studies described in Chapters 4 and 5 were longitudinal, which provides important insight into the temporal relationship between exposures and outcomes. Despite this, reverse causation cannot be excluded as an explanation for several findings in this thesis. For example, in Chapter 4, the association between lower disposable income and VLOSLP could be explained by social drift due to prodromal symptoms of psychotic disorder, as has been the subject of debate in those with a younger, more typical age-at-onset psychotic disorder (Gage, Smith, & Munafo, 2016; Sariaslan et al., 2016). However, this may be less plausible in relation to VLOSLP given that social standing in old age is strongly shaped by earlier socio-economic status. Additionally, in Chapter 4, I found that the rate of VLOSLP was higher among those who had no partner or children. This could implicate social isolation as a risk factor for VLOSLP, or conversely, this finding may be driven by reduced fecundity in those with psychotic disorders, as described in Chapter 4. Further, in Chapter 5 it was not possible to determine whether the association between VLOSLP and dementia implicated psychosis as a risk factor for dementia, or whether psychotic symptoms may be part of the dementia prodrome for some individuals. Reverse causation is also possible in Chapter 6, where associations between social isolation, loneliness and VLOSLP could operate in either direction, particularly given the cross-sectional study design.

7.2.4 Confounding

In Chapters 4 and 5 I have accounted for a range of potentially important confounders, although it was not always possible to obtain data on potential confounders from the Swedish register data. For example, I was not able to obtain data on antipsychotic medications, IQ, or health behaviours, which may be confounders of the association between VLOSLP and dementia. Additionally, there may have been residual confounding due to the use of proxy variables and imperfect measures of potential confounders. For instance, the death of a partner variable was partly based on census information recorded every 5 years, hence there was imprecision in the way in which this variable was defined, potentially leading to residual confounding. Additionally, while I was able to include a disposable income at age 60 variable to index socio-economic status, it was not possible to examine other potentially relevant social and environmental factors, such as drug and alcohol abuse, population density, social capital or childhood trauma. Although I was able to take into account offspring psychotic disorder diagnosis, it was not possible to obtain data on parents of this cohort; hence I cannot exclude the possibility that residual genetic confounding partially explains the observed associations found between VLOSLP and environmental factors. Further, it was not possible to account for family history of dementia.

Confounding may have explained the associations found between age, sex, migration and VLOSLP identified in the systematic review (Chapter 2). It was not possible to examine many of these potential confounders due to variation in covariates included across studies identified in the review and given that most included studies only reported crude incidence rates. In light of this, I was only able to adjust for study-level factors such as time period and study quality. In Chapter 6, I aimed to be comprehensive in taking into account potential confounding variables in the association between VLOSLP, social isolation, loneliness and social cognition. Potential confounders measured in this study included demographic information, adverse life events, depression, anxiety, and IQ, which were measured using well-validated questionnaires.

7.3 Meaning of findings and research in context

I have interpreted findings from this thesis in the context of the biopsychosocial model, as described in Chapter 1, which posits that the aetiology of psychotic disorders is shaped by the interplay between biological, environmental and psychological factors. In light of this, in the following section, I discuss the meaning of findings in relation to the previous psychotic disorder epidemiology literature and broader literature on the biological and psychological underpinnings of psychotic disorders.

7.3.1 VLOSLP incidence and sex differences

A key finding from this thesis was the relatively high burden of non-affective psychotic disorder incidence in old age identified in Chapters 2 and 4, which contrasts with the view that first-episode psychosis only affect younger people. In the Swedish register data (Chapter 4), I found an incidence rate of non-affective psychotic disorders of 44.61 per 100kpy (95%CI: 43.95–45.27). To contextualise this, in a recent meta-analysis, the pooled incidence rate of non-affective psychotic disorders (with a younger, more typical age-at-onset) in population register studies was 90.9 per 100,000 person-years (95%CI: 34.5–237.5), with substantial variation between studies (Jongsma et al., 2019). However, the rate of VLOSLP found in Chapter 4 is higher than the rates of non-affective psychotic disorders identified across studies in the systematic review focussed specifically on VLOSLP (Chapter 2), which ranged from 14.3 (95%CI: 10.5-18.1) to 39.9 per 100kpy (95%CI: 31.1–51.3). This corresponds with evidence that the rate of psychotic disorders tends to be higher in register-based studies relative to first-contact studies (Hogerzeil, Hemert, Rosendaal, Susser, & Hoek, 2019; Jongsma et al., 2019), which may reflect truly higher rates in regions where most case register studies are conducted (e.g. Nordic countries). Alternatively, administrative registers, which may have coverage of almost an entire population, may be more effective in ascertaining cases of psychotic disorder than is possible in first contact studies, given that administrative registers pick up cases across the breadth of emergency and secondary care settings nationally, whereas first contact studies may limit case ascertainment, for example, to secondary mental health care only. Conversely, it is also possible that standardised diagnostic instruments used in first contact studies screen out some people who would be wrongly identified as cases in administrative registers, given

their reliance on diagnoses made in clinical practice (Hogerzeil et al., 2019). While previous studies have found high validity for non-affective psychotic disorder diagnoses within the Swedish registers (Ludvigsson et al., 2016), the validity of these diagnoses in those aged 60 years old and above has not been examined, and requires investigation.

Findings from Chapters 2 and 4 add further weight to previous evidence of a higher preponderance of VLOSLP among women relative to men (Howard et al., 2000), demonstrating that this finding holds in a large, longitudinal population-based study. To put this in to context, in Chapter 4, I found a peak incidence rate of 93.42 per 100,000 person-years at risk in women aged between 85-89, while, for example, in a Danish register study the peak incidence rate of non-affective psychotic disorder (F20-F29) was found to be 211 per 100,000 person-years at-risk in men aged 19-24 in the years 2011-2012 (Kühl, Munk, Thorup, & Nordentoft, 2016).

Several potential explanations have been put forward for sex differences found in the incidence of non-affective psychotic disorders across the life course. In those with a younger, more typical age-at-onset, psychotic disorder incidence is consistently found to be higher among men (Abel et al., 2010; Aleman et al., 2003; Riecher-Rössler, Butler, & Kulkarni, 2018). This could be partly explained by bias, given evidence that the rate of psychotic disorder tends to be higher in men when narrower diagnostic criteria and upper age limits (e.g. age 40) are applied (Castle et al., 1993), although a recent systematic review found no evidence to support this (Aleman et al., 2003). By contrast, rather than reflecting bias, these differences in ascertainment could also reflect biological phenomena leading to a predisposition towards neurodevelopmental disorders in men, including autism spectrum disorders (Werling & Geschwind, 2013). In line with this, it has been argued that men tend to present with a more severe neurodevelopmental form of schizophrenia with a younger age-at-onset, a stronger family history of psychotic disorder, more cognitive impairment and negative symptoms, and poorer functional outcomes compared to women (Castle, Wessely, & Murray, 1993; Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012). Nonetheless, it remains possible that men do not have a higher rate of psychotic disorder than women but are more likely to contact services due to a more severe presentation, which could not be ruled out in the aforementioned review (Aleman et al., 2003). However, this is not supported by

evidence of a higher rate of psychotic disorder in men in register-based studies (Jongsma et al., 2019), which are likely to be less affected by this potential source of bias. An interesting caveat is that, while a higher incidence rate of more typical age-at-onset psychotic disorder has been found in men, several studies have found no sex difference in prevalence (McGrath, Saha, Chant, & Welham, 2008; Perälä et al., 2007; Saha et al., 2007). Reasons for this are unclear, although this may reflect a higher mortality rate and lower compliance rates in men (Aleman et al., 2003).

Additionally, several potential mechanisms have been put forward to explain the higher preponderance of women with late-onset schizophrenia (LOS) and VLOSLP. Perhaps the most widely discussed potential mechanism is the decline in oestrogen in women in mid-life, given its potential anti-dopaminergic properties (Riecher-Rössler & Hafner, 1993). Interestingly, this mechanism has also been implicated in the increased risk of dementia (Gilsanz et al., 2019), and heart disease in mid-life in women (Merz & Cheng, 2016). However, few studies have examined this mechanism in relation to psychotic disorders. It has also been posited that sex differences in exposure to inflammatory states and microglial activation at different stages of neurodevelopment may differentially predispose men and women to neurodevelopmental and neurodegenerative conditions (Hanamsagar & Bilbo, 2016). However, this theory is based on findings from animal models and requires further investigation in humans. To date, there has been limited discussion in the literature of potential psychosocial factors which may contribute to sex differences in psychotic disorder risk at different life stages, including different patterns of psychosocial stress, adversity and/or socio-economic status in women in middle- and old-age. This requires investigation in future research. Another consideration is that the higher rate of LOS and VLOSLP in women could partly be explained by higher mortality rates in men as a competing risk.

7.3.2 Potential environmental risk factors for VLOSLP

In Chapters 2 and 4 I identified several potential environmental risk factors associated with a higher rate of VLOSLP, including migration and socio-economic status, with weaker evidence of an association with adverse life events. The biopsychosocial framework highlighted above provides insight into the pathways through which environmental risk factors may impart risk for psychotic disorders.

First, in this thesis, I found narrative evidence of a higher rate of VLOSLP among migrants to the UK in a systematic review (Chapter 2), and a higher rate of VLOSLP among most migrant groups to Sweden (Chapter 4). This corresponds with a substantial body of evidence of a higher rate of psychotic disorder among migrants in those with a younger, more typical age-at-onset of psychotic disorder across a range of regions and migrant groups (Jongsma et al., 2019; Selten & Cantor-Graae, 2005; Selten et al., 2018). These findings do not appear to be due to a higher rate of psychotic disorder in migrants' regions of origin, and there is little evidence to date that findings can be fully explained by diagnostic bias related to cultural misunderstanding (Morgan & Hutchinson, 2017), although these possibilities require further investigation.

The mechanisms underlying the higher rate of psychotic disorders in migrants are not fully understood, but findings from epidemiology, psychology and cognitive neuroscience have helped to elucidate several potential pathways. First, evidence of a higher rate of psychotic disorders among refugee migrants relative to non-refugee migrants in Sweden (Hollander et al., 2016) suggests that trauma and adversity prior to and during migration may increase risk for psychotic disorders. Second, the rate of psychotic disorders has been found to be higher in those with visible minority status, indicating that post-migratory factors such as discrimination may play a role (Bourque et al., 2011; Veling et al., 2007). Third, the association between migration and psychotic disorders has been found to extend to second generation migrants (Selten et al., 2018). This adds further weight to the potential role of post-migratory factors and suggests that the association between migration and psychotic disorders is unlikely to be fully explained by selective migration in those already predisposed to psychotic disorders (Veling et al., 2007). Fourth, there is some evidence that ethnic density is a protective factor associated with a lower rate of psychotic disorder in migrants (Boydell et al., 2001; Schofield, Ashworth, & Jones, 2011), highlighting the potential relevance of factors such as social support, social isolation, cultural distance and exposure to racism.

It may be that adversity experienced at different stages of migration, including post-migration, contribute to social stress, sensitisation of the dopamine system and subsequent psychotic symptoms. Evidence from the field of cognitive neuroscience provides some initial

support for the role of heightened stress sensitivity. For instance, in a functional magnetic resonance imaging (fMRI) study, individuals with ethnic minority status living in Germany showed elevated levels of perceived chronic stress and increased activation and functional connectivity in the perigenual anterior cingulate cortex (pACC), which has been linked to social stress processing (Akdeniz et al., 2014). Additionally, as discussed above, social stress may contribute to dysfunction of the dopamine system and subsequent psychotic symptoms (Howes & Kapur, 2009). Correspondingly, two positron emission tomography (PET) case-control studies conducted in the UK and Canada found that striatal dopamine release and dopamine synthesis capacity in relation to stress were significantly higher in immigrants compared to non-immigrants, including in those with psychotic disorders (Egerton et al., 2017). Further investigation of these mechanisms is required in larger samples. Additionally, there is a need to examine whether the same mechanisms are relevant in explaining the association between migration and VLOSLP.

In Chapter 4, the higher rate of VLOSLP among most migrant groups did not attenuate after adjustment for disposable income, which was strongly and independently associated with VLOSLP. This corresponds with previous evidence that the higher rate of psychotic disorders in migrants does not appear to be entirely explained by socio-economic status (Kirkbride et al., 2008). In addition, the finding of a higher rate of VLOSLP in those with a lower income extended previous evidence of an association between socio-economic status and psychotic disorder in those with a more typical age-at-onset (Hollingshead & Redlich, 1958; Silver et al., 2002). However, I could not account for other potentially relevant social factors, such as social capital, which remain potential unmeasured confounders. It is possible that the associations found between VLOSLP, socio-economic status and migration are partly driven by social defeat, where long-term exposure to social exclusion from the majority group has been posited to increase risk for schizophrenia via social stress and sensitization of the mesolimbic dopamine system (Selten, van der Ven, Rutten, & Cantor-Graae, 2013; Selten & Cantor-graae, 2007; Selten et al., 2005).

Evidence regarding the rate of VLOSLP in relation to adverse life events was more mixed in this thesis (Chapter 4), with a slightly higher rate in those who experienced the death of a child in infancy but not between ages 12 months to 18 years. There was no evidence of a

higher rate of VLOSLP in those who experienced the recent death of a partner after adjustment for confounders. By contrast, several previous small-scale studies have identified associations between VLOSLP and adverse life events, including childhood trauma (Fuchs, 1994, 1999; Gurian et al., 1992; Reulbach et al., 2007). Further, there is a larger body of evidence demonstrating an association between more typical age-at-onset psychotic disorders and trauma, including recent adverse life events (Beards et al., 2013), childhood trauma, and bullying (Coughlan & Cannon, 2017; Van Dam et al., 2012; Varese et al., 2012), which may increase risk for mental health difficulties, including psychotic disorders, via heightened stress sensitivity and hyper-vigilance to perceived threat (McCrory, De Brito, & Viding, 2012). Further research is needed to examine other types of traumatic experience not investigated in this thesis in relation to VLOSLP, including childhood adversity. This is important, given evidence that maltreatment in childhood is associated with an increased risk of physical and mental health problems into late life (McCrory et al., 2015). Additionally, in Chapter 4, social isolation as indexed by having no partner or children, was associated with a higher rate of VLOSLP, although I cannot exclude the possibility of reverse causation, as described above. Further research is needed to investigate the association between social isolation, loneliness and VLOSLP, as discussed in Chapter 6.

Additionally, further longitudinal research is needed to examine the association between sensory impairment and VLOSLP. In Chapter 4, I found a lower rate of VLOSLP in those with hearing and visual impairment, which contrasts with previous evidence of associations between more typical age-at-onset psychotic disorders and hearing (Linszen, Brouwer, Heringa, & Sommer, 2016) and visual impairment (Hayes et al., 2019; Viertiö et al., 2007). These findings also differ from several previous studies which found an association between late-life psychotic disorders and sensory impairment (Cooper & Curry, 1976; Cooper et al., 1974; Cooper & Porter, 1976), although these studies were limited by small and unrepresentative samples, cross-sectional study designs and imprecise or poorly-defined measures of sensory impairment (Prager & Jeste, 1993). However, findings from Chapter 4 also contrast with a recent large, longitudinal cohort study of men which found a higher rate of incident psychotic disorders in old age in those with previous hearing loss (Almeida et al., 2018a). Given the mixed findings in this area, further large-scale longitudinal research is needed to investigate the association between hearing and visual impairment and VLOSLP in

greater depth. In particular, there is a need to differentiate between congenital versus acquired and mild versus severe sensory impairment and to examine variation related to age-at-onset of sensory impairment and proximity to diagnosis with VLOSLP.

The aetiology of VLOSLP may be more heterogeneous than the aetiology of psychotic disorders with a younger, more typical age-at-onset, given the potential for overlap with neurodegeneration and dementia. Although causality cannot be inferred directly from the observational studies in this thesis, these findings provide clues about the aetiology of VLOSLP to be investigated further in future studies. It is important to note that many of the potential risk factors found to be associated with VLOSLP are also associated with psychotic disorders in those with a younger, more typical age-at-onset (Table 7.1). These findings provide some evidence of the potential for shared underpinnings between VLOSLP and psychotic disorders with a more typical age-at-onset, in contrast to the view that VLOSLP is entirely explained by neurodegeneration or misdiagnosed dementia.

Table 7.1 Associations with socio-demographic factors in VLOSLP and more typical age-at-onset psychotic disorders

Potential risk factor[a]	Adult onset non-affective psychotic disorder (typical age-at-onset)[b]	VLOSLP[b]
Migration	+	+
Lower socio-economic status	+	+
Adverse life events	+	~
Social isolation	+	+
Sensory impairment	~	~

a: Only includes potential risk factors examined in this thesis
b: + Denotes higher rate of non-affective psychotic disorder or VLOSLP, - denotes lower rate of non-affective psychotic disorder or VLOSLP, ~ indicates mixed findings

7.3.3 Outcomes associated with VLOSLP

Findings from Chapter 5 highlight several adverse outcomes associated with VLOSLP, including a higher rate of subsequent dementia and mortality. This corresponds with previous evidence of a higher rate of dementia in those with subthreshold psychotic symptoms (Köhler et al., 2013), psychotic disorder with a more typical age-at-onset (Cai & Huang, 2018), and other mental health difficulties such as depression (Singh-Manoux et al., 2017) and anxiety (Gulpers et al., 2016). There are several potentially important mechanisms which may underlie a 'true' association between VLOSLP and subsequent

dementia, as discussed in Chapter 5, including lower cognitive reserve (Stern, 2006), a higher prevalence of physical health comorbidities such as Type-II diabetes (Bushe & Holt, 2004; Osborn et al., 2008) and heart disease (Crump et al., 2013; Hennekens et al., 2005; Osborn et al., 2007), social deprivation, negative lifestyle factors (McCreadie, 2002, 2003), and accelerated biological ageing (Kirkpatrick et al., 2008). It is also possible that dementia and VLOSLP share common causes, such as inflammation, which is associated with both conditions (Wium-Andersen, Orsted, & Nordestgaard, 2014). An important direction for future research is to investigate these potential mechanisms (see Section 7.5).

Conversely, it is possible that dementia neuropathology, which can develop decades before diagnosis (Villemagne et al., 2013), directly contributes to psychiatric symptoms, such as psychosis. Consistent with this possibility, in Chapter 5, individuals with VLOSLP were diagnosed with dementia at a quicker rate than the matched comparison group, with most being diagnosed relatively close to the time of diagnosis with VLOSLP, suggesting that psychotic symptoms may reflect prodromal dementia for some people.

However, importantly, while the rate of dementia was higher among those with VLOSLP in Chapter 5, the majority of individuals with VLOSLP were not subsequently diagnosed with dementia. Even considering the higher mortality rate in individuals with VLOSLP and the under-detection of dementia diagnoses in the registers, this does not support the idea that VLOSLP is entirely explained by misdiagnosed dementia or VLOSLP as part of the dementia prodrome. In further support of this, a previous review found that, while patients with VLOSLP showed mild cognitive deficits and decline above the level expected with healthy ageing, there was little evidence of cases of neuropathology or neurodegeneration beyond that observed in more typical age-at-onset psychotic disorders, after accounting for age (Van Assche et al., 2017). Additionally, in Chapter 5, the rate of dementia remained higher in those with VLOSLP throughout most of the follow-up period, which suggests that VLOSLP could also be a risk factor for dementia in some cases, or that the conditions may share common causes. This corresponds with previous evidence of a higher rate of subsequent dementia in those with late-onset psychotic disorders (age 40 years old and above) and younger, more typical age-at-onset psychotic disorders (Cai & Huang, 2018). Further

research is needed to directly compare and examine the association between dementia and psychotic disorders with varying age-at-onset.

Findings of a higher mortality rate among those with VLOSLP in Chapter 5 correspond with previous evidence of a higher mortality rate in those with psychotic disorders, including VLOSLP, with no difference in the rate by age-at-onset (Meesters et al., 2016). In contrast, another study reported a higher mortality rate among those with VLOSLP relative to those of the same age with a more typical age-at-onset of psychotic disorder (Talaslahti et al., 2015). Further research is needed to investigate potential mechanisms for the high mortality rate among individuals with VLOSLP, which requires greater insight into factors contributing to poor physical health in this group.

7.4 Implications of findings

It is important to note that causality cannot be directly inferred from associations between social factors and mental health outcomes identified in observational epidemiology studies, including findings from this thesis. The concept of causality has been debated by philosophers throughout history and continues to present a substantial challenge in medical research (Rothman & Greenland, 2005). Given that the aetiology of psychotic disorders is considered to be complex and multi-causal, it is unlikely that the environmental risk factors identified in Chapters 2 and 4 are sufficient to cause VLOSLP in the absence of other characteristics. However, it is possible that these environmental factors are causally associated with VLOSLP in the presence of relevant genetic factors, and/or vulnerability to neurodevelopmental impairments or neurodegeneration.

Throughout this thesis, where possible, I sought to examine and mitigate the possibility of non-causal explanations for findings via sensitivity analyses, as discussed above. For instance, in Chapter 5, I conducted sensitivity analyses to examine the potential roles of misdiagnosis and detection bias as potential explanations of the association between VLOSLP and dementia, and I conducted competing risks regression to examine whether findings were likely to be explained by differential mortality rates between groups. Further, a key strength of the studies described in Chapters 4 and 5 was the use of longitudinal datasets with long follow-up periods, which allowed insight into the temporal relationships

between exposures and outcomes. Nonetheless, findings from this thesis will require replication in other large, population-based cohorts, and triangulation with varied methods and study designs to increase confidence in the results.

Despite challenges in inferring causality, findings may have implications for policy and for informing clinical practice. First, in Chapter 4, I demonstrated an association between VLOSLP and several markers of social adversity. This adds to a considerable body of evidence demonstrating associations between social risk factors and mental health outcomes across the life course (Buttrick, 2017; McCrory & Viding, 2015; Ribeiro et al., 2017), including psychotic disorders, where a range of environmental factors including migration, urbanicity and social disadvantage have been implicated. These findings have played a key role in refuting earlier views that psychotic disorders can be entirely explained by genetic factors; instead, as discussed throughout this thesis, research suggests that the aetiology of psychotic disorders is biopsychosocial (Howes & Murray, 2014). Relative to genetics, environmental factors are more amenable to prevention and intervention (Kirkbride et al., 2010). However, further research is needed to investigate potential mechanisms underlying broad associations between the environment and psychotic disorders, and to examine whether these could be modifiable risk factors, with the aim of reducing psychotic disorder and VLOSLP incidence in the population.

Given that findings from Chapters 4 and 5 are based on register data from Sweden, caution should be taken in applying them directly to other contexts. Nonetheless, these findings may have implications for clinicians, particularly old age psychiatrists, and more broadly for service provision. The relatively high incidence rate of VLOSLP identified in Chapter 4 suggests that VLOSLP may be more common than was previously realised. It is important for general practitioners to be aware that first episode psychosis can also occur in later life. Additionally, the higher rate of dementia found in those with VLOSLP is likely to be relevant to old age psychiatrists in terms of monitoring cognitive decline and considering treatment options in this group. However, it is also important for clinicians to be aware that, while it is possible that VLOSLP could be part of the preclinical phase of dementia for some individuals, VLOSLP shares a number of risk factors with more typical age-at-onset psychotic disorders and is not always synonymous with neurodegeneration and subsequent dementia.

Findings may also have broader implications in relation to service provision, for example, with regard to Early Intervention in Psychosis (EIP) services. EIP services have typically focussed on younger people, with origins in the youth mental health model in Australia (McGorry, Bates, & Birchwood, 2013). While age 35 has traditionally been the age cut-off for accessing EIP services in the UK, in 2016, as part of a new Access and Waiting Time Standard for EIP services, the NICE guidelines recommended that the age range should be extended to include those aged 14-65 (NICE, 2016). This change is important given the gender inequity in access to EIP services where a younger age cut-off is implemented, due to the later age-at-onset of psychotic disorders in women (Lappin et al., 2016). Where an older age cut-off has been applied, those with a later age-at-onset have been found to make up around 25% of EIP services. While this change may lead to quicker and more effective treatments for those with a later age-at-onset who were previously excluded from services, it is important to consider that this group may have different needs from younger people with psychotic disorders (Greenfield et al., 2018). EIP services are not typically accessed by those aged 65 and above, who are normally seen by old age mental health services. This is important given the potential for differential diagnosis, including overlap with dementia (Greenfield et al., 2018). However, the NICE guidelines stated that EIP services may be appropriate for those outside of the age 14-65 age range in some cases, based on clinical judgment. Given the relatively high incidence rate of psychotic disorders in those aged 60 years old and above identified in Chapters 2 and 4, it is important that older people with a first episode of psychosis are able to access comparable levels of support as younger people accessing EIP services. Further, although a high proportion of mental health difficulties begin in adolescence (Kessler et al., 2007), there is a need to ensure that prevention and early intervention strategies are not entirely conflated with youth and that the mental health needs of older people are considered a priority.

7.5 Future questions and research directions in VLOSLP

Based on findings from this thesis, several key themes have emerged which require further investigation. First, questions remain about the aetiology of VLOSLP and how this differs from more typical age-at-onset psychotic disorders. A potential method for delineating these conditions in future would be to investigate the neurodevelopmental underpinnings

of VLOSLP, given that younger, more typical age-at-onset psychotic disorders are considered to be partly neurodevelopmental in origin (Murray & Lewis, 1987; Murray, Bhavsar, Tripoli, & Howes, 2017). This is evidenced by epidemiological findings of associations between psychotic disorders and neurodevelopmental markers, including: developmental delays (Dickson et al., 2012), exposure to viruses in utero and in early childhood (Brown, 2006; Dalman et al., 2008), exposure to famine in utero (Susser et al., 1998), and obstetric complications (Cannon et al., 2002). Additionally, psychotic disorders are comorbid with neurodevelopmental disorders such as autism (Selten, Lundberg, Rai, & Magnusson, 2015), and are associated with a higher prevalence of rare CNVs (Kavanagh et al., 2015), which are also implicated in other neurodevelopmental disorders (Sanders et al., 2011). Future studies examining VLOSLP in relation to these neurodevelopmental markers may provide clues into the aetiology of VLOSLP and how it may differ from psychotic disorders with a more typical age-at-onset. However, the Swedish registers do not currently go back far enough to allow those with VLOSLP to be linked with their parents, and it is likely to be challenging to identify other secondary data sources where data on early life can be linked with diagnoses of psychotic disorders later in later life.

Additionally, the association between VLOSLP and urbanicity remains under-examined, despite evidence of associations between urban birth and urban residence in those with more typical age-at-onset psychotic disorders (Fett et al., 2019; Marcelis et al., 1999; March et al., 2008; Vassos, Pedersen, Murray, Collier, & Lewis, 2012). Interestingly, recent data suggest that the association between urbanicity and psychotic disorders may not be present across all regions (Jongsma et al., 2018), although this requires further investigation, particularly in lower and middle-income countries, given limitations in the study by DeVylder et al. (2018) as highlighted in Chapter 1. Nonetheless, these findings suggest that urbanicity may not be a risk factor for psychotic disorder in itself, but rather, may be a proxy for other variables which are associated with urbanicity in some regions, but not others (Plana-Ripoll, Pedersen, & Mcgrath, 2018). Possible mechanisms proposed to underlie this association include stress associated with urban living, vitamin D deficiency, substance use, exposure to infections and pollutants, and social factors such as social cohesion and social isolation (Fett et al., 2019; March et al., 2008; McGrath & Scott, 2016; Plana-Ripoll et al., 2018), although there is currently little evidence to support these potential mechanisms.

Genetic selection may also play a role, although evidence to date is mixed (Paksarian et al., 2018; Sariaslan et al., 2016). Gaining further insight into this association in those with VLOSLP may provide further clues about the aetiology of VLOSLP and about the role of urbanicity as a potential risk factor for psychotic disorders across the life course.

More broadly, little is known about the genetic underpinnings of VLOSLP in comparison to psychotic disorders with a more typical age-at-onset, where a GWAS has identified 108 loci conferring a small amount of risk for schizophrenia (Ripke et al., 2014), and those with schizophrenia have also been found to have a higher burden of rare copy number variants (Kavanagh et al., 2015). By contrast, only several relatively small-scale studies have investigated family history of psychotic disorder in those with VLOSLP, with some evidence of a lower morbid schizophrenia risk among relatives in those with VLOSLP compared to those with younger, more typical age-at-onset psychotic disorders (Howard et al., 1997; Pearlson et al., 1989). In Chapter 4, although it was not possible to obtain data on the parents of cohort members, I found a higher rate of VLOSLP in those who had offspring with a non-affective psychotic disorder, relative to those who did not. However, this will have overestimated the prevalence of psychotic disorder family history. In light of this, further research is needed to gain a more in depth understanding of the genetic underpinnings of VLOSLP. This is important for delineating VLOSLP from more typical age-at-onset psychotic disorders and may provide insight into the aetiology of VLOSLP in relation to neurodevelopment and neurodegeneration.

Although most studies in this thesis focussed on risk factors associated with VLOSLP, it could be interesting to reframe this to consider potential protective factors. If VLOSLP is considered to be comparable to psychotic disorders with a more typical age-at-onset, this leads to the question of whether there are protective genetic and/or environmental factors which could serve to delay the onset of psychotic disorders until later life. This may help to elucidate potentially modifiable risk factors for VLOSLP and for younger, more typical age-at-onset psychotic disorders. There is also a need to better understand the previous mental health trajectories of those with VLOSLP before they first contact services in later life with a psychotic disorder, both in terms of previous subthreshold psychotic symptoms and other mental health difficulties such as depression, anxiety and drug and alcohol abuse.

Additionally, findings of a higher rate of dementia among those with VLOSLP (Chapter 5) lead to questions about the nature of this association. Going forward, there is a need to examine whether there are particular subgroups of individuals with VLOSLP with a more neurodegenerative form of the condition and an increased risk of dementia. This may require more in-depth information about symptoms and cognitive functioning, alongside brain imaging and genetic data, where possible. Additionally, there is a need to examine whether VLOSLP is associated with mild cognitive impairment, where there is a high risk of progression to dementia (Cohen, 2018).

Findings from Chapter 5 also lead to broader questions about the relationship between mental health and dementia, given existing epidemiological evidence of a higher rate of subsequent dementia in those with depression, bipolar disorder, schizophrenia, anxiety disorders and alcohol dependence (Gulpers et al., 2016; Singh-Manoux et al., 2017; Zilkens, Bruce, Duke, Spilsbury, & Semmens, 2014). As discussed above, this association could be driven by factors such as poor physical health and lower cognitive reserve. Alternatively, given that Alzheimer's Disease neuropathology can be present up to three decades before symptoms emerge (Villemagne et al., 2013), it is possible that this neuropathology leads to psychiatric symptoms in the preclinical, asymptomatic phase. Further research is needed to disentangle the complex relationship between psychiatric conditions and dementia.

7.6 Conclusion

This thesis has presented a varied body of work examining risk factors and outcomes associated with very late-onset schizophrenia-like psychosis via systematic review, cohort studies involving Swedish population register data and a feasibility study involving primary data collection. Findings addressed a substantial gap in knowledge regarding psychotic disorder incidence in older people, given that those aged 65 and above have consistently been excluded from research on the epidemiology of psychotic disorders. A key finding was the substantial burden of non-affective psychotic disorder incidence in older people, in contrast to the idea that first-episode psychosis only affects younger people and providing evidence of a higher rate of VLOSLP in women and migrants. This thesis also presented the first epidemiological evidence of an association between low income and VLOSLP incidence,

with some weaker evidence of an association with adverse life events. Importantly, these findings suggest that VLOSLP shares similar social risk factors to psychotic disorders with a more typical age-at-onset, demonstrating that associations between psychotic disorders and the environment persist into late life. In addition, I found evidence of a strong association between VLOSLP and incident dementia after adjusting for confounders and considering potential sources of bias, which is likely to be relevant to old age psychiatrists. Although causality cannot be directly inferred from the observational studies conducted in this thesis, findings help to complete the life course picture of psychotic disorder incidence, providing clues into the aetiology of VLOSLP and the pathways linking VLOSLP and dementia. Despite the substantial burden of VLOSLP incidence identified in this thesis, this group remain under-researched. Findings from this thesis have opened up new avenues for investigation, while highlighting the importance of including those with VLOSLP in epidemiological research focussed on psychotic disorders, and in ensuring that this group are able to access comparable levels of support to younger people experiencing a first episode of psychosis.

7.7 Dissemination of findings from this thesis

At the time of completion, adaptations of the following Chapters have been published:

Chapter 2

Stafford, J., Howard, R., & Kirkbride, J. B. (2018). The incidence of very late-onset psychotic disorders: a systematic review and meta-analysis, 1960–2016. *Psychological Medicine*, *48*(11), 1775-1786. doi:10.1017/S0033291717003452

Chapter 4

Stafford, J., Howard, R., Dalman, C., & Kirkbride, J. B. (2018). The Incidence of Nonaffective, Nonorganic Psychotic Disorders in Older People: A Population-based Cohort Study of 3 Million People in Sweden. *Schizophrenia Bulletin*, *45*(5), 1152-1160. doi:10.1093/schbul/sby147

Conference presentations

Findings from Chapters 2, 4, 5 and 6 have been presented as oral and/or poster presentations at national and international conferences, including the following: International Federation of Psychiatric Epidemiology (IFPE), MQ Mental Health Science Meeting, and the UCL Population Health Symposium.

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Appendix 1. Study documents for Chapter 6

1. Information sheet
2. Consent form
3. Demographic information sheet
4. Lubben Social Network Scale – Revised (LSNS-R)
5. UCLA Loneliness Scale
6. Ambiguous Intentions Hostility Questionnaire (AIHQ)
7. Faux Pas Test
8. National Adult Reading Test (NART)
9. Geriatric Adverse Life Events Scale (GALES)
10. Hospital Anxiety and Depression Scale (HADS)
11. Psychosis Rating Scale (PRS)
12. Positive and Negative Syndrome Scale (PANSS)

1. Participant information sheet

Social isolation and loneliness in people aged 60 and above (Student study)

Information about the study

We are researchers from University College London (UCL). We would like to invite you to take part in a research study. This study will form part of an academic qualification for Jean Stafford: a PhD student at UCL.

Before you decide if you would like to take part, it is important for you to understand why the research is being done and what it will involve for you.

Please read the following information carefully, and discuss it with others if you wish. Take your time to decide whether or not you wish to participate.

What is the purpose of the study?

We know that being socially isolated from other people and feeling lonely are sometimes linked with poor health and well-being. We would like to find out whether people aged 60 and above who have received treatment for mental health difficulties experience isolation and feelings of loneliness, and the possible reasons for this.

We hope that this study will help us to understand whether there is a need for more social support to people aged 60 and above who have experienced difficulties with their mental health.

Why have I been invited to take part?

Around 60 people aged 60 and above will be involved in this study. You have been invited to take part because you are aged 60 or above and are currently receiving or have previously received support or treatment from Camden and Islington NHS Foundation Trust (Community Mental Health Team) for a mental health difficulty.

What would taking part involve?

If you decide to take part in the study, you will meet with a researcher, Jean Stafford, who will ask you some questions. This should take up to two hours, including breaks as needed. As in many studies, the researcher will ask you some questions about yourself, including about your age, ethnicity, living arrangements, marital status, education and employment history. Jean will also ask you about your relationships with your family and friends and the amount of social support that you are receiving. She will also ask some questions about your mental health and any major life events you have experienced recently.

Jean will also read you some short stories about people in different social situations and ask you some questions about the stories. She will also ask you to read a list of words aloud. Your answers will be entered into a computer and will be stored securely (see section below on confidentiality).

You will only meet with Jean once to complete the study. The time taken to complete the study will vary, although we estimate that it may take around two hours, including

breaks as needed. The study will take place at a location convenient for you and the researcher, which could be at your home, within a clinical setting or at UCL, depending on your needs and preference. We will reimburse travel costs for those travelling to take part in the study. We are not offering any treatment as part of this study.

Are there any risks or benefits of taking part?

There are no specific risks from taking part in the study and no changes will be made to your usual health care in relation to this study.

It is possible that answering personal questions about your mental health, major life events or social isolation and loneliness could be distressing. If the interview does cause you any significant distress the research team will contact your mental health service provider to arrange further support for you, as needed.

Although there are no direct benefits from taking part in the study, we hope that findings could be used to benefit and support people with mental health difficulties in the future.

Will my taking part in the study be kept confidential?

If you take part in the study, the data we collect from questionnaires will only be seen by authorised members of the study team. In line with the Data Protection Act (1998) we have a duty of confidentiality. This means we will keep your data confidential and secure. The answers you provide will be stored in the UCL Data Safe Haven: a system for securely storing and handling data. Your answers will be stored separately from any potentially personal identifying information that is specific to you, like your name, address, telephone number, email address and date or birth. This personal identifying information will be kept at UCL within the Data Safe Haven, separately from your answers to the questionnaires, so that we can contact you to arrange a study visit. Study data will not be shared with anyone outside of the study team. Personally identifiable data will not be kept for longer than 12 months after the study has ended. Data from the questionnaires, without personally identifiable data, will be stored securely at UCL for ten years after the end of the study and then securely destroyed.

Your GP and mental health care professionals currently involved in your care will be informed of your participation in the study. Relevant sections of your medical notes may be looked at by members of the research team or the NHS trust where it is relevant to you taking part in the study. If the research team become concerned about any risk of harm to yourself or others, we will need to pass this on to your GP or mental health service provider so that they can offer you any help and support necessary.

What will happen if I don’t want to carry on with the interview?

You are free to end your participation in the study at any point. Your care will not be affected by any decision that you make to take part or withdraw from the study. If you decide to withdraw your consent from the study, the information from the

questionnaires you have completed up to that point will be used anonymously in the analysis of the study results. Please let the researcher know if you would prefer for this data not to be used.

What if there is a problem?

If you have a concern about any part of this study, please speak to Jean (contact details listed below), or another member of the research team, who will try their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this by contacting the Camden and Islington NHS Foundation Trust Advice and Complaints Service.

What will happen to results of the study?

We will keep participants informed about results of the study via a newsletter, should you wish to receive this. We have pre-registered the study at https://clinicaltrials.gov, and our findings will be reported here at the end of the study. We hope to publish findings of the study in peer-reviewed academic journals and to present the findings at academic meetings and conferences. No names or other identifiable information will be included in any presentations, reports or publications.

Who has organised and approved the research?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Queen Square Research Ethics Committee.

Further information about study data

University College London (UCL) is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. UCL will keep identifiable information about you for 1 year after the study has ended.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting the researchers (see below).

Camden and Islington NHS Foundation Trust will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from UCL and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Camden and Islington NHS Foundation Trust will pass these details to UCL along with the information collected from you. The only people in UCL who will have access to information that

identifies you will be people who need to contact you to arrange study visits, to send out the study newsletter (if you have consented to receive this) or to audit the data collection process.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

2. Consent form

Study Title: Social isolation and loneliness in people aged 60 and above (Student study)

Name of Researcher:

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated 30/10/2017 Version 2.0 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that I can ask to take a break at any time during the study. ☐
4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
5. I agree to my GP and other health professionals involved in my care being informed of my participation in the study. ☐
6. I understand that if the research team becomes concerned about risk of harm to myself or others during the study they will need to contact my mental health service provider. ☐
7. In the event that I decide to stop taking part in the study, I agree to the data up to that point being used in the anonymous analysis of the study results. ☐
8. I agree to being sent a newsletter by the research team with results from the study by email or post after the end of the study. ☐
9. I agree to taking part in the above study. ☐

Name of participant	Signature	Date
Name of person taking consent	Signature	Date

3. Demographic information sheet

General information

Thank you for agreeing to take part in this study. This section asks some general questions about yourself.

1. How old are you? _____

2. What is your gender? _____

3. What is your ethnicity?

- ☐ White British or White Other
- ☐ Black African
- ☐ Black Caribbean
- ☐ Bangladeshi
- ☐ Indian
- ☐ Pakistani
- ☐ Mixed ethnicity
- ☐ Other Black, Asian or Other ethnicity, *please specify* _____

4. What is your marital status?

- ☐ Married
- ☐ Living with partner, unmarried
- ☐ Have partner, unmarried and living separately
- ☐ Divorced
- ☐ Divorced (in the last 12 months)
- ☐ Widowed or separated
- ☐ Widowed or separated (in the last 12 months)
- ☐ Single, never married or with long-term partner(s)
- ☐ Single, previously had long term partner(s)

5. What are your current living arrangements?

- ☐ Living alone
- ☐ Living with spouse or partner
- ☐ Living with another person apart from spouse or partner
- ☐ Institutional living arrangements

6. What level of education have you had?

- ☐ No qualification
- ☐ Clerical, commercial or trade qualification
- ☐ O level or equivalent
- ☐ A level or equivalent
- ☐ No qualification
- ☐ Other qualification (please specify) _____

7. What was your last occupation? _____

8. What was your partner's last occupation (if applicable)? _____

9) a. How many children do you have, if any? _____

b. How often do you see or hear from them (if applicable)?

- ☐ Daily
- ☐ Few times a week
- ☐ Weekly
- ☐ Few times a month
- ☐ Once a month
- ☐ Few times a year
- ☐ Once a year
- ☐ Less than once a year

10) a. How many grandchildren do you have, if any? _____

b. How often do you see or hear from them (if applicable)?

- ☐ Daily
- ☐ Few times a week
- ☐ Weekly
- ☐ Few times a month
- ☐ Once a month
- ☐ Few times a year
- ☐ Once a year
- ☐ Less than once a year

11) a. Has anyone in your family ever been diagnosed with a mental health condition (such as depression or schizophrenia)?

- ☐ Yes
- ☐ No
- ☐ Unsure

b. If yes, what was the name of the diagnosis (if known)?

_____

c. How is/was this person related to you (e.g. mother, sibling, son, aunt) [if applicable]?

_____

4. Lubben social network scale – revised (LSNS-R)

FAMILY: Considering the people to whom you are related by birth, marriage, adoption, etc…

1. How many relatives do you see or hear from at least once a month?

0 = none 1 = one 2 = two 3 = three or four 4 = five thru eight 5 = nine or more

2. How often do you see or hear from the relative with whom you have the most contact?

0 = less than monthly 1 = monthly 2 = few times a month 3 = weekly 4 = few times a week 5 = daily

3. How many relatives do you feel at ease with that you can talk about private matters?

0 = none 1 = one 2 = two 3 = three or four 4 = five thru eight 5 = nine or more

4. How many relatives do you feel close to such that you could call on them for help?

0 = none 1 = one 2 = two 3 = three or four 4 = five thru eight 5 = nine or more

5. When one of your relatives has an important decision to make, how often do they talk to you about it?

0 = never 1 = seldom 2 = sometimes 3 = often 4 = very often 5 = always

6. How often is one of your relatives available for you to talk to when you have an important decision to make?

0 = never 1 = seldom 2 = sometimes 3 = often 4 = very often 5 = always

FRIENDSHIPS: Considering all of your friends including those who live in your neighborhood…

7. How many of your friends do you see or hear from at least once a month?

0 = none 1 = one 2 = two 3 = three or four 4 = five thru eight 5 = nine or more

8. How often do you see or hear from the friend with whom you have the most contact?

0 = less than monthly 1 = monthly 2 = few times a month 3 = weekly 4 = few times a week 5 = daily

9. How many friends do you feel at ease with that you can talk about private matters?

0 = none 1 = one 2 = two 3 = three or four 4 = five thru eight 5 = nine or more

10. How many friends do you feel close to such that you could call on them for help?

0 = none 1 = one 2 = two 3 = three or four 4 = five thru eight 5 = nine or more

11. When one of your friends has an important decision to make, how often do they talk to you about it?

0 = never 1 = seldom 2 = sometimes 3 = often 4 = very often 5 = always

12. How often is one of your friends available for you to talk to when you have an important decision to make?

0 = never 1 = seldom 2 = sometimes 3 = often 4 = very often 5 = always

5. UCLA Loneliness Scale

Scale:
INSTRUCTIONS: Indicate how often each of the statements below is descriptive of you.

C indicates "I often feel this way"
S indicates "I sometimes feel this way"
R indicates "I rarely feel this way"
N indicates "I never feel this way"

1.	I am unhappy doing so many things alone	O S R N
2.	I have nobody to talk to	O S R N
3.	I cannot tolerate being so alone	O S R N
4.	I lack companionship	O S R N
5.	I feel as if nobody really understands me	O S R N
6.	I find myself waiting for people to call or write	O S R N
7.	There is no one I can turn to	O S R N
8.	I am no longer close to anyone	O S R N
9.	My interests and ideas are not shared by those around me	O S R N
10.	I feel left out	O S R N
11.	I feel completely alone	O S R N
12.	I am unable to reach out and communicate with those around me	O S R N
13.	My social relationships are superficial	O S R N
14.	I feel starved for company	O S R N
15.	No one really knows me well	O S R N
16.	I feel isolated from others	O S R N
17.	I am unhappy being so withdrawn	O S R N
18.	It is difficult for me to make friends	O S R N
19.	I feel shut out and excluded by others	O S R N
20.	People are around me but not with me	O S R N

6. Ambiguous Intentions Hostility Questionnaire

PLEASE READ EACH OF THE SITUATIONS LISTED BELOW AND IMAGINE THE SITUATION HAPPENING TO YOU. FOR EACH SITUATION, RATE WHETHER YOU THINK THE PERSON ACTED THAT WAY TOWARD YOU ON PURPOSE. YOU WILL THEN BE ASKED TO RATE HOW ANGRY THAT SITUATION MAKES YOU FEEL AND HOW MUCH YOU BLAME THE OTHER PERSON.

1. Someone jumps in front of you on the grocery line and says, "I'm in a rush."

A. Did that person jump in front of you on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame that person for jumping in front of you on line?

1	2	3	4	5
Not at All				Very Much

2. A friend of yours slips on the ice, knocking you onto the ground.

A. Do you think your friend knocked you onto the ground on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame your friend for knocking you onto the ground?

1	2	3	4	5
Not at All				Very Much

3. You've been at a new job for three weeks. One day, you see one of your new co-workers on the street. You start to walk up to this person and start to say hello, but she/he passes by you without saying hello.

A. Do you think your co-worker did this to you on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame the co-worker for passing by you?

1	2	3	4	5
Not at All				Very Much

4. While walking outside during the rain, a car swerves to avoid hitting a cat, and drives into a puddle, splashing water onto you.

A. Do you think the driver of the car splashed water onto you on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame the person in the car for splashing water onto you?

1	2	3	4	5
Not at All				Very Much

5. You have an appointment with an important person. When you arrive at your appointment, the secretary informs you that the person is not in; they took the day off.

A. Do you think the person did this to you on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame the person for not keeping your appointment?

1	2	3	4	5
Not at All				Very Much

6. You are on a bus sitting in an aisle seat. A person gets on the bus at the next stop, begins walking as the bus moves, and steps on your foot.

A. Do you think the person did this to you on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame the person for stepping on your foot?

1	2	3	4	5
Not at All				Very Much

7. Your neighbors are playing loud music. You knock on the door and ask them to turn it down. Fifteen minutes later, the music is loud again.

A. Do you think your neighbors raised the music on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame them for raising the music again?

1	2	3	4	5
Not at All				Very Much

8. You walk past a bunch of teenagers at a mall and your hear them start to laugh.

A. Do you think the teenagers did this to you on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame the teenagers for laughing as you walked past them?

1	2	3	4	5
Not at All				Very Much

9. While driving, the person in the car behind you honks their horn and then cuts you off.

A. Do you think the person cut you off on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame the driver of the car for cutting you off on the road?

1	2	3	4	5
Not at All				Very Much

10. You are supposed to meet a new friend for lunch at a restaurant but she/he never shows up.

A. Do you think your new friend did this to you on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame your new friend for not showing up at the restaurant?

1	2	3	4	5
Not at All				Very Much

11. You've been looking for a parking spot for awhile, when you see one up ahead. You put your signal on, proceed toward the spot, but someone passes your car and takes the parking space.

A. Do you think the person in the other car took your parking space on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

C. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

D. How much would you blame the person in the other car for taking your parking space?

1	2	3	4	5
Not at All				Very Much

12. You're dancing at a club and someone bumps into you from behind.

A. Do you think the person bumped into you on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame the person for bumping into you at the club?

1	2	3	4	5
Not at All				Very Much

13. You call a friend and leave a message on their answering machine, asking them to call you back. One week passes and they have not called you back.

A. Do you think your friend didn't call you back on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame your friend for not calling you back?

1	2	3	4	5
Not at All				Very Much

14. You're at a bar watching a football game and having a drink. Suddenly, the home team scores, people begin to cheer, and someone hits your arm, spilling the drink onto your clothes.

A. Did the other person hit your arm on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame the other person for hitting your arm?

1	2	3	4	5
Not at All				Very Much

15. A day before meeting someone for a date, she/he calls to cancel. This is the third straight time they've done that.

A. Did the other person cancel the date on purpose?

1	2	3	4	5	6
Definitely No	Probably No	Maybe No	Maybe Yes	Probably Yes	Definitely Yes

B. How angry would this make you feel?

1	2	3	4	5
Not at all Angry				Very Angry

C. How much would you blame the other person for canceling the date?

1	2	3	4	5
Not at All				Very Much

7. Faux pas test

Story 1. Helen's husband was throwing a surprise party for her birthday. He invited Sarah, a friend of Helen's, and said, "Don't tell anyone, especially Helen." The day before the party, Helen was over at Sarah's and Sarah spilled some coffee on a new dress that was hanging over her chair.
"Oh!" said Sarah, "I was going to wear this to your party!"
"What party?" said Helen.
"Come on," said Sarah, "Let's go see if we can get the stain out."

1. Did anyone say something they shouldn't have said or something awkward?

If yes, ask:
1. Who said something they shouldn't have said or something awkward?
2. Why shouldn't he/she have said it or why was it awkward
3. Why do you think he/she said it?
4. Did Sarah remember that the party was a surprise party?
5. How do you think Helen felt?

Control question:
7. In the story, who was the surprise party for?
8. What got spilled on the dress?

Story 2. Jim was shopping for a shirt to match his suit. The salesman showed him several shirts. Jim looked at them and finally found one that was the right colour. But when he went to the fitting room and tried it on, it didn't fit. "I'm afraid it's too small," he said to the salesman. "Not to worry," the salesman said. "We'll get some in next week in a larger size."

"Great. I'll just come back then," Jim said.

1. Did anyone say something they shouldn't have said or something awkward?

If yes, ask:
2. Who said something they shouldn't have said or something awkward?
3. Why shouldn't he/she have said it or why was it awkward?
4. Why do you think he/she said it?
5. When he tried on the shirt, did Jim know they didn't have it in his size?
6. How do you think Jim felt?

Control question:
7. In the story, what was Jim shopping for?
8. Why was he going to come back next week?

Story 3. Bob went to the barber for a haircut. "How would you like it cut?" the barber asked. "I'd like the same style as I have now, only take about an inch off," Bob replied. The barber cut it a little uneven in the front, so he had to cut it shorter to even it out. "I'm afraid it's a bit shorter than you asked for," said the barber.
"Oh well," Bob said, "it'll grow out."

1. Did anyone say something they shouldn't have said or something awkward?

If yes, ask:
2. Who said something they shouldn't have said or something awkward?
3. Why shouldn't he/she have said it or why was it awkward?
4. Why do you think he/she said it?
5. While he was getting the haircut, did Bob know the barber was cutting it too short?
6. How do you think Bob felt?

Control question:
7. In the story, how did Bob want his hair cut?
8. How did the barber cut his hair?

Story 4. Joan took her dog, Zack, out to the park. She threw a stick for him to chase. When they had been there a while, Pam, a neighbour of hers, passed by. They chatted for a few minutes. Then Pam asked, "Are you heading home? Would you like to walk together?"

"Sure," Joan said. She called Zack, but he was busy chasing pigeons and didn't come. "It looks like he's not ready to go," she said. "I think we'll stay."
"OK," Pam said. "I'll see you later."

1. Did anyone say something they shouldn't have said or something awkward?

If yes, ask:
2. Who said something they shouldn't have said or something awkward?
3. Why shouldn't he/she have said it or why was it awkward?
4. Why do you think he/she said it?
5. When she invited her, did Pam know that Joan wouldn't be able to walk home with her?
6. How do you think Pam felt?

Control question:
7. In the story, where had Joan taken Zack?
8. Why didn't she walk with her friend Pam?

Story 5. Jean West, a manager in Abco Software Design, called a meeting for all of the staff. "I have something to tell you," she said. "John Morehouse, one of our accountants, is very sick with cancer and he's in hospital." Everyone was quiet, absorbing the news, when Robert, a software engineer, arrived late. "Hey, I heard this great joke last night!" Robert said. "What did the terminally ill patient say to his doctor?" Jean said, "Okay, let's get down to business in the meeting."

1. Did anyone say something they shouldn't have said or something awkward?

If yes, ask:
2. Who said something they shouldn't have said or something awkward?
3. Why shouldn't he/she have said it or why was it awkward?
4. Why do you think he/she said it?
5. When he came in, did Robert know that the accountant was sick with cancer?
6. How do you think Jean, the manager, felt?

Control question:
7. In the story, what did Jean, the manager, tell the people in the meeting?
8. Who arrived late to the meeting?

Story 6. Jeanette bought her friend, Anne, a crystal bowl for a wedding gift. Anne had a big wedding and there were a lot of presents to keep track of. About a year later, Jeanette was over one night at Anne's for dinner. Jeanette dropped a wine bottle by accident on the crystal bowl and the bowl shattered. "I'm really sorry. I've broken the bowl," said Jeanette. "Don't worry," said Anne. "I never liked it anyway. Someone gave it to me for my wedding."

1. Did anyone say something they shouldn't have said or something awkward?

If yes, ask:
2. Who said something they shouldn't have said or something awkward?
3. Why shouldn't he/she have said it or why was it awkward?
4. Why do you think he/she said it?
5. Did Anne remember that Jeannette had given her the bowl?
6. How do you think Jeanette felt?

Control question:
7. In the story, what did Jeanette give Anne for her wedding?
8. How did the bowl get broken?

Story 7. Tim was in a restaurant. He spilled some coffee on the floor by accident. "I'll get you another cup of coffee," said the waiter. The waiter was gone for a while. Jack was another customer in the restaurant, standing by the cashier waiting to pay. Tim went up to Jack and said, "I spilled coffee over by my table. Can you mop it up?"

1. Did anyone say something they shouldn't have said or something awkward?

If yes, ask:
2. Who said something they shouldn't have said or something awkward?
3. Why shouldn't he/she have said it or why was it awkward?
4. Why do you think he/she said it?
5. Did Tim know that Jack was another customer?
6. How do you think Jack felt?

Control question:
7. In the story, why was Jack standing by the cashier?
8. What did Tim spill?

Story 8. Eleanor was waiting at the bus stop. The bus was late and she had been standing there a long time. She was 65 and it made her tired to stand for so long. When the bus finally came, it was crowded and there were no seats left. She saw a neighbour, Paul, standing in the aisle of the bus. "Hello, Eleanor," he said. "Were you waiting there long?" "About 20 minutes," she replied. A young man who was sitting down got up. "Ma'am, would you like my seat?"

1. Did anyone say something they shouldn't have said or something awkward?

If yes, ask:
2. Who said something they shouldn't have said or something awkward?
3. Why shouldn't he/she have said it or why was it awkward?
4. Why do you think he/she said it?
5. When Eleanor got on the bus, did Paul know how long she had been waiting?
6. How do you think Eleanor felt?

Control question:
7. In the story, why was Eleanor waiting at the bus stop for 20 minutes?
8. Were there any seats available on the bus when she got on?

Story 9. Roger had just started work at a new office. One day, in the coffee room, he was talking to a new friend, Andrew. "What does your wife do?" Andrew asked. "She's a lawyer," answered Roger. A few minutes later, Claire came into the coffee room looking irritated. "I just had the worst phone call," she told them. "Lawyers are all so arrogant and greedy. I can't stand them." "Do you want to come look over these reports?" Andrew asked Claire. "Not now," she replied, "I need my coffee."

1. Did anyone say something they shouldn't have said or something awkward?

If yes, ask:
2. Who said something they shouldn't have said or something awkward?
3. Why shouldn't he/she have said it or why was it awkward?
4. Why do you think he/she said it?
5. Did Claire know that Roger's wife was a lawyer?
6. How do you think Roger felt?

Control question:
7. In the story, what does Roger's wife do for a living?
8. Where were Roger and Andrew talking?

Story 10. Louise went to the butcher to buy some meat. It was crowded and noisy in the shop. She asked the butcher, "Do you have any free-range chickens?" He nodded and started to wrap up a roasted chicken for her. "Excuse me," she said, "I must not have spoken clearly. I asked if you had any free-range chickens." "Oh, sorry," the butcher said, "we're all out of them."

1. Did anyone say something they shouldn't have said or something awkward?

If yes, ask:
2. Who said something they shouldn't have said or something awkward?
3. Why shouldn't he/she have said it or why was it awkward?
4. Why do you think he/she said it?
5. When he started wrapping up a chicken for Louise, did the butcher know that she wanted a free range chicken?
6. How do you think Louise felt?

Control question:
7. In the story, where did Louise go?
8. Why did the butcher start to wrap up a roasted chicken for her?

8. National Adult Reading Test (NART)

CHORD	COURTEOUS	HIATUS	FAÇADE	GAUCHE
ACHE	RAREFY	SUBTLE	ZEALOT	TOPIARY
DEPOT	EQUIVOCAL	PROCREATE	DRACHM	LEVIATHAN
AISLE	NAÏVE	GIST	AEON	BEATIFY
BOUQUET	CATACOMB	GOUGE	PLACEBO	PRELATE
PSALM	GAOLED	SUPERFLUOUS	ABSTEMIOUS	SIDEREAL
CAPON	THYME	SIMILE	DÉTENTE	DEMESNE
DENY	HEIR	BANAL	IDYLL	SYNCOPE
NAUSEA	RADIX	QUADRUPED	PUERPERAL	LABILE
DEBT	ASSIGNATE	CELLIST	AVER	CAMPANILE

9. Hospital anxiety and depression scale

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

10. Geriatric Adverse Life Events Scale (GALES)

Event	Yes	No
Financial/Work Difficulties		
1) Major financial difficulties	Y	N
2) Retirement	Y	N
3) Sudden loss of employment	Y	N
Physical illness/Accident		
4) New major physical illness	Y	N
5) Other major physical illness	Y	N
6) Major physical illness of a close family member	Y	N
7) Accident or injury	Y	N
Interpersonal conflicts		
8) Marital separation or divorce	Y	N
9) Other marital difficulties	Y	N
10) Major family problems/conflicts other than with spouse	Y	N
11) Major problems/conflicts with friends or neighbours	Y	N
12) Break-up of a long-term relationship other than marriage	Y	N
13) Separation from any other close friend or relative	Y	N
Interpersonal loss		
14) Death of spouse	Y	N
15) Death of child	Y	N
16) Death of parent	Y	N
17) Death of brother or sister	Y	N
18) Death of other relative or close friend	Y	N
19) Death of pet	Y	N
Disruption in Living Situation		
20) Forced to leave or lose home (e.g. eviction)	Y	N
21) Voluntarily changed place of residence	Y	N
22) Individual moved out of house (excluding marriage/relationship break-up)	Y	N
23) Individual moved into house	Y	N
Other Life Events		
24) Difficulty getting adequate professional services	Y	N
25) Victim of crime	Y	N
26) Became caretaker for relative or friend	Y	N

11. Psychosis rating scale

	0. Absent	1. Mild	2. Moderate	3. Severe
Delusions	Includes presence of unusual ideas; e.g. religious or grandiose that don't meet criteria for delusions.	Delusions encapsulated and only revealed by direct question; e.g. "How do you get on with your neighbour"?	Spontaneously reveals delusional system involving persecutory, grandiose, intrusions, fantastic or sexual themes, but can move to discuss alternative subject areas without reference to delusions.	Preoccupied with delusional system involving persecutory, grandiose, intrusions, fantastic or sexual themes, with or without distress. Can't move to alternative subject without reference to delusions.
Hallucinations	Includes complaints of music or noise from neighbours when this can be heard, even if only faintly, by others.	Simple sounds that are not detectable by others; e.g. machinery hum, or more complex sounds, voices, tactile experiences and images present less often than daily.	Complex or intrusive sounds, voices, tactile experiences or images present at least daily.	Complex or intrusive sounds, voices, tactile experiences or images present at least several times per day or patient observed responding to them during examination.
Impact	Includes understandable restriction of activity; e.g. not going out after dark.	Some evidence that behaviour or routine has been altered because of delusions, but only minor impact.	Delusions have caused significant distress and have restricted activity, but not to the point of increasing risk or causing major disruption to life.	Has acted on delusions in a way that has severely increased risk or disrupted life; e.g. angry confrontation with neighbour or moved out of home.
Insight Impairment		Prepared to entertain idea that difficulties might arise from an illness and accept treatment.	Does not accept that problems arise from a mental health difficulty but is prepared to try treatment.	Completely rejects possibility of mental health problem and refuses to even consider treatment.

12. Positive and Negative Syndrome Scale (PANSS)

Positive symptoms

P1. Delusions Beliefs which are unfounded, unrealistic, and idiosyncratic. Basis for rating thought content expressed in the interview and its influence on social relations and behavior.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Presence of one or two delusions which are vaque, uncrystallized, and not tenaciously held. Delusions do not interfere with thinking, social relations, or behavior.	☐
4 Moderate - Presence of either a kaleidoscopic array of poorly formed, unstable delusions or of a few wellformed delusions that occasionally interfere with thinking, social relations, or behavior.	☐
5 Moderate severe - Presence of numerous well-formed delusions that are tenaciously held and occasionally interfere with thinking, social relations, or behavior.	☐
6 Severe - Presence of a stable set of delusions which are crystallized, possibly systematized, tenaciously held, and clearly interfere with thinking, social relations, and behavior.	☐
7 Extreme - Presence of a stable set of delusions which are either highly systematized or very numerous, and which dominate major facets of the patient's life. This frequently results in inappropriate and irresponsible action, which may even jeopardize the safety of the patient or others.	☐

P2. Conceptual disorganization Disorganized process of thinking characterized by disruption of goal-directed sequencing, e.g., circumstantiality, tangentiality, loose associations non sequiturs, gross illogicality, or thought block. Basis for rating: cognitive-verbal processes observed during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Thinking is circumstantial, tangential, or paralogical. There is some difficulty in directina thoughts toward a goal and some loosening o7 associations may be evidenced under pressure.	☐
4 Moderate - Able to focus thoughts when communications are brief and structured, but becomes loose or irrelevant when dealing with more complex communications or when under minimal pressure.	☐
5 Moderate severe - Generally has difficulty in organizing thoughts, as evidenced by frequent irrelevances, disconnectedness. or loosening of associations even when not under pressure.	☐
6 Severe - Thinking is seriously derailed and internally inconsistent, resulting in gross irrelevancies and disruption of thought processes, which occur almost constantly.	☐
7 Extreme - Thoughts are disrupted to the point where the patient is incoherent. There is marked loosening of associations, which results in total failure of communication, e.g., "word salad. or mutism.	☐

P3. Hallucinatory behavior Verbal report or behavior indicating perceptions which are not generated by external stimuli. These may occur in the auditory visual, olfactory, or somatic realms. Basis for rating: Verbal report and physical manifestations during the course of interview as well as reports of behavior by primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - One or two clearly formed but infrequent hallucinations, or else a number of vaque abnormal perceptions which do not result in distortions of thinking or behavior.	☐
4 Moderate - Hallucinations occur frequently but not continuously, and the patient's thinking and behavior are affected only to a minor extent.	☐
5 Moderate severe - Hallucinations are frequent, may involve more than one sensory modality, and tend to distort thinking and/or disrupt behavior. Patient may have a delusional interpretation of these experiences and respond to them emotionally and, on occasion, verbally as well.	☐
6 Severe - Hallucinations are present almost continuously, causing major disruption of thinking and behavior. Patient treats these as real perceptions, and functioning is impeded by frequent emotional and verbal responses to them.	☐
7 Extreme - Patient is almost totally preoccupied with hallucinations, which virtually dominate thinking and behavior. Hallucinations are provided a rigid delusional interpretation and provoke verbal and behavioral responses, including obedience to command hallucinations.	☐

P4. Excitement Hyperactivity as reflected in accelerated motor behavior, heightened responsivity to stimuli hypervigilance, or excessive mood lability. Basis for rating: Behavioral manifestations during the course of interview as well as reports of behavior by primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Tends to be slightly agitated, hypervigilant, or mildly overaroused throughout the interview, but without distinct episodes of excitement or marked moolabitity. Speech may be slightly pressured.	☐
4 Moderate - Agitation or overarousal is clearly evident throughout the interview, affecting speech and general mobility, or episodic outbursts occur sporadically	☐
5 Moderate severe - Significant hyperactivity or frequent outbursts of motor activity are observed, making it difficult for the patient to sit still for longer than several minutes at any given time.	☐
6 Severe - Marked excitement dominates the interview delimits attention, and to some extent affects personal functions such as eating and sleeping.	☐
7 Extreme - Marked excitement seriously interferes in eating and sleeping and makes interpersonal interactions virtually impossible. Acceleration of speech and motor activity may result in incoherence and exhaustion.	☐

P5. Grandiosity Exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power, and moral righteousness. Basis for rating: thought content expressed in the interview and its influence on behavior.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Some expansiveness or boastfulness is evident, but without clear-cut grandiose delusions.	☐
4 Moderate - Feels distinctly and unrealistically superior to others. Some poorly formed delusions about special status or abilities may be present but are not acted upon.	☐
5 Moderate severe - Clear-cut delusions concerning remarkable abilities, status, or power are expressed and influence attitude but not behavior.	☐
6 Severe - Clear-cut delusions of remarkable superiority involving more than one parameter (wealth, knowledge, fame, etc.) are expressed, notably influence interactions, and may be acted upon.	☐
7 Extreme - Thinking, interactions, and behavior are dominated by multiple delusions of amazing ability, wealth knowledge, fame, power, and/or moral stature; which may take on a bizarre quality.	☐

P6. Suspiciousness/persecution Unrealistic or exaggerated ideas of persecution, as reflected in guardedness, a distrustful attitude, suspicious hypervigilance, or frank delusions that others mean one harm. Basis for rating: thought content expressed in the interview and its influence on behavior.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Presents a guarded or even openly distrustful attitude, but thoughts, interactions, and behavior are minimally affected.	☐
4 Moderate - Distrustfulness is clearly evident and intrudes on the interview andior behavoir, but there is no evidence of persecutorv delusions. Alternatively, there may be indication of loosely formed persecutory delusions, but these do not seem to affect the patient's attitude or interpersonal relations	☐
5 Moderate severe - Patient shows marked distrust fulness, leading to major disruption of interpersonal relations, or else there are clear-cut persecutory delusions that have limited impact on interpersonal relations and behavoir.	☐
6 Severe - Clear-cut pervasive delusions of persecution which may be svstematized and significantly interfere in interpersonal relations.	☐
7 Extreme - A network of systematized persecutory delusions dominates the patient's thinking, social relations, and behavior.	☐

P7. Hostility Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behavior, verbal abuse, and assaultiveness. Basis for rating: interpersonal behavoir observed during the interview and reports by primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Indirect or restrained communication of anger such as sarcasm, disrespect, hostile expressions, and occasional irritability.	☐
4 Moderate - Presents an overtly hostile attitude, showing frequent irritability and direct expression of anger or resentment.	☐
5 Moderate severe - Patient is highly irritable and occasionally verbally abusive or threatening.	☐
6 Severe - Uncooperativeness and verbal abuse or threats notably influence the interview and seriously impact upon social relations. Patient may be violent and destructive but is not physically assaultive toward others.	☐
7 Extreme - Marked anger results in extreme uncooperativeness, precluding other interactions, or in eoisede(s) of physical assault toward others.	☐

PANSS – Negative symptoms

N1. Blunted affect Diminished emotional responsiveness as characterized by a reduction in facial expression, modulation of feelings, and communicative gestures. Basis for rating: observation of physical manifestations of affective tone and emotional responsiveness during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Changes in facial expression and communicative gestures seem to be stilted, forced, artificial, or lacking in modulation.	☐
4 Moderate - Reduced range of facial expression and few expressive gestures result in a dull appearance.	☐
5 Moderate severe - Affect is generally ~flat-, with only occasional changes in facial expression and a paucity of communicative gestures.	☐
6 Severe - Marked flatness and deficiency of emotions exhibited most of the time. There may be unmodulated extreme affective discharges, such as excitement, rage, or inappropriate uncontrolled laughter.	☐
7 Extreme - Changes in facial expression and evidence of communicative gestures are virtually absent. Patient seems constantly to show a barren or "wooden" expression.	☐

N2. Emotional withdrawal Lack of interest in, involvement with, and affective commitment to life's events. Basis for rating: reports of functioning from primary care workers or family and observation of interpersonal behavoir during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Usually lacks initiative and occasionally may show deficient interest in surrounding events.	☐
4 Moderate - Patient is generally distanced emotionally from the milieu and its challenges but, with encouragement, can be engaged.	☐
5 Moderate severe - Patient is clearly detached emotionally from persons and events in the milieu, resisting all efforts at engagement. Patient appears distant, docile, and purposeless but can be involved m communication at least briefly and tends to personal needs, sometimes with assistance.	☐
6 Severe - Marked deficiency of interest and emotional commitment results in limited conversation with others and frequent neglect of personal functions, for which the patient requires supervision	☐
7 Extreme - Patient is almost totally withdrawn, uncommunicative, a nd neglectful of personal needs as a result of profound lack of interest and emotional commitment.	☐

N3. Poor rapport Lack of interpersonal empathy, openess in conversation, and sense of closeness, interest, or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and nonverbal communication. Basis for rating: interpersonal behavior during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Conversation is characterized by a stilted strained or artificial tone. It may lack emotional depth or tend to remain on an impersonal, intellectual plane.	☐
4 Moderate - Patient typically is aloof, with interpersonal distance quite evident. Patient may answer questions mechanically, act bored, or express disinterest.	☐
5 Moderate severe - Disinvolvement IS obvious and clearly impedes the productivity of the interview. Patient may tend to avoid eye or face contact.	☐
6 Severe - Patient is highly indifferent, with marked interpersonal distance. Answers are perfunctory, and there is little nonverbal evidence of involvement. Eye and face contact are frequently avoided.	☐
7 Extreme - Patient is totally uninvolved with the interviewer. Patient appears to be completely indifferent and consistently avoids verbal and nonverbal interactions during the interview.	☐

N4. Passive/apathetic social withdrawal Diminished interest and initiative in social interactions due to passivity, apathy, anergy, or avolition. This leads to reduced interpersonal involvement and neglect of activities of daily living. Basis for rating: reports on social behavior from primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Shows occasional interest in social activities but poor initiative. Usally engages with others only when approached first by them.	☐
4 Moderate - Passively goes along with most social activities but in a disinterested or mechanical way. Tends to recede into the background.	☐
5 Moderate severe - Passively participates in only a minority of activities and shows virtually no interest or initiative Generally spends little time with others	☐
6 Severe - Tends to be apathetic and isolated, participating very rarely in social activities and occasionally neglecting personal needs. Has very few spontaneous social contacts.	☐
7 Extreme - Profoundly apathetic, socially isolated, and personally neglectful.	☐

N5. Difficulty in abstract thinking Impairment in the use of the abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalizations, and proceeding beyond concrete or egocentric thinking in problemsolving tasks. Basis for rating: responses to questions on similarities and proverb interpretation, and use of concrete vs. abstract mode during the course of the interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Tends to give literal or personalized interpretations to the more difficult proverbs and may have some problems with concepts that are fairly abstract or remotely related.	☐
4 Moderate - Often utilizes a concrete mode Has difficulty with most proverbs and some categories. Tends to be distracted by functional aspects and salient features	☐
5 Moderate severe - Deals primarily in a concrete mode, exhibiting difficulty with most proverbs and many categories.	☐
6 Severe - Unable to grasp the abstract meaning of any proverbs or figurative expressions and can formulate classifications for only the most simple of similarities. Thinking is either vacuous or locked into functional aspects, salient features, and idiosyncratic interpretations.	☐
7 Extreme - Can use only concrete modes of thinking. Shows no comprehension of proverbs, common metaphors or similes, and simple categories. Even salient and functional attributes do not serve as a basis for classification. This rating may apply to those who cannot interact even minimally with the examiner due to marked cognitive impairment.	☐

N6. Lack of spontaneity and flow of conversation Reduction in the normal flow of communication associated with apathy, avolition, defensiveness, or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal-interactional process. Basis for rating: cognitive-verbal processes observed during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Conversation shows little initiative. Patient's answers tend to be brief and unembellished, requiring direct and leading questions by the interviewer.	☐
4 Moderate - Conversation lacks free flow and appears uneven or halting. Leading questions are frequently needed to elicit adequate responses and proceed with conversation.	☐
5 Moderate severe - Patient shows a marked lack of spontaneity and openness, replying to the mterviewer's questions with only one or two brief sentences.	☐
6 Severe - Patient's responses are limited mainly to a few words or short phrases intended to avord or curtail communication. (E g., "I don't know," "I'm not at libertv to say.") Conversation is seriously impaired as a result, and the interview is highly unproductive	☐
7 Extreme - Verbal output is restricted to, at most, an occasional utterance, making conversation not possible.	☐

N7. Stereotyped thinking Decreased fluidity, spontaneity, and flexibility of thinking, as evidenced in rigid, repetitious, or barren thought content. Basis for rating: cognitiveverbal processes observed during the interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Some rigidity shown in attitudes or beliefs. Patient may refuse to consider alternative positions or have difficulty in shifting from one idea to another.	☐
4 Moderate - Conversation revolves around a recurrent theme, resulting in difficulty in shifting to a new topic.	☐
5 Moderate severe - Thinkinq is rigid and repetitious to the point that despite the interviewer's efforts conversation is limited to only two or three dominating topics.	☐
6 Severe - Uncontrolled repetition of demands, statements, ideas, or questions which severely impairs conversation.	☐
7 Extreme - Thinking, behavior, and conversation are dominated by constant repetition of fixed ideas or limited phrases, leading to gross rigidity, inappropriateness, and restrictiveness of patient's communication.	☐

PANSS – General psychopathology

G1. Somatic concern Physical complaints or beliefs about bodily illness or malfunctions. This may range from a vague sense of ill being to clear-cut delusions of catastrophic physical disease. Basis for rating: thought content expressed in the interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Distinctly concerned about health or somatic issues, as evidenced by occasional questions and desire for reassurance.	☐
4 Moderate - Complains about poor health or bodily malfunction, but there is no delusional conviction, and overconcern can be allayed by reassurance.	☐
5 Moderate severe - Patient expresses numerous or frequent complaints about physical illness or bodily malfunction, or else patient reveals one or two clearcut delusions involving these themes but is not preoccupied by them.	☐
6 Severe - Patient is preoccupied by one or a few clearcut delusions about physical disease or organic malfunction, but affect is not fully immersed in these themes, and thoughts can be diverted by the interviewer with some effort.	☐
7 Extreme - Numerous and frequently reported somatic delusions, or only a few somatic delusions of a catastrophic nature, which totally dominate the patient's affect and thinking.	☐

G2. Anxiety Subjective experience of nervousness, worry, apprehension, or restlessness, ranging from excessive concern about the present or future to feelings of panic. Basis for rating: verbal report during the course of interview and corresponding physical manifestations.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Expresses some worry, overconcern, or subjective restiessness, but no somatic and behavioral consequences are reported or evidence.	☐
4 Moderate - Patient reports distinct symptoms of nervousness, which are reflected in mild physical manifestations such as fine hand tremor and excessive perspiration.	☐
5 Moderate severe - Patient reports serious problems of anxiety which have significant physical and behavioral consequences, such as marked tension, poor concentration, palpitations, or impaired sleep.	☐
6 Severe - Subjective state of almost constant fear associated with phobias, marked restlessness, or numerous somatic manifestations.	☐
7 Extreme - Patient's life is seriously disrupted by anxiety, which is present almost constantly and at times reaches panic proportion or is manifested in actual panic attacks.	☐

G3. Guiltfeelings Sense of remorse or self-blame for real or imagined misdeeds in the past. Basis for rating: verbal report of guilt feelings during the course of interview and the influence on attitudes and thoughts.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Questioning elicits a vague sense of guilt or selfblame for a minor incident, but the patient clearly is not overly concerned	☐
4 Moderate - Patient expresses distinct concern over his responsibility for a real incident in his life but is not preoccupied with it, and attitude and behaviour are essentially unaffected.	☐
5 Moderate severe - Patient expresses a strong sense of quilt associated with self-deprication or the belief that he deserves punishment. The guilt feelings may have a delusional basis, may be volunteered spontaneously, may be a source of preoccupation and/or depressed mood, and cannot be allayed readily by the interviewer.	☐
6 Severe - Strong ideas of guilt take on a delusional quality and lead to an attitude of hopelessness or worthlessness The patient believes he should receive harsh sanctions for the misdeeds and may even regard his current life situation as such punishment.	☐
7 Extreme - Patient's life is dominated by unshakable delusions of guilt, for which he feels deserving of drastic punishment, such as life imprisonment, torture, or death. There may be associated suicidal thoughts or attribution of others' problems to one's own past misdeeds.	☐

G4. Tension Overt physical manifestations of fear, anxiety, and agitation, such as stiffness, tremor, profuse sweating, and restlessness. Basis for rating: verbal report attesting to anxiety and, thereupon, the severity of physical manifestations of tension observed during the interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Posture and movements indicate slight apprehensiveness, such as minor rigidity, occasional restlessness, shifting of position, or fine rapid hand tremor.	☐
4 Moderate - A clearly nervous appearance emerges from various manifestations, such as fidgety behaviour, obvious hand tremor, excessive perspiration, or nervous mannerisms.	☐
5 Moderate severe - Pronounced tension is evidenced by numerous manifestations, such as nervous shaking, profuse sweating, and restlessness, but conduct in the interview is not significantly affected.	☐
6 Severe - Pronounced tension to the point that interpersonal interactions are disrupted. The patient for example, may be constantly fidgeting, unable to sit still for long, or show hyperventilation.	☐
7 Extreme - Marked tension is manifested by signs of panic or gross motor acceleration, such as rapid restless pacing and inability to remain seated for longer than a minute, which makes sustained conversation not possible	☐

G5. Mannerisms and posturing Unnatural movements or posture as characterized by an awkward, stilted, disorganized, or bizarre appearance. Basis for rating: observation of physical manifestations during the course of interview as well as reports from primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Slight awkardness in movements or minor rigidity of posture.	☐
4 Moderate - Movements are notably awkward or disjointed, or an unnatural posture is maintained for brief periods.	☐
5 Moderate severe - Occasional bizarre rituals or contorted posture are observed, or an abnormal position is sustained for extended periods.	☐
6 Severe - Frequent repetition of bizarre rituals, mannerisms, or stereotyped movements, or a contorted posture is sustained for extended periods..	☐
7 Extreme - Functioning is seriously impaired by virtually constant involvement in ritualistic, manneristic, or stereotyped movements or by an unnatural fixed posture which is sustained most of the time.	☐

G6. Depression Feelings of sadness, discouragement, helplessness, and pessimism. Basis for rating: verbal report of depressed mood during the course of interview and its observed influence on attitude and behavior.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Expresses some sadness or discouragement only on questioning. but there is no evidence of depression in general attitude or demeanor.	☐
4 Moderate - Distinct feelings of sadness or hopelessness, which may be spontaneously divulqed, but depressed mood has no major impact on behavior or social functioning, and the patient usally can be cheered up.	☐
5 Moderate severe - Distinctly depressed mood is associated with obvious sadness, pessimism, loss of social interest psychomotor retardation, and some interference in appetite and sleep. The patient cannot be easily cheered up.	☐
6 Severe - Markedly depressed mood is associated with sustained feelings of misery, occasional crying, hopelessness, and worthlessness. In addition, there is major interference in appetite and/or sleep as well as in normal motor and social functions, with possible signs of self-neglect.	☐
7 Extreme - Depressive feelings seriously interfere m most major functions. The manifestations include frequent crying, pronounced somatic symptoms, impaired concentration, psychomotor retardation, social disinterest, self-neglect, possible depressive or nihilistic delusions, and/or possible suicidal thoughts or action.	☐

G7. Motor retardation Reduction in motor activity as reflected in slowing or lessening of movements and speech, diminished responsiveness to stimuli, and reduced body tone. Basis for rating: manifestations during the course of interview as well as reports by primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Slight but noticeable diminution in rate of movements and speech Patient may be somewhat underproductive in conversation and gestures.	☐
4 Moderate - Patient is clearly slow in movements, and speech may be characterized by poor productivity, including long response latency, extended pauses, or slow pace.	☐
5 Moderate severe - A marked reduction in motor activity renders communication highly unproductive or delimits functioning in social and occupational situations. Patient can usually be found sitting or Iying down.	☐
6 Severe - Movements are extremely slow, resulting in a minimum of activity and speech. Essentially the day is spent sitting idly or lying down.	☐
7 Extreme - Patient is almost completely immobile and virtually unresponsive to external stimuli.	☐

G8. Uncooperativeness Active refusal to comply with the will of significant others, including the interviewer, hospital staff, or family, which may be associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility, or belligerence. Basis for rating interpersonal behavior observed during the course of interview as well as reports by primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Complies with an attitude of resentment, impatience, or sarcasm. May inoffensively object to sensitive probing during the interview.	☐
4 Moderate - Occasional outright refusal to comply with normal social demands, such as making own bed, attending scheduled programs, etc. The patient may project a hostile, defensive, or negative attitude but usually can be worked with.	☐
5 Moderate severe - Patient frequently ~s incompliant with the demands of his milieu and may be characterized by others as an "outcast" or having "a serious attitude problem." Uncooperativeness is reflected in obvious defensiveness or irritability with the interviewer and possible unwillingness to address many questions.	☐
6 Severe - Patient is highly uncooperative, negativistic, and possibly also belligerent. Refuses to comply with most social demands and may be unwilling to initiate or conclude the full interview.	☐
7 Extreme - Active resistance seriously impact on virtually all major areas of functioning. Patient may refuse to join in any social activities, tend to personal hygiene, converse with family or staff, and participate even briefly in an interview.	☐

G9. Unusual thought content Thinking characterized by strange, fantastic, or bizarre ideas, ranging from those which are remote or atypical to those which are distorted, illogical, and patently absurd. Basis for rating: thought content expressed during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Thought content is somewhat peculiar or idiosyncratic, or familiar ideas are framed in an odd context.	☐
4 Moderate - Ideas are frequently distorted and occasionally seem quite bizarre.	☐
5 Moderate severe - Patient expresses many strange and fantastic thoughts (e.g., being the adopted son of a king, being an escapee from death row) or some which are patently absurd (e.g., having hundreds of children, receiving radio messages from outer space through a tooth filling).	☐
6 Severe - Patient expresses many illogical or absurd ideas or some which have a distinctly bizarre quality (e.g., having three heads, being a visitor from another planet).	☐
7 Extreme - Thinking is replete with absurd, bizarre, and grotesque ideas.	☐

G10. Disorientation Lack of awareness of one's relationship to the milieu, including persons, place, and time, which may be due to confusion or withdrawal. Basis for rating: responses to interview questions on orientation.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - General orientation is adequate but there is some difficulty with specifics. For example, patient knows his location but not the street address, knows hospital staff names but not their functions, knows the month but confuses the day of week with an adjacent day, or errs in the date by more than two days. There may be narrowing of interest evidenced by familiarity with the immediate but not extended milieu such as ability to identify staff but not the Mayo;, Governor, or President.	☐
4 Moderate - Only partial success in recognizing persons, places, and time. For example, patient knows he is in a hospital but not its name, knows the name of his city but not the burrough or district, knows the name of his primary therapist but not many other direct care workers, knows the year and season but not sure of the month.	☐
5 Moderate severe - Considerable failure in recognizing persons, place, and time. Patient has only a vague notion of where he is and seems unfamiliar with most people in his milieu. He may identify the year correctly or nearly so but not know the current month, day of week, or even the season.	☐
6 Severe - Marked failure in recognizing persons, place, and time. For example, patient has no knowledge of his whereabouts, confuses the date by more than one year, can name only one or two individuals in his current life.	☐
7 Extreme - Patient appears completely disoriented with regard to persons, place, and time. There is gross confusion or total ignorance about one's location, the current year, and even the most familiar people, such as parents, spouse, friends, and primary therapist.	☐

G11. Poor attention Failure in focused alertness manifested by poor concentration, distractibility from internal and external stimuli, and difficulty in harnessing, sustaining, or shifting focus to new stimuli. Basis for rating: manifestations during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Limited concentration evidenced by occasional vulnerability, to distraction or faltering attention toward the end of the interview.	☐
4 Moderate - Conversation is affected by the tendency to be easily distracted, difficulty in long sustaining concentration on a given topic, or problems in shifting attention to new topics.	☐
5 Moderate severe - Conversation is seriously hampered by poor concentration, distractibility, and difficulty in shifting focus appropriately.	☐
6 Severe - Patient's attention can be harnessed for only brief moments or with great effort. due to marked distraction by internal or external stimuli.	☐
7 Extreme - Attention is so disrupted that even brief conversation is not possible.	☐

G12. Lack of judgment and insight Impaired awareness or understanding of one's own psychiatric condition and life situation. This is evidenced by failure to recognize past or present psychiatric illness or symptoms, denial of need for psychiatric hospitalization or treatment, decisions characterized by poor anticipation of consequences, and unrealistic short-term and long-range planning. Basis for rating: thought content expressed during the interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Recognizes having a psychiatric disorder but clearly underestimates its seriousness, the implications for treatment, or the importance of taking measures to avoid relapse. Future planning may be poorly conceived.	☐
4 Moderate - Patient shows only a vague or shallow recognition of illness. There may be fluctuations in acknowledgement of being ill or little awareness of major symptoms which are present, such as delusions, disorganized thinking, suspiciousness, and social withdrawal. The patient may rationalize the need for treatment in terms of its relieving lesser symptoms, such as anxiety, tension, and sleep difficulty.	☐
5 Moderate severe - Acknowledges past but not present psychiatric disorder. If challenged, the patient may concede the presence of some unrelated or insignificant symptoms, which tend to be explained away by gross misinterpretation or delusional thinking. The need for psychiatric treatment similarly goes unrecognized.	☐
6 Severe - Patient denies ever having had a psychiatric disorder. He disavows the p resence of any psychiatric symptoms in the past or present and, though compliant, denies the need for treatment and hospitalization.	☐
7 Extreme - Emphatic denial of past and present psychiatric illness. Current hospitalization and treatment are given a delusional interpretation (e.g.. as punishment for misdeeds, as persecution by tormentors, etc.), and the patient may thus refuse to cooperate with therapists, medication, or other aspects of treatment.	☐

G13. Disturbance of volition Disturbance in the wilful initiation, sustenance, and control of one's thoughts, behavior, movements, and speech. Basis for rating thought content and behavior manifested in the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - There is evidence of some indecisiveness in conversation and thinking, which may impede verbal and cognitive processes to a minor extent.	☐
4 Moderate - Patient is often ambivalent and shows clear difficulty in reaching decisions. Conversation may be marred by alternation in thinking, and in consequence verbal and cognitive functioning are clearly impaired.	☐
5 Moderate severe - Disturbance of volition interferes in thinking as well as behavior. Patient shows pronounced indecision that impedes the initiation and continuation of social and motor activities, and which also may be evidenced in halting speech.	☐
6 Severe - Disturbance of volition interferes in the execution of simple, automatic motor functions, such as dressing and grooming, and markedly affects speech.	☐
7 Extreme - almost complete failure of volition is manifested by gross inhibition of movement and speech, resulting in immobility and/or mutism.	☐

G14. Poor impulse control Disordered regulation and control of action on inner urges resulting in sudden, unmodulated, arbitrary, o; misdirected discharge of tension and emotions without concern about consequences. Basis for rating: behavior during the course of interview and reported by primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Patient tends to be easily angered and frustrated when facing stress or denied gratification but rarely acts on impulse.	☐
4 Moderate - Patient gets angered and verbally abusive with minimal provocation. May be occasionally threatening, destructive, or have one or two episodes involving physical confrontation or a minor brawl.	☐
5 Moderate severe - Patient exhibits repeated impulsive episodes involving verbal abuse destruction of property, or physical threats. There may be one or two episodes involving serious assault, for which the patient requires isolation, physical restraint, or p.r n. sedation.	☐
6 Severe - Patient frequently is impulsively aggressive, threatening, demanding, and destructive, without any apparent consideration of consequences. Shows assaultive behavior and may also be sexually offensive and possibly respond behaviorally to hallucinatory commands.	☐
7 Extreme - Patient exhibits homicidal attacks, sexual assaults, repeated brutality, or self-destructive behavior. Requires constant direct supervision or external constraints because of inability to control dangerous impulses.	☐

G15. Preoccupation Absorption with internally generated thoughts and feelings and with autistic experiences to the detriment of reality orientation and adaptive behavior. Basis for rating: interpersonai behavior observed during the course of interview.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Excessive involvement with personal needs or problems, such that conversation veers back to egocentric themes and there is diminished concern exhibited toward others.	☐
4 Moderate - Patient occasionally appears selfabsorbed, as if daydreaming or involved with internal experiences, which interferes with communication to minor extent.	☐
5 Moderate severe - Patient often appears to be engaged in autistic experiences, as evidenced by behaviors that significantly intrude on social and communicational functions, such as the presence of a vacant stare, muttering or talking to oneself, or involvement with stereotyped motor patterns.	☐
6 Severe - Marked preoccupation with autistic experiences, which seriously delimits concentration, ability to converse, and orientation to the milieu. The patient frequently may be observed smiling, laughing, muttering, talking, or shouting to himself.	☐
7 Extreme - Gross absorption with autistic experiences, which profoundly affects all major realms of behavior. The patient constantly may be responding verbally and behaviorally to hallucinations and show little awareness of other people or the external milieu.	☐

G16. Active social avoidance Diminished social involvement associated with unwarranted fear, hostility, or distrust. Basis for rating: reports of social functioning by primary care workers or family.	
1 Absent - Definition does not apply	☐
2 Minimal - Questionable pathology; may be at the upper extreme of normal limits.	☐
3 Mild - Patient seems ill at ease in the presence of others and prefers to spend time alone, although he participates in social functions when required.	☐
4 Moderate - Patient begrudgingly attends all or most social activities but may need to be persuaded or may terminate prematurely on account of anxiety, suspiciousness, or hostility.	☐
5 Moderate severe - Patient fearfully or angrily keeps away from many social interactions despite others' efforts to engage him. Tends to spend unstructured time alone.	☐
6 Severe - Patient participates in very few social activities because of fear, hostility, or distrust. When approached, the patient shows a strong tendency to break off interactions, and generally he tends to isolate himself from others.	☐
7 Extreme - Patient cannot be engaged in social activities because of pronounced fears, hostility, or persecutory delusions. To the extent possible, he avoids all interactions and remains isolated from others.	☐