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Non-Psychotic Outcomes and Personality Disorders in Young People at Ultra-High Risk of Developing a Psychotic Disorder: A Long-Term Follow-Up Study

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**Non-Psychotic Outcomes and Personality Disorders in Young People
at Ultra-High Risk of Developing a Psychotic Disorder: A Long-
Term Follow-Up Study**

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*PhD in Youth Mental Health
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Philosophy

Abstract

Background: Despite there being a large body of research available on the precursors of psychosis (the “prodromal” phase), there is a paucity of literature available on pre or comorbid mental and personality disorders in the ultra-high risk (UHR) for psychosis population. Most research thus far has been cross-sectional, with only a few long-term follow-ups, limiting the ability to investigate the long-term pattern and outcomes of comorbidity.

Aims: The current study investigated comorbidity of non-psychotic mental and personality disorders in the UHR population - specifically, the prevalence of these disorders at entry and follow-up and their association with clinical and functional outcomes over the long-term (6 to 12 years). In addition, this study investigated the issue of whether UHR status is specific to psychosis outcomes or for a range of non-psychotic mental disorders, including major depressive disorder, anxiety disorder and personality disorders. The current study also aimed to identify baseline clinical predictors of the long-term trajectories of mental disorder.

Method: The sample comprised 172 young people from the Personal Assessment & Crisis Evaluation (PACE) Clinic considered to be at UHR of developing a psychotic disorder. The majority of the original sample ($n=125$, 72.7%) presented for follow-up assessment (mean=8.8 years, range = 6.8 to 12.1 years since baseline assessment). Comorbid non-psychotic mental and personality disorders were assessed using the Structured Clinical Interview for DSM-IV (SCID I and II). Global functioning was assessed using the global assessment of functioning (GAF) scale, the Social and Occupational Functioning Assessment Scale (SOFAS) and the Quality of Life Scale (QLS).

Results: Only 13% of participants did not meet criteria for a non-psychotic mental disorder diagnosis at baseline. The remaining 87% of participants were

diagnosed with mental disorders, the majority of which were mood disorders (79%), followed by anxiety disorders (48%) and substance use disorders (18%). The pattern of disorder prevalence present at baseline continued at follow-up, though at a reduced rate, with 48.8% not meeting criteria for non-psychotic mental disorder. The disorder that proved to be most persistent for participants over time was mood disorder, with 45% of the sample experiencing this continuously. Baseline clinical predictor variables were unable to predict remission of a non-psychotic mental disorder. However, meeting Trait Vulnerability UHR criteria predicted incidence of a non-psychotic disorder ($HR = 3.54, p < .05$) and high scores on baseline psychopathology predicted continuous non-psychotic disorder over time ($HR = 1.06, p < .01$). Presence of a continuous non-psychotic mental disorder was also associated with lower functional outcomes on multiple measures at follow-up ($p < .05$). Baseline mental disorder was not significantly associated with transition to psychosis ($HR = .68, p = .44$). Persistence of attenuated psychotic symptoms was experienced by 30% of the sample at follow up assessment and this was significantly associated with impairment in social and occupational functioning ($\chi^2 = 7.96, p < .05$). Personality disorders were reported by 19% of the sample at follow-up. The most prevalent disorder was borderline personality disorder (11%). Personality disorders were associated with poorer clinical and functional outcomes: presence of personality disorders (compared to no personality disorder) was associated with an increased rate of transition to psychosis ($HR = 3.03, p < .05$), and was associated with presence of comorbid non-psychotic mental disorder ($\chi^2 = 9.43, p < .01$) and poorer social and functional outcomes ($t = 4.20, p < .01$).

Conclusions: Most (84%) participants meeting UHR criteria at baseline did not go on to develop psychosis. The majority did, however, present with persisting non-psychotic mental disorders that were associated with poorer functional outcomes

at follow-up. The course of non-psychotic mental disorders in UHR participants over time was able to be predicted for continuous and incident disorders using baseline clinical variables, though the strength of the predictions was modest. Therefore, the link between baseline clinical predictors and long-term mental health outcomes would benefit from further investigation. Almost one-third of UHR participants continued to experience attenuated psychotic symptoms over the longer term. Those who also met criteria for personality disorders at follow-up were also more likely to be experiencing comorbid non-psychotic mental disorders, poorer functional outcomes and an increased risk of transition to psychosis than those who did not have a personality disorder. This research indicates that people meeting criteria for UHR are at risk of experiencing a range of other non-psychotic psychiatric problems over time.

Declaration

This is to certify that:

- i) the thesis comprises only my original work towards the degree of Doctor of Philosophy,
- ii) due acknowledgement has been made in the text to all other material used,
- iii) the thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Anneliese Elizabeth Spiteri-Staines

October 2019

I, Anneliese Elizabeth Spiteri-Staines, declare that the research reported in this thesis was conducted with the principles for the ethical treatment of human participants as approved for this research by the University Human Research Ethics Committee.

.....

Anneliese Elizabeth Spiteri-Staines
October 2019

Statement of Candidate's Contribution to the Study

The current study was part of a larger project undertaken by one full-time research assistant, three researchers, and myself as the PhD candidate, under the primary supervision of Professor Barnaby Nelson. I was not involved at study inception, but was involved from the point of ethics submission onwards. I worked with the research assistant to prepare the participant assessment materials, as well as in recruitment and interviewing of participants. I conducted all the data analyses included in this thesis.

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List of Acronyms

APA	American Psychiatric Association
APD	Antisocial Personality Disorder
APS	Attenuated Psychotic Symptoms
ARMS	At risk mental state
BLIPS	Brief Limited Intermittent Psychotic Symptoms
BPD	Borderline Personality Disorder
BPRS	Brief Psychiatric Rating Scale
BS	Basic Symptoms
CAARMS	Comprehensive Assessment of At-Risk Mental State
CHR	Clinical High Risk
CI	Confidence Intervals
CTQ	Childhood Trauma Questionnaire
DS	Disorganised Speech
DSM-IV	Diagnostic and Statistical Manual of the American Psychiatric Association - 4th edition
DSM-5	Diagnostic and Statistical Manual of the American Psychiatric Association
DUP	Duration of Untreated Psychosis
EIPS	Early Initial Prodromal State
EPOS	European Prediction of Psychosis Study
EPPIC	Early Psychosis Prevention and Intervention Centre
FEP	First Episode of Psychosis
FIGS	Family Interview for Genetic Studies
GAF	Global Assessment of Functioning
HR	Hazard Ratio

HRSA	Hamilton Rating Scale for Anxiety
HRSD	Hamilton Rating Scale for Depression
ICD-10	International Statistical Classification of Diseases and Related Health Problems - 10th revision
IPS	Initial Prodromal State
LCS	Life Chart Schedule
LIPS	Late Initial Prodromal State
NAPLS	North American Prodrome Longitudinal Study
NBI	Non-bizarre ideas
OYH	Orygen Youth Health
OR	Odds ratio
PA	Perceptual Abnormalities
PACE	Personal Assessment and Crisis Evaluation Clinic
PD	Personality disorder
PRIME	Prevention through Risk Identification, Management and Education
PTSD	Post-traumatic Stress Disorder
QLS	Quality of Life Scale
RAP	Recognition and Prevention
SANS	Scale of Assessment of Negative Symptoms
SCID I	Structured Clinical Interview for DSM-IV, Axis I disorders
SCID II	Structured Clinical Interview for DSM-IV, Axis II disorders
SIPS	Structured Interview for Prodromal Syndromes
SOFAS	Social and Occupational Functioning Assessment Scale
SOPS	Scale of Prodromal Symptoms
SPD	Schizotypal Personality Disorder
SUD	Substance Use Disorder (includes dependence and abuse)

TTP	Transition to Psychosis
UHR	Ultra-high risk
UTC	Unusual Thought Content
WHO	World Health Organisation

List of Notations

β Beta	Standardised Regression Coefficient
B	Unstandardised Regression Coefficient
χ^2	Chi Squared
df	Degrees of Freedom
DV	Dependent Variable
η^2	Eta squared
F	F-value or F distribution
M	Mean
Md	Median
IV	Independent Variable
N	Total Participant Number
n	Subset of Participant Number
p	p-value: the Estimated Probability of Rejecting the Null Hypothesis
r	Correlation Coefficient
R^2	Coefficient of Determination or Amount of Variability Explained
SD	Standard Deviation
SE	Standard Error
<	Less Than
>	Greater Than
$\leq$	Less Than or Equal To
t	t-Test

Preface

Epidemiological research indicates that the lifetime prevalence of psychotic disorders might be as high as 3.5% in the general population (Perala et al., 2007), most often first appearing in late adolescence or early adulthood, with an average earlier onset for males of four years (Riecher-Rossler & Hafner, 2000). Psychotic disorders are known to be associated with significant levels of burden as defined by the World Health Organization and can be one of the most devastating illnesses as measured by both human and economic costs (Jablensky, 2000). Psychosis is defined by abnormalities in one or more of the following five domains: hallucinations, delusions, disorganised thinking, negative symptoms and grossly disorganised or abnormal motor behaviour (DSM: American Psychiatric Association [APA], 2013). Psychotic disorders encompass a range of disorders, from schizophrenia spectrum disorders to affective psychoses. Schizophrenia, in particular, is one of the most severe psychotic disorders and ranks amongst the top ten strongest contributors to the global burden of disease (Knapp, Mangalore, & Simon, 2004).

Schizophrenia is the top ranked chronic illness having the most lost years of life or lived with disability, and the real financial costs being estimated at \$1.85 billion/annum in Australia alone (Economics, 2008). On average, people with a diagnosis of schizophrenia die 12-15 years before the average population (Saha, Chant, & McGrath, 2007). The main reasons for increased mortality relate to physical causes, resulting from increased frequency of routine risk factors (little exercise, poor diet, obesity, and smoking) and decreased access to medical care, as well as suicide (Saha et al., 2007).

The psychiatric symptoms associated with schizophrenia often lead to unemployment, homelessness and incarceration (Insel, 2010). Throughout Europe,

less than 20% of people with schizophrenia are employed (Marwaha et al., 2007) and a large US study ($n= 4,307$) found nearly 20% of people with schizophrenia to be homeless at one-year follow up (Folsom et al., 2005). Such is the burden of schizophrenia that it has been described as “arguably the worst disease affecting mankind” (Editorial, 1988).

Early intervention during the first episode of psychosis (FEP) has been shown to result in improved outcomes for people, including a greater management of their symptoms and reduced social disability (Corell et al., 2018; Reading, 2005). The positive outcomes resulting from swift intervention during the FEP led to attempts to identify people even earlier, with the hopes of further improving outcomes and perhaps even avoiding the onset of full blown psychosis all together. In order to detect and treat psychotic disorders before the onset of full-blown symptoms, the Ultra-High Risk (UHR) criteria for psychosis were developed (Yung & McGorry, 1996). These criteria are described in detail in Chapter One.

The Current Study

Most research in the ultra-high risk (UHR) for psychosis population thus far has focused on transition to psychosis, though there has been growing interest in comorbid non-psychotic mental disorders due to their high prevalence in this population. The research into comorbid disorders has often been cross-sectional, however, with fewer studies investigating the long-term pattern and outcomes of comorbidity. A recent systematic review of the UHR literature revealed that research on long-term trans-diagnostic clinical and functional outcomes in this population remains scarce (Beck et al., 2019). The current study aimed to expand on the existing knowledge base by investigating comorbidity of non-psychotic mental and personality disorders in the UHR population; specifically, the prevalence of these disorders at entry and long-term follow-up and their impact on outcomes over long-term follow-

up (6-12 years). The current study investigated baseline predictors of the long-term course of non-psychotic mental disorders. In addition, this study investigated the issue of whether UHR status is a specific risk state for psychosis or for a range of non-psychotic disorders, including major depressive disorder, anxiety disorder and personality disorders. The terms Axis I (mental disorders) and II (personality disorders) are retained in some sections of this thesis as the participants in this study were assessed using the DSM-IV¹, and therefore diagnosed using the multi-axial system (APA, 2000).

The review of the literature is presented in Chapters One to Six. Chapter One provides background into the prodromal phase of illness and introduces the UHR concept. Chapter Two discusses research findings on mental disorder comorbidity in the psychosis population and in the UHR population. Whether UHR criteria are specific to psychotic outcomes or to more generalizable psychopathology is explored in Chapter Three. Current findings on the long-term outcomes of UHR individuals, such as transition to psychosis and other mental health outcomes are described in Chapter Four. Baseline clinical predictors of trajectories of non-psychotic disorders are discussed in Chapter Five. Personality disorders in the psychotic disorders and UHR population are examined in Chapter Six. The study rationale and aims are described in Chapter Seven, with a detailed methodology in Chapter Eight. The results are presented in Chapters Nine and Ten and discussed in Chapter Eleven.

¹ In the updated DSM-5, the multi-axial system was removed, with personality disorders and mental disorders being presented within the same section - Section II: Disorders. Classification of anxiety disorders also changed, with obsessive compulsive disorder being removed from the anxiety disorders category and being categorised under the heading Obsessive Compulsive and Related Disorders in the DSM-5. Eating disorders, were also removed from anxiety disorders and categorised under Feeding and Eating Disorders in DSM-5.

Chapter 1

The Psychosis Prodrome

1.1 Duration of Untreated Psychosis

By recognising the early warning signs of psychosis, it is hoped that early intervention and treatment can be implemented, and thus minimise the delay between the onset of psychosis and treatment. The time delay between onset of psychosis and treatment is referred to as the duration of untreated psychosis (DUP) (Harrigan, McGorry, & Krstev, 2003; McGorry, 2000) and a reduction in DUP has been shown to alleviate symptom severity (Marshall et al., 2005). In a study of 354 people experiencing first episode psychosis (FEP), reduction of DUP consistently predicted better outcomes (functional, positive and negative symptoms), independently of other variables (Harrigan et al., 2003).

The early stage of psychosis is considered a critical period in which treatment, or lack thereof, can have a significant impact on long-term outcomes experienced by the person (Reading, 2005). Intervention during the prodromal phase has also been shown to impact long-term outcomes, including possible reduction of incidence and attenuation or delay in the onset of psychosis (Yung et al., 1996; Yung et al., 2003). Several meta-analyses of studies involving a variety of interventions² preceding onset of first episode psychosis support this position, concluding that transition to psychosis could be preventable or at least delayed (Devoe, Farris, Townes, & Addington, 2019; Hutton & Taylor, 2014; Stafford, Jackson, Mayo-Wilson, Morrison, & Kendall, 2013; van der Gaag et al., 2013). In addition, Yung et al. (2003) found that people receiving

² These interventions included pharmacological, psychological, cognitive behavioural, and nutritional trials.

early intervention also reported a sense of control over their illness and the disruption caused to their life was minimised.

Three influential meta-analyses concluded that extended periods of DUP were associated with poorer prognosis (Boonstra et al., 2012; Marshall et al., 2005; Perkins et al., 2005). This effect was maintained even when pre-morbid functioning was controlled for. In a community-based study, Addington et al. (2015) found that at baseline, longer DUP was associated with higher levels of positive symptoms, increased general psychopathology, and lower ratings of quality of life.

This evidence highlights the imperative to implement intervention as early as possible, before the frank onset of the first episode of psychosis. The phase preceding first episode thus represents not only an opportunity to prevent or delay onset of frank psychosis, but treatment for current symptoms and related disability.

1.2 Identifying Individuals in the “Prodromal” Phase of Illness

A major focus of schizophrenia and other psychosis research has become the early detection of psychotic disorder, including the pre-onset or “prodromal” phase (Addington et al., 2011; Yung et al., 1996). The last 30 years has seen substantial growth of research in this area (Fusar-Poli et al., 2012). The presence of sub-threshold signs and symptoms that precede the onset of the first episode of psychosis has long been recognised, and this gradual onset has been retrospectively labelled the “prodrome” (Keith & Matthews, 1991). The term “prodrome”, derived from clinical medicine, refers to the early signs of disease that are observed prior to the manifestation of a full-blown illness (Yung et al., 1996).

The “prodrome” preceding the psychotic disorder is characterised by a sustained period of non-specific emotional and behavioural changes (McGorry et al., 2006). These changes include the gradual emergence of depressed mood, decreased drive and motivation, reduced concentration, sleep disturbance, anxiety,

suspiciousness, social withdrawal, irritability and deterioration in role functioning (Cornblatt et al., 2003; Meyer et al., 2005). Yung and McGorry (1996) and Hafner et al. (1993) observed that in the vast majority of cases, symptoms accumulated over time, starting with the aforementioned non-specific symptoms of mood disturbance and deterioration in functioning, and positive symptoms appearing later. Positive attenuated symptoms include obsessional perseveration of thought and intrusion of thoughts, paranoid themes such as suspiciousness, magical ideation, increased acuity, and perceptual aberration (distortion in the perception of one's own body and external objects) and these more closely reflect the psychotic state (Gourzis, Katrivanou, & Beratis, 2002).

The prodromal period can last anywhere from a few days to years. In a retrospective assessment of 128 people with a psychotic disorder, Schultze-Lutter, Ruhrmann, Berning, Maier, & Klosterkötter (2010) found that 98.4% of the participants had experienced at least one month of prodromal symptoms before full onset of psychosis and a mean duration of 5.9 years. Fusar-Poli et al. (2009) described a shorter prodromal period of around two years in their sample. However, Schultze-Lutter et al. (2010) included unspecific mental complaints in their prodrome, whereas Fusar-Poli et al. (2009) examined mood disturbances associated with a later course of prodrome as defined by Basic Symptoms Criteria (see Section 1.2.3). Hafner et al. (1999) found the duration of prodromal symptoms to be more variable, ranging from one to five years, though most generally lasting a few years. In contrast, Shah et al. (2017) found that 32% of their first episode psychosis sample did not experience any prodrome preceding onset. This variation in the prodromal period can make the onset of full psychosis difficult to detect.

The actual onset of full threshold psychosis (i.e., first episode psychosis) has been operationalised as daily frank psychotic symptoms for longer than a week (Yung

et al., 1996). This stage is characterised by the emergence of frank psychotic symptoms, such as hallucinations, delusions, disorganisation of thought and behaviour and psychomotor abnormalities (Insel, 2010). Onset can be acute (symptoms fully developed from a non-symptomatic state within a week) or insidious (symptoms developed over a month or longer) (Alvarez-Jimenez et al., 2011).

It is important to note, however, that people who exhibit symptoms consistent with a prodromal state may not go on to develop a psychotic illness. Firstly, the signs and symptoms exhibited by the person may be indicative of a different pathology, and the person never goes on to develop a psychotic disorder. This is referred to as a false-positive (Yung et al., 2007). On the other hand, it is possible that a person may have a vulnerability or pre-disposition for psychosis, but full development of a psychotic disorder is averted, perhaps by external intervention, such as social support and/or treatment, as well as the individual's own coping skills. Some individuals may also experience persistent attenuated psychotic symptoms that remain below the psychosis threshold. This may be due to effective early intervention to prevent psychosis, or because the individual was never at risk of transition (Yung et al., 2007).

1.2.1 The Ultra High Risk for Psychosis (UHR) concept.

Given the importance of early intervention to enable best outcomes for people at risk of developing psychosis, research has been focused on early identification of these at risk groups. In recognition that the early clinical picture will not inevitably lead to diagnosis of psychotic disorder, McGorry & Singh (1995) suggested using an alternative term to “prodrome” when referring to individuals who exhibit potential early signs of psychosis. These early signs and symptoms would be better described as an “at-risk mental state” (ARMS), which implies that the clinical picture will not inevitably be followed by full disorder (McGorry & Singh, 1995). Since then, the “prodromal” state has been variably termed “At-Risk Mental State,” “Ultra High

Risk,” (UHR) or “Clinical High Risk” (CHR) around the world (Cornblatt et al., 2007; Fusar-Poli et al., 2012; Woods et al., 2009).

With early detection and intervention in mind, Yung and McGorry (1996) established a method of identifying people at “ultra high risk” (UHR) for developing a psychotic disorder. While this state describes a sub-threshold syndrome that confers an increased risk for psychosis in the near future, such an outcome is not inevitable (Yung & McGorry, 1996). Age has been identified as a risk factor that increases the likelihood of developing a psychotic illness, so the UHR target group is adolescents and young adults (usually aged 15-30) (Yung, & McGorry, 1996). In addition to meeting age criteria, individuals are classified as UHR if they meet criteria for one of the following (Yung & McGorry, 1996):

1. Vulnerability Group: Person has a first-degree relative diagnosed with a psychotic disorder, or the person has schizotypal personality disorder, plus a significant recent drop in functioning or chronic low functioning.
2. Attenuated Psychotic Symptoms (APS): Presence of sub-threshold psychotic symptoms that are considered below the intensity or frequency required for a diagnosis of a psychotic disorder.
3. Brief Limited Intermittent Psychotic Symptoms (BLIPS): Brief episode of frank psychotic symptoms that spontaneously resolve within seven days (i.e. without anti-psychotic medication).

Furthermore, the APS and BLIPS group require the presence of psychotic symptoms within the last 12 months.

1.2.2 Validity of UHR criteria.

The UHR concept was validated in early work at the Personal Assessment and Crisis Evaluation (PACE) Clinic (Yung et al., 1996), with over 40% of individuals identified as UHR making the transition to psychosis within 12 months (Yung et al., 2003), a rate several thousand-fold above the expected rate in the general population. The UHR criteria have been adopted and adapted in a number of other settings around the world (Yung, 2007) and is the most commonly used method to help identify those in a putatively prodromal phase of a psychotic disorder (Armando et al., 2010). The one-year transition rate has since decreased to 9.2% in the PACE Clinic, however this transition rate is still significantly higher than that found in the general population (Yung et al., 2006). Fusar-Poli (2012) and colleagues conducted a review of transition rates of patients identified as high risk across a variety of centres internationally. They concluded that “high risk” status was associated with a very high risk of developing psychosis, specifically, transition rates of 18% at 6 months, increasing each year until 36% after three years (Fusar-Poli et al., 2012). Despite declining transition rates over the short term (Yung et al., 2007) these rates are similar to risk syndromes in general medicine (e.g. dementia risk syndrome or pre-diabetes) (Fusar-Poli & Borgwardt, 2012; Tabák, Herder, Rathmann, Brunner, & Kivimäki, 2012) and are hundreds fold greater than the risk of the general population (Yung et al., 2012).

1.2.3 Basic symptoms concept.

A complimentary approach to identifying young people in an at risk mental state is the use of basic symptoms, first described in the work of Huber (1966) (Huber, 1966) and Janzarik (1968). These criteria describe subtle disturbances in cognition, speech, motor function, initiative and perception processes that are often only perceived by the individual experiencing them (Klosterkotter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001). Examples of these include perseveration,

pressure of blockages in thought, thought interference, disturbance of receptive language, derealization, decreased ability to discriminate between ideas and perception or some visual or auditory disturbance (Schultze-Lutter et al., 2010). Basic symptoms can be compensated for by the individual (e.g. by making more effort) and are thus not easily observable to others. These criteria are thought to detect an earlier stage of prodrome, whereas UHR detects a later stage (Häfner et al., 2004).

These two sets of criteria (BS and UHR) are thought to be most effective at detecting those at risk for psychosis when applied in combination (Olsen & Rosenbaum, 2006). The two approaches were combined by the German Research Network on Schizophrenia in their operationalisation of the Early Initial Prodromal State (EIPS) and Late Initial Prodromal State (LIPS) (Häfner et al., 2010), whereby EIPS comprise mostly BS criteria and/or genetic risk and functional decline, and LIPS reflects attenuated psychotic symptoms or brief limited intermittent psychotic symptoms. The theory behind this approach is that the earliest stages of prodrome start with unspecific mental health problems, followed by BS and then APS (Schultze-Lutter et al., 2010). However, research on this sequence is lacking, given the large sample size and the long prospective follow-up time needed (at least ten years) (Schultze-Lutter et al., 2010).

1.2.4 Risk state or a syndrome in itself?

Recently, the attenuated psychosis syndrome was introduced into the DSM-5 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (APA, 2013; Carpenter, 2009; Nelson & Yung, 2011). This syndrome was derived from UHR/CHR criteria and includes attenuated positive psychotic symptoms, frequency and recency criteria. The rationale for inclusion was that these criteria had predicted the onset of psychosis in several studies, most often schizophrenia, and that they could be used for early intervention. However, the attenuated psychosis syndrome had

not yet been validated as a syndrome in itself (Yung, Nelson, Thompson, & Wood, 2010) and was thus relegated to the experimental appendix of the DSM-5. The prospect of the attenuated psychotic symptom state being a designated syndrome is an important issue to consider—It may maximise the opportunity for intervention and development of evidence-based treatments. On the other hand, there is also the potential for unnecessary diagnosis, treatment and stigma (self and other) resulting from a formal diagnosis, especially given that there is a high probability that the individual may never go on to develop psychosis (Corcoran, First, & Cornblatt, 2010; Corcoran, Malaspina, & Hercher, 2005; Yang, Wonpat-Borja, Opler, & Corcoran, 2010).

An argument against the UHR concept being applied as a syndrome in itself, is that the signs and symptoms associated with this syndrome may reflect normal developmental processes, or may be symptoms associated with concurrent or emerging non-psychotic disorders (Castle, 2012; Simon & Umbricht, 2010; Verdoux & van Os, 2002). Sub-threshold transitory psychotic symptoms are common in young adults and could be caused by an inability to distinguish between relevant and irrelevant stimuli, compounded by age related stress (Wigman et al., 2011).

Even if these signs and symptoms are not reflective of normal developmental processes, individuals presenting with prodromal features, though being at increased risk of developing a psychotic disorder, may not necessarily do so (Fusar-Poli et al., 2012). Not only has the rate of transition in UHR samples been declining (Yung et al., 2007), but the risk of transition in samples of patients more broadly identified as being at increased risk shows wide variability amongst studies (Fusar-Poli et al., 2012). Individuals are generally referred from clinical care services in states of distress and/or dysfunction, and their help-seeking behaviours may not necessarily be linked directly to the experience of psychotic symptoms, nor indicate risk for

psychosis (Fusar-Poli et al., 2013).

However, a strong argument against dismissing the Attenuated Psychosis Syndrome is that individuals who meet the criteria are in a state of distress and would benefit from targeted treatment. A meta-analysis of UHR literature (30 articles, $n=3,608$) revealed significant distress/impairment in functioning was associated with UHR, indicating that it wasn't just a state of risk but a disorder in its own right (Fusar-Poli et al., 2015). Compared with healthy controls, UHR individuals experienced a significantly lower quality of life and poorer functional outcomes. These outcomes were similar to individuals diagnosed with frank psychosis—their scores were not as poor but the gap in functioning between psychosis and UHR was closer than the gap between UHR and healthy controls. Fusar-Poli et al. (2015) concluded that their meta-analytic review showed support for the idea that UHR should be given credence as a syndrome in its own right. Given the increased recognition of the UHR state in clinical services and its consideration as a disorder, it is important to develop our understanding of the implications and the outcomes expected for people who meet UHR criteria or receive a diagnosis of APS.

1.3 Summary of Chapter One: the Psychosis Prodrome

Much psychosis research over the last 20 years has focused on identification of the early warning signs of psychosis, in the hopes early intervention can be implemented. The period preceding the first episode of psychosis presents both the opportunity to prevent or delay onset of frank psychosis, as well as treat current symptoms and related disability (Stafford et al., 2013).

The period preceding the onset of psychosis has been described as the 'prodrome'. During this period, which can last from a few days to a few years (Schultze-Lutter et al., 2010), sub-threshold signs and symptoms have been observed (Keith et al., 1991; Yung and McGorry, 1996). These include non-specific emotional

and behavioural changes, such as depressed mood, anxiety, reduced concentration, sleep disturbance, suspiciousness, social withdrawal, irritability and deterioration in role functioning and motivation, (McGorry et al., 2006; Meyer et al., 2005; Cornblatt et al., 2003) and attenuated positive psychotic symptoms (Gourzis et al., 2002; Yung & McGorry, 1996).

Incipient psychosis may be difficult to detect, however. As many as a third of people with first episode psychosis may not experience a prodrome (Shah et al., 2017). In contrast, some people who experience symptoms consistent with the prodrome, may not actually ever go on to develop psychosis (also making the term 'prodrome' inaccurate as it implies unavoidable progression) (Yung et al., 2007).

In order to assist with detection of people at risk of psychosis, Yung and McGorry (1996) devised the Ultra High Risk for psychosis criteria. The goal of early identification was to help prevent or delay onset of frank psychosis or to ameliorate symptoms. The criteria comprise three risk groups: 1) vulnerability, 2) attenuated psychotic symptoms and 3) brief limited intermittent psychotic symptoms group. The description of 'risk' here implies progression to full psychosis may be avoidable. The UHR concept has been validated (Yung & McGorry, 1996) and adopted in many centres around the world (Yung, 2007).

There has been some debate about whether at risk criteria constitute a syndrome in itself, with individuals meeting UHR criteria experiencing significant distress and impairment in functioning, as well as reduction in quality of life (Fusar-Poli et al., 2015). The attenuated psychosis syndrome, based on UHR criteria, was introduced to the DSM-5 as a condition requiring the experience of attenuated psychotic symptoms that cause distress, and in the absence of a previously diagnosed psychotic disorder (APA, 2013). While the attenuated psychosis syndrome has not yet been validated, it bolsters the opportunity for intervention and development of

evidence-based treatments. Given the increased recognition of the UHR state, it is important to develop our understanding of the implications and the outcomes for people who fall into this category. The current study will address the need for further research into the Attenuated Psychosis Syndrome (APA, 2013); and will map the clinical trajectories experienced by people meeting criteria for APS.

Chapter 2

Mental Illness Comorbidity in Psychosis

A branch of UHR research has previously considered the early nonspecific clinical symptoms, including depressive and anxiety symptoms that have been associated with the “at risk phase” of psychosis (Yung & McGorry, 1996). This follows from the recognition that a range of concurrent or antecedent non-psychotic psychiatric symptoms, especially disturbances in mood, are often observed in psychotic disorder, particularly schizophrenia (Meyer, 2005; Rosen, 2006). The experience of distress associated with these disturbances is in itself important to consider in terms of treatment for help-seeking individuals.

In addition to helping ameliorate the distress caused by these symptoms, the understanding of how mental illness comorbidities fit into the ‘bigger picture’ of the psychosis prodrome and onset is important. The UHR state appears to be associated with a variety of comorbid psychiatric illness, and thus may not merely represent a state of risk for psychosis, but potentially for non-psychotic illness (Hartmann et al., 2017). Alternatively, comorbid symptoms, such as depression, may be both a risk factor for developing psychosis and also an intrinsic part of the ongoing psychotic experience (Stefanis, 2002). So far, the relationship between the “at risk” phase and its comorbid psychiatric symptoms is not well understood. The relationship between depression and psychosis is particularly important given the difficulties establishing whether it is entirely distinguishable from psychosis or is potentially part of the same pathology. The following section reviews the literature around comorbid psychiatric illness, schizophrenia, and the early stages of psychosis in order to determine possible links to UHR and comorbid psychiatric illness, as comorbidity has not been researched to the same depth in the UHR population.

2.1 Mental Illness Comorbidity in Schizophrenia and First Episode

Psychosis

Individuals with schizophrenia often describe a history of premorbid non-psychotic mental illness (Lewis, David, Malmberg, & Allebeck, 2000). A study of a large national US community-based sample of people with psychotic illness ($n=50,054$, those diagnosed with a psychotic disorder: $n=386$) revealed that this population had experienced a history of mood, anxiety and personality disorders and were more likely to have a history of substance use disorder (SUD) (McMillan, Enns, Cox, & Sareen, 2009). Numerous other studies have shown associations between psychotic disorders and mood disorders (Lyons et al., 2003; Matthias, 2007), SUDs (Duke, Pantelis, McPhillips, & Barnes, 2001; Swadi & Bobier, 2003), anxiety disorders (Braga, Mendlowicz, Marrocos, & Figueira, 2005; Braga, Petrides, & Figueira, 2004; Pallanti, Quercioli, & Hollander, 2004) and personality disorders (Fogelson et al., 2007; Moran & Hodgins, 2004).

Similarly, non-psychotic mental illness comorbidity is a significant problem in first episode psychosis (FEP) as well as in schizophrenia (Bendall et al., 2008; Strakowski et al., 1993; 1995). Various studies have found high prevalence of both lifetime (resolving before the FEP) and current comorbid non-psychotic psychiatric disorders in the FEP population. In a sample of FEP patients ($n=62$), Bendall et al. (2008) found that there was a high prevalence (84%) of at least one other psychiatric disorder in the lifetime of people experiencing FEP (prior to, during or following FEP onset). Similar to schizophrenia, disorders most commonly reported were SUDs, mood and anxiety disorders (Bendall et al., 2008a). The prevalence of non-psychotic mental health disorders that had resolved prior to admission for FEP was 69%.

In their study of people with FEP, Bendall et al. (2008a) found that almost half of the comorbidity concurrent with FEP developed over the year preceding admission

(Bendall et al., 2008a). This is similar to another study reporting that over 80% of concurrent comorbidity had also developed prior to FEP (Strakowski et al., 1995). These findings support reports of FEP patients who describe the phase prior to onset as being marked by non-specific clinical states such as anxiety and depressive symptoms (van der Heiden & Hafner, 2000; Yung & McGorry, 1996). It thus appears that the presence of non-psychotic mental disorders during childhood or adolescence may indicate a premorbid vulnerability to psychosis (Lewis et al., 2000; Rubino et al., 2009; Weiser et al., 2001).

Bendall et al. (2008b) subsequently conducted a literature review of studies assessing the range of mental illnesses within the FEP population. These studies reported non-psychotic mental illness comorbidity rates of between 34% and 69% (Sim et al., 2005; Strakowski et al., 1993; 1995). The differences in prevalence rates reported may be attributed to methodological issues, including retrospective versus prospective data collection and diagnoses of schizophrenia versus FEP.

2.1.1 Depression in schizophrenia and first episode psychosis.

Unipolar depression is a mental disorder often experienced by patients with schizophrenia (Häfner et al., 2005). Depressive symptoms have thus far been most often examined in the chronic schizophrenia population rather than in the FEP or UHR populations. The prevalence figures of depression reported in schizophrenia studies vary considerably. In a cross-sectional study of chronic schizophrenia ($n=120$), Baynes et al. (2000) reported a prevalence of 13.3% for current depression (Baynes et al., 2000). A subsequent review by Siris and Bench (2003) reported prevalence rates in chronic and first episode schizophrenia that ranged between 6% and 75% with a modal value of 25% (Sim et al., 2004).

McMillan et al. (2009) found a comorbid rate of 71% of mood disorders in people who had been diagnosed with schizophrenia, or previously experienced a

psychotic episode. However, the looser definition of psychosis to include people who have experienced any one episode in their lifetime, as well as the diagnosis being based on participant self-report, could explain the very high prevalence (McMillan et al., 2009).

Majadas et al. (2012) found that even patients with stable schizophrenia who had not been diagnosed with depression often had clinical symptoms of depression, and that these symptoms could be separated from other symptoms of their disorder, with the possible exception of a contribution from negative symptoms (Majadas, Olivares, Galan, & Diez, 2012). Thirty-one per cent of their sample ($n=90$, including those diagnosed with schizophrenia, schizoaffective disorder and schizophreniform) had symptoms of depression, with 33% of those diagnosed with schizophrenia in particular, showing signs of depression.

Similarly, studies examining the depressive syndrome in FEP patients report rates of depression significantly higher than in the general population (Subotnik et al., 1997), with rates of concurrent depression varying from 16.7% (Sim, Mahendran, Siris, Heckers, & Chong, 2004) to 34% (Wassink, Falum, Nopoulos, & Andreasen, 1999). Lifetime rates are even higher, with 85% ($n=232$) of people with FEP having experienced at least one major depressive episode (Hafner et al., 1999). In 42% of these cases, the depressive symptoms had preceded the onset of psychotic symptoms, leading the researchers to conclude that depression was not a reaction to the disturbing changes in cognition, perception and social situation, but rather “a direct expression of the illness” (Hafner et al., 1999).

However, depressive symptoms are viewed by some to be a secondary consequence of psychotic disorders, resulting from treatment with neuroleptics (neuroleptic-induced dysphoria) (Birchwood, Iqbal, & Upthegrove, 2005; Strakowski et al., 1995). It is argued that depression may also result from the dejection or

hopelessness associated with diagnosis and the experience of the illness. The relationship between depression and psychosis remains poorly understood and therefore it is beneficial to further study the early stages of emerging psychosis.

2.1.1.1 Is depression separate to the psychotic process?

Whether depression should be seen as separate to psychosis, or as part of the psychotic process, has been a topic of controversy (Birchwood et al., 2005). Some authors view depression as part of the psychotic process, driven by the accompanying loss of functioning associated with psychosis (Birchwood et al., 2005; Strakowski et al., 1995). Hafner et al. (2005) failed to distinguish the prodromal stage of schizophrenia from that of depression in a retrospective study (Häfner et al., 2005). However, it is important to note that in many of the studies mentioned, patients met full diagnostic criteria for the mental disorders, which suggests that they experienced a significant level of disorder. Furthermore, the assumption that depression is part of the psychotic process has led to the pathogenesis of these mood co-morbidities being poorly understood and thus few effective treatments exist (Birchwood et al., 2005). Birchwood (2005) has argued that we need to make a clear distinction between three core, but not mutually exclusive, pathways to depression in psychosis: depression that is integral to the psychosis process, a psychological reaction to psychosis, and the outcome of disturbed developmental pathways resulting from developmental trauma and the childhood antecedents of psychosis.

2.1.1.2 Depression and functional outcomes in schizophrenia and first episode psychosis.

Regardless of whether one views depression as separate to psychosis or as part of the process, it has been reported to have an important association with poorer functional outcomes in psychosis, including higher rates of unemployment, less

involvement in activities, higher rates of re-hospitalisations and greater suicidal tendencies (Sands & Harrow, 1999). Patients with schizophrenia who exhibit symptoms of depression also demonstrate greater impairment at work (Sands & Harrow, 1999) and report a poorer quality of life (Reine, Lançon, Di Tucci, Sapin, & Auquier, 2003; Sim et al., 2004; Zisook et al., 2007). In a sample of 66 FEP patients, those with a comorbid depressive syndrome had greater awareness of their mental illness, its social consequences and treatment efficacy. These patients also reported poorer overall quality of life, especially in relation to the physical and psychological health, social relationships and environmental domains (Sim et al., 2004). It was thought that the greater degree of insight in these patients and their ability to attribute their problems to poor health, negative environment and poor social support led to the poorer quality of life scores (Sim et al., 2004). Depression has also been associated with impaired performance of social roles, including difficulties in relationships with others (Glazer, Prusoff, & Williams, 1981).

2.1.2 Anxiety in schizophrenia.

Relative to depression, there is a paucity of data regarding the occurrence of anxiety syndromes in schizophrenia (Braga et al., 2004). Several studies have reported elevated presence of comorbid anxiety symptoms/disorders in patients experiencing psychosis (Davidson, Hughes, George, & Blazer, 1993; Turnbull & Bebbington, 2001). However, studies examining anxiety and psychosis have generally only reported prevalence and not explored the relationship between these comorbidities in any depth. As such, anxiety syndromes in schizophrenia, like the depressive syndrome, are poorly understood. The boundaries between anxiety symptoms that coexist with schizophrenia and anxiety-like symptoms that are due to psychotic disorder are still blurred (Braga et al., 2004). A number of studies show improvement in anxiety symptoms with anxiolytic medications in these patients. They

show a significantly different neuropsychological profile of people with psychosis and anxiety comorbidity when compared to people with schizophrenia without comorbid anxiety (Hwang, Morgan, & Losconzcy, 2000; Lysaker et al., 2000; 2002), indicating that anxiety may occur in a distinct cluster of people with schizophrenia. However more research in this area is needed.

There is wide variation in the rates of anxiety disorders reported in the psychosis population (Ciapparelli et al., 2007). Ciapparelli et al. (2007) found that anxiety disorders, particularly obsessive-compulsive disorder³ (OCD), panic disorder and social anxiety disorder (SAD), seem to be frequently comorbid (49.6%) in remitted patients with psychotic illness (schizophrenia, schizoaffective or bipolar disorder). In a review of the literature, these authors found prevalence rates of between 0% and 35% for OCD, 3.3% and 33% for panic disorder, 8.2% and 39.5% for SAD, 2.5% and 16.7% for generalized anxiety disorder (GAD), 0% and 16.6% for posttraumatic stress disorder (PTSD), and 2.5% and 13.6% for simple phobias (Ciapparelli et al., 2007).

Studies examining comorbid anxiety symptoms in people with schizophrenia have found a relationship with greater severity of illness, increased impairment in psychosocial functioning and in quality of life (Cassano, Pini, Sacttoni, & Dell'Osso, 1999; Huppert, Weiss, Lim, Pratt, & Smith, 2001), as well as a higher rate of suicidality (Taiminen et al., 2001). Obsessive-compulsive disorder, in particular, has been linked to higher rates of suicide attempts and suicidal ideation in people with schizophrenia (Sevincok, Akoglu, & Kokcu, 2007).

³ OCD was classified as an anxiety disorder in DSM-IV, when this research was conducted. It was moved to the category of Obsessive-Compulsive and Related Disorders in the DSM-5.

2.1.3 Substance use in schizophrenia and first episode psychosis.

Substance use disorders (SUD) are highly prevalent in psychotic disorders. The United States Epidemiologic Catchment Area Study, which analysed data from 20,291 participants from the general population, found that 47% of people with a diagnosis of schizophrenia had a co-occurring substance abuse or dependence disorder (Regier et al., 1990). An even greater prevalence of SUD was found in a sample of 643 patients with FEP. Seventy-four per cent had experienced a lifetime SUD, 62% had an SUD in the 3 months prior to admission and 36% had an SUD 18 months later (Lambert et al., 2005). Similarly, in a study of 103 FEP patients, semi-structured interviews revealed that 73% of patients had experienced a lifetime SUD, with 52% continuing their use during a 15-month prospective follow up period, after onset of FEP (Wade et al., 2006). The substances reported to be most often abused by people with psychosis were cannabis (Duke et al., 2001; McMillan et al., 2009) and alcohol (Margolese et al., 2004; McMillan et al., 2009). However, despite strong evidence that SUD is a commonly occurring comorbid disorder in psychosis, there is a lack of research investigating the pattern of comorbidity and functional outcomes prior to and during the FEP (Bendall et al., 2008a).

2.2 Mental Illness Comorbidity in the Ultra High Risk Population.

The comorbid psychiatric disorders described above have also been observed at elevated rates in the UHR population, though less research has been conducted with this population than with schizophrenia (Fusar-Poli et al., 2013; Salokangas et al., 2012). Addington et al. (2017) observed that 79% of their Clinical High Risk (CHR) patients, drawn from the North American Prodrome Longitudinal Study (NAPLS2, $n=744$), had a comorbid diagnosis, with many of them having at least 2-3 comorbid disorders, as measured by the DSM-IV (Addington et al., 2017).

Over half of help-seeking people who meet UHR/CHR criteria initially present with a major depressive or anxiety disorder, similar to their schizophrenia and FEP counterparts (Addington et al., 2010; Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014; Velthorst et al., 2009; Yung, Phillips, Yuen, & McGorry, 2004). The European Prediction of Psychosis Study (EPOS) found that at least 71% of their 245 CHR participants experienced at least one lifetime non-psychotic DSM-IV diagnosis (Salokangas et al., 2012). Current diagnoses were present in 62% of these individuals at time of assessment; of these, anxiety disorder (39%) and depression (34%) were the most common. Similar rates were observed at follow-up in the NAPLS2 cohort (Addington et al., 2017). Depressive disorder was present in 32.2% ($n=86$) and anxiety disorder affected 37.5% ($n=100$) at 24-month follow-up. These rates were even higher at baseline, with 42.5% ($n=316$) and 47.8% ($n=355$) being affected by depression and anxiety disorder, respectively. In another study with adolescents at clinical high risk of psychosis ($n=82$), Lencz et al. (2004) reported a 30% rate of lifetime depression ($n=82$). Phillips et al. (2009) also found that major depressive disorder was the most common non-psychotic mental disorder experienced by patients at UHR for psychosis ($n=193$). They found that 87% of their UHR participants met diagnostic criteria for at least one DSM-IV condition. Almost two-thirds of their cohort had reported at least one previous occurrence of self-harm (Phillips et al., 2009).

While the high prevalence rates of these disorders in the UHR and CHR populations have been well documented, the impact of mental disorders in the UHR population has not been as widely researched as in the schizophrenia population (Fusar-Poli et al., 2012). Depression and anxiety, as well as the associated functional impairment, are often the main concern reported by help-seeking CHR/UHR individuals (Falkenberg et al., 2015). Falkenberg et al. (2015) found that 47.1%

($n=104$) of young people meeting UHR criteria and presenting at a specialised early intervention service in London (OASIS, $n=290$) reported depressive and anxiety symptoms as their primary reason for seeking help. These individuals, though not more likely to transition to psychosis, were more likely to have poorer functional outcomes at follow-up as well as higher rates of disorders such as depression, anxiety and substance misuse, than individuals who did not cite depressive and anxiety symptoms as their main reason for help-seeking. Fusar-Poli et al.'s (2012) study with at risk subjects ($n=509$) revealed that a comorbid diagnosis of depression and/or anxiety was associated with higher suicidality or self-harm and impaired global functioning than those without a comorbid diagnosis. The importance of depressive and anxiety symptoms to patients is further demonstrated by the tailoring of psychological interventions to ameliorate these symptoms in UHR individuals (Fusar-Poli et al., 2012).

In contrast to the findings above, Fusar-Poli et al. (2015) have since argued that a decline in functioning is a core feature of an at-risk state and cannot solely be explained by comorbidity of psychiatric disorders. Their 2015 meta-analysis ($n=3,012$) revealed significant and consistent lower functioning in high risk individuals across studies when compared to healthy controls, as measured by the Global Assessment of Functioning. Average Global Assessment of Functioning scores in high risk individuals ($M=50$) were more similar to patients with fully developed psychosis ($M=45$) than healthy controls ($M=79$). Similar results for quality of life were also found, with high risk individuals showing a significant reduction in quality of life scores compared to healthy controls, but no significant difference between high risk and psychosis groups was seen (Fusar-Poli, Rocchetti et al., 2015). The authors concluded that deterioration in functioning and quality of life are core features of the high risk state. However, this meta-analysis did not control for the

presence of comorbid non-psychotic disorders. Thus, it could be argued that healthy controls were faring better than their high risk counterparts as rates of DSM disorders are lower in the general population than in the high risk population.

The evidence to date indicates that comorbid diagnoses can increase the burden of attenuated psychotic symptoms (through additional functional impairment and distress) experienced by the UHR population. The evidence reviewed illustrates that this extra burden often results in poorer long-term outcomes, both clinical and functional.

2.2.1 Persistence of mental disorders in UHR population.

There is evidence to suggest that comorbid non-psychotic mental disorders in a UHR population may persist over time. Lin et al. (2012) found that elevated rates of non-psychotic disorders identified in a UHR population at baseline ($n=226$) persisted at follow-up (between 2-14 years), with the most commonly observed disorders being mood disorder (48.7%), anxiety disorder (34.5%) and SUD (29.2%). Twenty-eight per cent of the sample remained at UHR for psychosis at follow-up. This group had an even higher prevalence of comorbid non-psychotic mental disorders than the total sample, with 65.5% experiencing a current mood disorder. Furthermore, onset of an anxiety and/or SUD that had not been present at baseline occurred in almost 20% of the total sample. This study illustrates the importance of understanding the role of non-psychotic mental disorders in the UHR population, as these disorders may persist long-term, even when UHR status remits, and there may even be incidence of new non-psychotic mental disorders.

In a systematic review of long-term clinical and functional outcomes of non-transitioned UHR people ($n=10$ papers), Beck et al. (2019) found that 20-82% still met criteria for at least one clinical diagnosis at follow-up, however, only four papers presented findings on clinical outcomes beyond diagnosis of a DSM disorder

(Addington et al., 2011; de Wit et al., 2014; Lemos-Giráldez et al., 2009; Rutigliano et al., 2016). Rutigliano et al. (2016) found that non-psychotic mental disorders were persistent or recurrent in the UHR population over a 6-year follow-up (identified using CAARMS, $n=74$). They found that 61.5% of those who presented with a comorbid disorder at baseline, also reported a persistent or repeating course of the same disorder (Rutigliano et al., 2016). Within this sample, almost half of the participants developed a new disorder (45.4%) since baseline. Of these, non-psychotic comorbid disorders were associated with poor functional outcomes at follow-up. This highlights that people at UHR are more likely to experience mental health difficulties that cause distress and disability, irrespective of whether they transition to psychosis. Addington et al. (2017) examined course of illness over a shorter follow-up period (24 months). Improvements in rates of both anxiety and depression were seen in their NAPLS2 UHR cohort ($n=276$). Despite the improvements, around 30% of participants continued to meet criteria for non-psychotic mental disorders.

2.2.1.1 Psychotic symptoms present in mood disorders – shared vulnerability?

It could be that the difference between psychotic and mood disorders are not as distinct as DSM classifications would make them out to be. Ever since Kraepelin first described dementia praecox, there has been controversy surrounding how best to classify psychotic disorders. Kraepelin (1896) thought that this distinction, between what later became labelled as bipolar disorder and schizophrenia, would aid investigation into aetiology of these disorders (Boks, Leask, Vermunt, & Kahn, 2007). However, since then, studies have shown a substantial overlap in clinical and neuropathological findings between bipolar disorder and schizophrenia (Boks et al., 2007). Recently, research has also illustrated that the genetic vulnerability for schizophrenia, depression and bipolar disorder is shared (Cardno, Rijsdijk, Sham,

Murray, & McGuffin, 2002; Lewis et al., 2003). In particular, family and twin studies have reported a degree of overlap in genetic liability between non-affective psychotic disorders (such as schizophrenia) and affective psychotic disorders (e.g., bipolar disorder) (Craddock, 2007; Lichtenstein et al.). Longitudinal studies have shown that sub-threshold psychotic symptoms may predict subsequent onset not just of psychotic disorders, but also affective disorders (Rössler & Angst, 2011). In line with the findings from aetiological research, affective and psychotic phenomena often co-occur, partly on the basis of shared vulnerability as well as on the basis of reciprocal causal influence (Wigman et al., 2012).

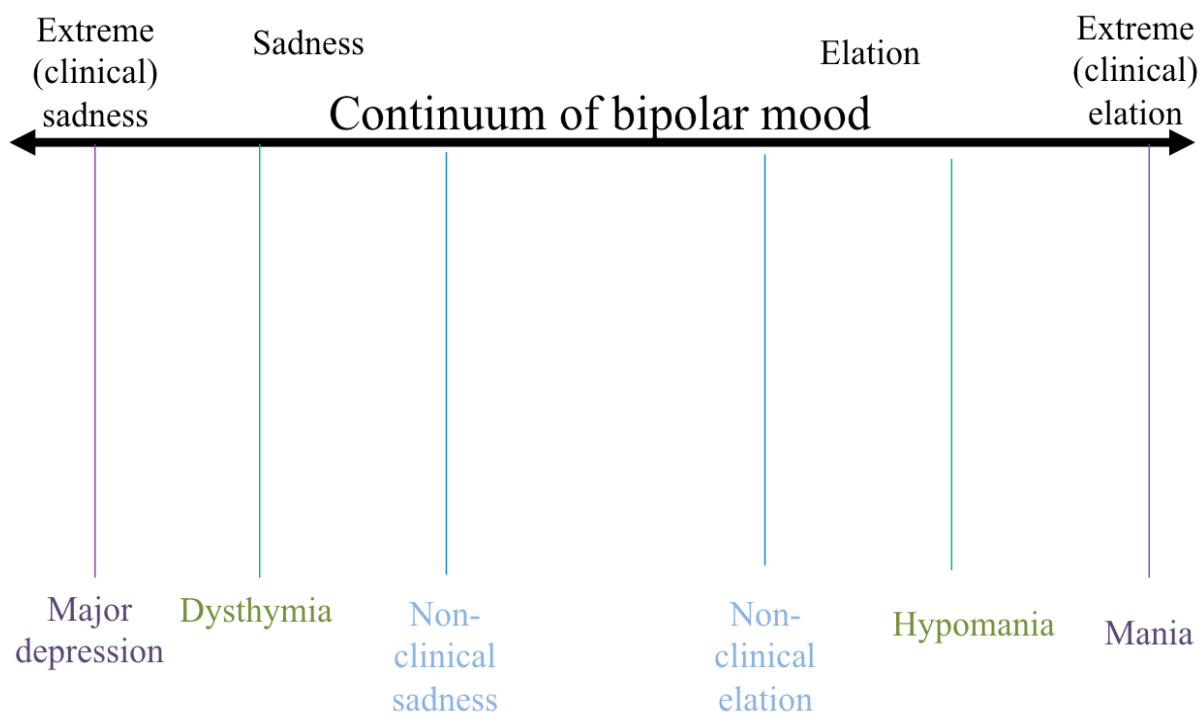
Some studies have illustrated that psychotic experiences are reported within a range of affective clinical disorders (Dunayevich & Keck, 2000; Sareen, Cox, Goodwin, & Asmundson, 2005). Conversely, high rates of affective symptoms have been demonstrated in patients diagnosed with non-affective psychotic disorders (as classified by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV))(Peralta & Cuesta, 2009; Zisook et al., 1999). A longitudinal, prospective study of a community sample of young adults ($n=3,021$), revealed that psychotic symptoms were present in 27% of people who were diagnosed with a depressive or anxiety disorder at baseline (using the DIA-X/M-CIDI) (Wigman et al., 2012). Furthermore, people with a disorder of anxiety/depression were more likely to report psychotic symptoms than those without a disorder.

Longitudinal studies have shown that sub-threshold psychotic symptoms predict onset of affective disorders, not just psychotic disorders (Rössler & Angst, 2011). This may indicate a common underlying factor associated with the development of both psychotic and affective disorders. Deterioration experienced in social and emotional functioning are also predictive of development of either type of disorder (Häfner et al., 2005).

The above studies illustrate that affective symptoms and reality distortion often co-occur, consistent with other research in this area (Boks et al., 2007; Buckley, Miller, Lehrer, & Castle, 2009; van Rossum, Dominguez, Lieb, Wittchen, & van Os, 2011; Varghese et al., 2011). However, most of the research exploring the overlap between psychotic symptoms and affective disorders is cross-sectional and conducted with clinical samples. This makes it difficult to determine the direction of effects between cognitive and affective processes, and to distinguish illness cause and illness consequence (van Rossum et al., 2011).

2.2.1.2 Can we separate mental disorders from features of an at-risk state?

The prospect of mood and anxiety disorders as co-occurring with UHR features assumes a clear distinction between these constructs as separate entities (Fusar-Poli et al., 2012). This view is currently reinforced by the categorical diagnostic manual-based approach (i.e. a SCID interview) (Fusar-Poli et al., 2012). However, more recently, the categorical definition of psychosis has been contested in favour of a continuum approach to disorder (Stefanis et al., 2002; Verdoux & van Os, 2002). When viewing psychosis categorically, the approach is dichotomous: the individual either has or does not have, the disorder (see Figure 1 for illustration of categories versus dimensions in mood disorder). From a dimensional view of psychosis, the question becomes not whether an individual has the disorder, but rather to what degree the individual has psychotic experiences, measured on several dimensions (Hanssen et al., 2003). This consideration is especially important when looking at individuals identified as being at UHR for psychosis and whether or not a categorical syndrome to describe these people is appropriate.



Categories of bipolar mood

Figure 1: Dimensional versus categorical approach to bipolar disorder

Many studies indicate that positive psychotic symptoms, in particular, exist on a continuum, for example, with schizophrenia at one end and “psychotic-like experiences” that do not impair functioning nor cause distress at the other (Dhossche, Ferdinand, Van Der Ende, Hofstra, & Verhulst, 2002; Johns & Bebbington, 2004). These studies suggest that individuals in the general population frequently have psychotic like experiences. Furthermore, these experiences are not necessarily associated with the onset of psychotic disorders, nor with help seeking and distress (Dominguez, Wichers, Lieb, Wittchen, & van Os, 2011; Hanssen et al., 2003; van Os, Linscott, Myin-Germeys, Delespau, & Krabbendam, 2009).

Van Os and Guloksuz (2017) have argued that UHR/CHR criteria do not pick

up people specifically at a higher risk for psychosis. Rather, they argue for a trans-diagnostic approach, whereby psychotic experience occurs in common mental disorders, such as anxiety, depression and SUD. Epidemiological studies in community samples and in the general population have also reported a significant relationship between affective symptoms and sub-threshold expression of psychotic symptoms (Armando et al., 2010; Varghese et al., 2011). A study of two community samples of adolescents ($n=2243$, assessed via survey and $n=423$ assessed using in-depth diagnostic interviewing) found that psychotic symptoms are prevalent in a wide variety of non-psychotic mental health disorders (Kelleher et al., 2012).

In a meta-analytic review of all reported incidence and prevalence studies of subclinical psychotic symptoms in the general population, Van Os et al. (2009) found a median prevalence rate of 5% and an incidence rate of 3% in the general population (van Os et al., 2009). However, research has also indicated that although 75–90% of developmental psychotic experiences are transient (Dominguez et al., 2011), individuals in the general population who frequently experience intense, yet sub-threshold psychotic symptoms, are five times more likely to be diagnosed with a psychotic disorder 4 years later (Hanssen et al., 2003). Two independent community studies found that a large majority of young people reporting psychotic symptoms also had at least one non-psychotic mental disorder (Kelleher et al., 2012). The suggestion that depressive and anxiety symptoms are of greater or equal concern as the psychotic symptoms is consistent with the observation that high prevalence of psychotic-like experiences in the general population are not necessarily associated with subjective distress, psychosocial impairments or low functioning and that, therefore, do not trigger help-seeking behaviours (Fusar-Poli et al., 2012).

It is unclear to what extent current high risk criteria provide specific and sensitive identification of individuals most likely to develop psychosis, amongst others who

exhibit similar clinical presentations (Fusar-Poli & Borgwardt, 2007). In research to date, small sample sizes have often been used and thus studies have yielded uncertain and sometimes conflicting results about the types of disorders that develop (Fusar-Poli et al., 2013).

2.3 Summary of Chapter 2: Mental Illness Comorbidity in Psychosis

Individuals with schizophrenia, FEP and at UHR for psychosis describe similar histories of premorbid non-psychotic mental illness, in particular mood, anxiety and substance use disorders (Bendall et al., 2008a; McMillan et al., 2009). This is consistent with findings that FEP patients describe the phase prior to onset as being marked by nonspecific clinical states such as depressive and anxiety symptoms (Yung & McGorry, 1996). However, the relationship and underlying pathology between these non-psychotic symptoms and psychosis remains poorly understood.

The current evidence suggests that despite some remission, non-psychotic illness appears to persist or recur for many individuals at UHR for psychosis. Beck et al. (2019) recommend that further research into the various trajectories experienced by UHR individuals who do not transition is needed, since relatively few studies have addressed this research question. Thus far, most of the research on trajectories of outcomes has focused on preventing or delaying psychotic disorder. This is a limited approach, given that the majority of UHR individuals will not transition, with many not fully recovering from their clinical symptoms.

The persistence of non-psychotic mental disorders over time has been shown to be associated with poorer clinical and functional outcomes over the longer-term (Cropley et al., 2016). This relationship has not been thoroughly explored within the UHR population. The only recent systematic review of literature addressing clinical and functional long-term outcomes of UHR people (Beck et al., 2019) revealed that only 10 studies attempted to investigate these outcomes for individuals who do not

transition. Of these, no study addressed prevalence of sub-threshold clinical symptom outcomes beyond APS and only four studies reported on clinical diagnoses at follow-up, with more than half of participants meeting criteria for a diagnosis (Addington et al., 2011; de Wit et al., 2014; Lemos-Giráldez et al., 2009; Rutigliano et al., 2016). Research on psychosocial outcomes for UHR individuals also remained scarce, though the few studies investigating this showed long-term poor functioning for approximately half of UHR individuals. Given the poor outcomes indicated for a substantial subset of non-transitioned UHR individuals, it is evident that further research on their trajectories is needed.

Chapter 3

Are UHR Outcomes Specific to Psychosis or Pluripotential?

It has been argued that sub-threshold psychotic symptoms are indicative of a wider range of non-psychotic psychiatric problems, rather than only part of a psychosis prodrome. It could be that a variety of disorders develop from the initial nonspecific symptoms currently associated with the psychosis prodrome (Yung et al., 2012). Non-specific risk factors (such as environmental influence and genetics) have been implicated across a range of psychiatric disorders (Yung et al., 2012). A general population study ($n=4,894$) found links between the experience of sub-threshold psychotic symptoms and symptoms of other psychiatric disorders (Breetvelt et al., 2010). This study showed that the majority of people experiencing sub-threshold psychotic symptoms were experiencing concurrent depressive, anxiety or phobic symptoms (89%), compared to 11% of participants who did not have any psychotic symptoms. The majority of UHR/CHR individuals have been shown to meet criteria for mood, anxiety and substance use disorders (Beck et al., 2019; Fusar-Poli et al., 2014; Lin et al., 2015; Rutigliano et al., 2016). It is thus not well established whether UHR and CHR outcomes are specific for psychosis or whether they capture people who are at an elevated risk for nonpsychotic psychiatric disorders (pluripotent). In recognition of this, there is increased acceptance in the field that treatments in the UHR stage should not focus solely on prevention of transition, but address the variety of unfavourable trajectories and continuing clinical symptoms (McGorry, Hartmann, Spooner & Nelson, 2018; Nelson et al., 2018; Yung, 2017).

The concept of pluripotency is consistent with the clinical staging model of psychiatry (Hickie et al., 2013; McGorry, 2013) whereby a number of trajectories and outcomes are possible from the initial nonspecific symptoms (reduction in

functioning, depressed and anxious mood, experience of distress) that cause young people to be help seeking. It should be noted that this definition of pluripotency does not seek to characterise the initial state (i.e. UHR), but rather addresses the diversity of potential outcomes. Within this model, mental disorders are viewed as dynamic, with the potential to change over time. Individuals may experience different stages of illness. For example, Stage 1a corresponds to help-seeking with distress, Stage 1b = attenuated (sub-threshold syndrome, where UHR criteria sits), up to stages 2-4 which describe full blown disorder, and ranges in severity and persistence. The model was originally proposed with the outcome of full-blown psychotic disorder, but can also accommodate a variety of exit syndromes, including the presence of 'comorbid' disorders such as depression (Hartmann et al., 2017). This model has also been described as a 'trunk and branch' model (Hickie et al., 2013) whereby the trunk represents sub-threshold phenomena and early signs, with the branches representing the various disorders these signs and symptoms could evolve into. Within this framework, disorders share aetiologies and symptoms.

The high prevalence of non-psychotic psychiatric problems in those at UHR, and the variable trajectories they experience, supports the notion that UHR outcomes are not specific to psychosis (McGorry, Hartmann, Spooner, & Nelson, 2018). While the studies investigating trajectory are limited (Beck et al., 2019), current evidence suggests a variety of exit syndromes⁴ for those who do not transition to psychosis. As many as 17 clinical trajectories were identified in one study of a UHR sample (Polari et al., 2018)(see Appendix A1 for details). Of these, more than half (57%) of the outcome trajectories were classed as 'unfavourable', meaning participants experienced

⁴ Please note that the term *exit syndrome* in the current context describes a syndrome that develops from the at-risk state a person has experienced. This *exit* does not exclude the possibility that other psychotic or non-psychotic psychiatric disorders may emerge at later points in time, or that the person might develop multiple exit syndromes.

recurrence, relapse, no remission or transition of symptoms. Forty-three per cent exhibited 'favourable' outcomes at follow-up (recovery or remission from UHR state). However, these trajectories were only based on APS and functional outcomes, and did not include clinical diagnoses. There is currently a gap in the research exploring trajectories encompassing the overall picture of APS, functional outcomes as well as disorder level clinical diagnoses (Beck et al., 2019).

The increasing recognition of the at-risk mental state being a syndrome within itself (Carpenter, 2015; Fusar-Poli et al., 2015) has triggered further research into outcomes of non-transitioned UHR cases, which constitute the majority of UHR participants. However, these outcomes and trajectories of illness for this population have been difficult to ascertain, as most research has focused solely on APS and social/occupational functioning. The research on trajectories has lacked clear definitions on what the trajectories comprise (i.e. what is meant by remission, relapse etc.) and mostly ignored the impact of non-psychotic psychiatric disorders (Lim et al., 2015; Polari et al., 2018), despite their prevalence (Lin et al., 2015). Understanding these trajectories in full would help us to identify what the at-risk mental state means in the long term for those meeting these criteria.

De Wit et al. (2014) argue that the at-risk mental state captures non-specific psychotic symptoms and general psychopathology, rather than specifically identifying those at risk for psychosis. Furthermore, they argue that clinical and functional outcomes of people who do not transition to psychosis may be similar to people who transition (in comparison to healthy controls). This was based on their six-year follow-up of UHR individuals ($n=44$). They found that around 40% of participants had fully remitted from UHR status but were still experiencing significant psychiatric difficulties ($n=18$). One third of UHR patients who had fully remitted were still diagnosed with non-psychotic mental disorders at follow up. An even greater portion

(56%), who were still identified as being UHR but had not transitioned were also diagnosed with non-psychotic mental disorders. The authors suggested that the high prevalence of non-psychotic mental disorders and decreased functioning of non-transitioning participants implied that the UHR outcomes captured a wider spectrum of psychopathological risk, rather than a specific risk for psychosis. The small sample at follow-up was a limitation of this study, however, their findings of prevalence of non-psychotic disorder and poor functioning at follow-up are similar to others (Beck et al., 2019; Polari et al., 2018; Schlosser et al., 2012).

In contrast, Velthorst et al. (2011) uncovered positive long-term outcomes for their UHR sample ($n=57$) and argue that UHR may represent a temporary state, rather than a specific risk for severe psychiatric disorders. They found that 75% of the non-transitioned patients remitted from UHR symptoms within 3 years (Velthorst et al., 2011). Eighty-five percent of those who remitted from UHR status went on to find a new job and/or start study, a significant improvement from baseline rates. An improvement in global functioning as well as employment status was also observed in this group. They found that the likelihood of remission to a non-risk state was over four times greater than the chance of transition to psychosis within a year of being identified as UHR. These results indicate that UHR status may only be temporary for young people, and that over time the associated problems (clinical and functional) may resolve. This is consistent with the observation that UHR criteria are not predicting transition or long-term problems for the majority of young people. However, as with many long-term follow-ups, the sample size was small, and these positive outcomes do not appear to have been replicated in other studies (Beck et al., 2019).

In keeping with the argument for pluripotent outcomes, Conrad et al. (2017) found that their UHR clients had a comparable transition rate to their non-UHR help-

seeking counterparts (Conrad et al., 2017). They followed up the two comparison groups of UHR individuals ($n=191$), and help-seekers presenting with depression, anxiety and substance use concerns, who had no prior mental health admissions ($n=706$) over a two-year period at a specialized early psychosis mental health service⁵. After two years, the transition to psychosis rates for the UHR clients versus the comparison group were 8.9% vs 9.1%, respectively. This rate, while substantially lower than the mean 2-year transition to psychosis rate of 17.4% established by a meta-analysis of transition rates (Schultze-Lutter et al., 2015), was still significantly higher than that seen in the general population (Perala et al., 2007). It could be that people at UHR are not specifically at risk of psychotic outcomes, but rather at risk of severe mental health disorders. Having a severe mental disorder itself may increase the chance of having psychotic experiences in comparison to the general population (van Os & Guloksuz, 2017). The authors also posited that lower transition rates in their UHR group could be due to the treatment provided through active interventions in their clinic.

Woods et al. (2017) also argued that they found no evidence to support pluripotent outcomes. They found similar rates of persistent disorders among their UHR participants ($n=80/147$) compared to help-seeking controls ($n=48/84$), indicating that individuals at UHR were not more likely to be at risk for a range of mental disorder outcomes. Furthermore, Woods et al. (2017) did not find sub-groups of other trajectories that differed between the two groups (UHR and non-UHR help-seeking) to indicate pluripotential outcomes. Emergence of new non-psychotic disorders have also been reported to be fairly uncommon in UHR individuals and

⁵ Other groups followed up included those with existing psychosis, recent psychosis, people with non-psychotic disorders at baseline, with or without psychiatric admissions, and those with incomplete baseline assessment. People were assessed using the CAARMS.

were comparable with non-UHR individuals (Fusar-Poli et al., 2017). However, the authors noted that these findings needed replication, as trajectories of non-psychotic disorders in at risk samples have rarely been investigated.

In contrast to the above findings (Conrad et al., 2017; Woods et al., 2017), other authors argue that UHR outcomes are specific to psychosis. A study comparing UHR participants ($n=271$) to help seeking controls ($n=171$) indicated that there were significant differences in transition rates between the two groups, with UHR individuals more likely to convert to a psychotic disorder (Webb et al., 2015). Participants were assessed using DSM-IV and SIPS⁶. Despite high rates of non-psychotic disorders in both UHR and help seeking controls, UHR participants were significantly more likely to develop a psychotic disorder than a non-psychotic one (19.6% transition to psychosis, compared to 4.4% developing depression and 5.2% developing an anxiety disorder). Similarly, help seeking controls were significantly less likely to develop a psychotic disorder than a non-psychotic one. The authors concluded that diagnostic outcomes for help-seeking individuals meeting CHR criteria were specific for psychosis. Their results for transition are similar to Lin et al. (2015), who observed a transition rate of 27.3%, with rates of depression being 7.3%, and incident anxiety rates of 13.9%. It is important to note that though incident rates for nonpsychotic diagnoses were lower than psychotic diagnoses in the CHR/UHR samples, these non-psychotic rates are still higher than rates observed in population-based studies of young people (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Roberts, Roberts, & Chan, 2009).

There is support for both pluripotent outcomes as well as outcomes specific to psychosis in people identified as being UHR. Difficulties in maintaining large sample sizes over a long enough period of follow-up hinder progress in this area. The

⁶ Structured Interview for Prodromal Syndromes

heterogeneous outcomes from different samples may result from these varied follow-up periods, and varied recruitment strategies, leaving the question of whether UHR outcomes are specific to psychosis or pluripotent unresolved. However, given the large portion of non-transitioned cases over the longer-term, it is important to further our understanding of the clinical trajectory in addition to focusing on psychosis outcomes.

3.1 Summary of Chapter 3: Are UHR Outcomes Specific to Psychosis or Pluripotential?

The high prevalence of non-psychotic mental disorders in UHR and the variability in the small amount of trajectory outcome data collected to date provides evidence that UHR outcomes are pluripotential, rather than being specific to psychosis. The concept of pluripotency fits within the clinical staging model of psychiatry (Hickie et al., 2013, McGorry, 2013), whereby the initial nonspecific clinical and functional symptoms may result in a variety of outcomes. Further to this, shared risk factors (including environment and genetic factors) across psychiatric disorders indicate a shared basis of pathology. The variability in outcomes has resulted in treatments in the UHR field that do not focus solely on prevention of transition but address the broader clinical outcomes seen (McGorry et al., 2018; Nelson et al., 2018; Yung, 2017). However, the lack of long-term trajectory data in UHR populations that explores outcomes other than transition means that the question of pluripotentiality needs further exploration, with researchers unresolved on this issue.

Some authors argue that UHR outcomes are specific to psychosis. Webb et al. (2015) showed that UHR individuals are significantly more likely to develop a psychotic mental disorder than a non-psychotic one. Woods et al. (2017) also support the notion of diagnostic specificity, finding that UHR criteria were not more likely to

capture people at risk of a range of psychiatric disorders than non-UHR help seeking individuals. Instead of UHR criteria capturing individuals at risk of pluripotent outcomes, having a mental disorder in itself may simply predispose an individual to having psychotic symptoms (van Os & Guloksuz 2017).

In support of the pluripotential argument, some authors found that the transition rate in a UHR sample is comparable to non-UHR help-seeking samples, indicating that UHR outcomes are not specific to psychosis (Conrad et al., 2017). The high prevalence of non-psychotic disorders in UHR individuals that persist over the longer-term also supports the notion that UHR outcomes are not specific to psychosis (McGorry et al., 2018). A review of the UHR literature further demonstrated that there are a variety of exit syndromes for people who do not transition to psychosis (Beck et al., 2019). However, this review indicated that further research is needed, given the paucity of studies examining long-term trajectories of UHR samples who do not transition. Research has especially ignored the impact of non-psychotic mental disorders on long-term outcomes (Lim et al., 2015; Polari et al., 2018).

Chapter 4

Longer-term Outcomes of UHR Individuals

4.1 Comorbid Non-Psychotic Mental Health Disorders and Transition to Psychosis

Depression and poor functioning have been found to increase risk of developing a psychotic disorder within UHR individuals at the PACE clinic (Yung et al., 2003; Yung et al., 2004). As previously described, depressive symptoms are common in the ‘prodromal’ phase of psychosis (Schultze-Lutter et al., 2010). However, the role of comorbid non-psychotic disorders in transition to psychosis has also not been extensively explored (Addington et al., 2017). The few studies examining this relationship have shown that baseline non-psychotic disorders were not predictive of later transition (Fusar-Poli et al., 2014; Lim et al., 2015; Ryan, Graham, Nelson, & Yung, 2017; Thompson et al., 2012). In addition, the majority of studies that investigated the impact of non-psychotic mental disorders on transition in the UHR population focused on specific disorders, such as borderline PD (Ryan et al., 2017; Thompson et al., 2012), and OCD (Fontenelle et al., 2012; Niendam, Berzak, Cannon, & Bearden, 2009). The overall impact of comorbid non-psychotic disorders on transition is currently under-explored, with the studies that have investigated the link presenting heterogeneous and sometimes conflicting results.

Fusar-Poli et al.’s (2014) meta-analysis of 1683 CHR individuals over a mean follow-up period of 3.7 years showed no association between comorbid non-psychotic disorders at baseline and later transition to psychosis (Fusar-Poli et al., 2014). Within the NAPLS1 cohort, comorbid diagnoses were not associated with transition to psychosis, with the exception of substance use (Woods et al., 2009). The authors posited that the lack of association between non-psychotic comorbid disorders at

baseline and later transition may have been due to the low transition rate (14.9%). However, with a similar transition rate of 15.1%, affective disorders (bipolar and depression) as well as somatoform disorders were shown to predict transition in the European Prediction of Psychosis Study (EPOS) (Salokangas et al., 2012).

In the EPOS 18 month follow up assessment of CHR patients ($n=245$, assessed using the SIPS), Salokangas et al. (2012) found that 71% of their sample had one or more life-time and 62% one or more current non-psychotic DSM-IV diagnoses, with about a half in each category receiving a diagnosis of life-time depressive and anxiety disorder. Current comorbidity rates included 34% suffering from depressive disorder, 39% from anxiety disorder, 6.5% somatoform disorder and 4% received a diagnosis of bipolar disorder. Salokangas et al. (2012) argued that not only are non-psychotic mental disorders more highly prevalent in the at-risk population than in the general population, but that these disorders are related to transition in psychosis. They found that among clinical high risk patients (assessed using the SIPS) occurrence of bipolar, somatoform and depressive disorders seems to predict transition to psychosis. In contrast, the presence of anxiety disorder at baseline was negatively correlated with transition to psychosis (Salokangas et al., 2012).

Given the conflicting evidence, it is clear that the relationship between non-psychotic mental health disorders in UHR individuals and the potential relationship to transition needs further exploration. It is possible that depressive and anxiety symptoms might be the result of both psychotic and non-psychotic mental health disorders and thus be difficult to determine their impact on transition rates, but further research is needed.

4.1.1 Outcomes of non-converters.

Irrespective of the predictors of transition, further research is also needed into the outcomes of individuals at UHR who do not develop psychosis as relatively few studies have investigated the outcomes of non-transitioning individuals (Addington et al. 2011; Beck et al., 2019; Haroun, Dunn, Haroun, & Cadenhead, 2006; Lemos-Giráldez, 2009; Miller et al., 2002; Schlosser et al., 2012; Simon & Umbricht, 2010; Velthorst et al., 2011; Zimmerman, Rothschild, & Chelminski, 2005). Findings in this area have been mixed, with UHR/CHR individuals having heterogeneous outcomes over time.

Addington et al. (2011; 2017) found that non-transitioning individuals demonstrated significant improvement of their social and role functioning, in addition to improvement on attenuated positive symptoms and negative symptoms. Over half of this group showed a completed remission of prodromal symptoms, within this one to two-year follow-up. (Addington et al., 2011). However, this non-converting group continued to function at a lower level than healthy comparison subjects, suggesting that meeting CHR/UHR criteria represents persistent disability for a significant proportion of individuals.

A meta-analysis by Simon et al. (2013) ($n=8$ studies) showed that 73% of 773 subjects did not convert to psychosis over a two-year follow up. Of these, 46% fully remitted from baseline attenuated psychotic symptoms, with corresponding clinical remission of 35% of the baseline high risk sample (Simon et al., 2013). Schlosser et al. (2012) conducted a two-year follow up of a group of 84 prospectively identified individuals meeting CHR criteria. They found that around 30% converted to psychosis within two years, with 36% symptomatically remitting and 30% showing full functional recovery. In their two-year follow-up of CHR subjects, Schlosser et al.

(2012) found that better concurrent social and role functioning were associated with an increased likelihood of attenuated symptom remission.

Velthorst et al. (2011) found that patients identified as UHR at baseline recover from positive, negative, disorganisation and general symptoms within the first year of follow-up. These UHR symptoms remained improved over the three-year follow-up (Velthorst et al., 2011). They concluded that complaints made at baseline are likely to be transitory for a large number of their participants.

However, UHR/CHR classification has previously been shown to be associated with persistent, long-term functional difficulties (Carrión et al., 2013). A long-term follow-up study (three years) showed that poor functional outcomes for CHR patients were not dependent on the development of psychosis (Carrión et al., 2013). At the conclusion of this study, almost half of the sample (47.8%) experienced a poor social outcome, and 48.9% a poor role outcome. One-third (32.6%) experienced both poor social and role outcomes. These findings suggest that early intervention focussing on improvement of functional outcomes is important regardless of whether those at risk for psychotic disorder transition to psychosis or not.

In a prospective, longitudinal three to five year follow-up study ($n=92$), patients who demonstrated poor social outcome at follow-up, showed higher negative and disorganised symptoms, as well as poorer social functioning at baseline, compared to those who had good social outcome at follow-up (Carrión, 2013). These patients with poor outcomes displayed consistent impairments in functioning over time, whereas those who had better social functioning at baseline, showed modest improvement over time.

4.1.2 No transition but sustained UHR status.

Recent studies have shown that even if high risk individuals do not transition, attenuated psychotic symptoms continue to persist for up to 50% of them (Addington

et al., 2017; Lee et al., 2014; Lemos-Giráldez et al., 2009; Lin et al., 2015; Velthorst et al., 2011). However, the impact of non-psychotic mental disorders on remission of APS remains under investigated (Beck et al., 2019; Rutigliano et al., 2016).

Current research indicates that individuals with sustained APS represent a heterogeneous group and sometimes even exhibit worse outcomes than those who transition to psychosis (Schlosser et al., 2012). Ultra High Risk for psychosis participants who did not remit from UHR status in Schlosser et al.'s (2012) study demonstrated functioning similar to that of the patients who transitioned to full psychosis or had schizotypal PD. Those with persistent UHR status also experienced functional deficits. Functional impairment often remains despite remission of positive symptoms in prodromal patients. This impairment could therefore be partially attributed to comorbid mood and anxiety symptoms in more functionally impaired cases (Schlosser, 2012).

Ruhrmann et al. (2008) compared the subjective quality of life ratings people in a putatively prodromal state ($n=215$) to those of healthy controls ($n=87$). The quality of life construct reflected a mismatch between the expectations of an individual in various areas of their life, and their real-life experience. New emerging functional impairments thus may influence perception of quality of life through drawing social comparisons, for example, one's position in life, work and social roles (Ruhrmann et al., 2008). Individuals in a putative prodromal state usually are likely to compare themselves to healthy peers while experiencing increasingly serious functional impairment both socially and in their work/academic life.

Ruhrmann et al. (2008) found that those at risk for psychosis experienced diminished subjective quality of life in many domains compared to healthy controls. Depression emerged as the most significant predictor of lower quality of life scores. In contrast, there was no significant association between quality of life and the

presence of positive symptoms. This finding was explained by the authors as potentially being linked to depressed patients having a greater awareness of their symptoms, similar to studies that linked depression in schizophrenia patients to awareness of their psychotic illness and the resulting loss of quality of life.

4.1.3 Impact of comorbid non-psychotic disorders on functional outcomes of non-converters.

The presence of comorbid non-psychotic disorders in high risk individuals is associated with poorer prognosis. However, this area remains under-researched, with most studies of the impact of comorbid non-psychotic disorders on functional outcomes being cross-sectional (Beck et al., 2019). A meta-analysis of cross-sectional studies has found that a comorbid diagnosis of depression and/or anxiety was associated with higher suicidality or self-harm and impaired global functioning (Fusar-Poli et al., 2012). Comorbid depression and/or anxiety diagnoses also significantly reduced scores of global functioning at baseline (Fusar-Poli et al., 2012). The presence of comorbid non-psychotic disorders may further impair the abilities of individuals to cope with the social and occupational challenges they face as a result of their UHR status (Fusar-Poli et al., 2012). Given the impact of comorbid disorders on concurrent outcomes, it is important to investigate the potential longer-term impacts.

4.2 Summary of Chapter 4: Longer-Term Outcomes of UHR Individuals

The relationship between non-psychotic mental disorders and transition to psychosis remains under-explored (Addington et al., 2017). Some research has linked depression to transition to psychosis within UHR individuals (Yung, et al., 2003; Yung et al., 2004). Other studies have found links between transition to psychosis and affective disorders (Salokangas et al., 2012) and substance use (Woods et al., 2009), but these links have not been replicated. A meta-analysis of the literature showed no

relationship between comorbid non-psychotic disorders at baseline and transition to psychosis but this finding might have been affected by the low transition rate in the analysis (Fusar-Poli et al., 2014). Further research is needed to investigate possible links between non-psychotic mental disorders and transition in the UHR population.

Data on long-term outcomes of UHR individuals who do not transition is also lacking (Addington et al., 2011; Beck et al., 2019). The majority of individuals being identified as UHR will not go on to transition (73%) (Simon et al., 2013). It is therefore imperative that the long-term outcomes for this group be understood and appropriate treatments developed, but findings so far have been mixed. Addington et al. (2017) observed significant improvement in their non-transitioning UHR sample, with complete remission from prodromal symptoms. However, this group continued to function more poorly than their healthy comparison participants, indicating that even when UHR individuals are doing well, they may present with long-term disability and functional difficulties (Carrión, 2013). Other studies found that complete remission from UHR was associated with better social and role functioning (Schlosser et al., 2012).

Some individuals who do not transition to psychosis retain UHR status over the longer term. Outcomes for those who retain UHR status have been shown to be similar to people who have transitioned (Schlosser et al., 2012). As many as 50% of individuals may retain UHR status over the longer-term (Addington et al., 2017; Lin et al., 2015; Lee et al., 2014; Lemos-Giraldez et al., 2009) and it is important to understand the type of intervention this group may require.

The impact of non-psychotic mental disorders in the UHR population also remains poorly understood. Functional impairment has persisted even when positive APS have remitted, therefore the impairment could be symptomatic of non-psychotic mental illness experienced by these individuals (Schlosser et al., 2012). Depression

has been revealed to be a predictor of poorer ratings of quality of life in UHR individuals (Ruhrmann et al., 2008). Overall, the outcomes for UHR individuals who do not transition, whether or not they remit from UHR status, and the impacts of the non-psychotic mental illness they are likely to be experiencing over the longer-term remains poorly understood and under-researched (Beck et al., 2019).

Chapter 5

Baseline Clinical Predictors of Trajectories of Non-Psychotic Disorders in UHR Participants

Baseline clinical predictors of trajectories of non-psychotic disorders in the UHR population have not been specifically addressed by previous studies. Where they have been, the focus has been on whether the presence of a non-psychotic disorder at baseline predicts disorder at follow-up, with other baseline clinical variables, such as UHR intake group, negative and positive symptoms for example, not considered.

The literature is lacking in information on whether type of UHR group (vulnerability intake group, BLIPS or APS intake group) predicts longer-term outcomes in experience of comorbid mental disorders. The effect of baseline clinical predictors such as these on longer term outcomes (specifically trajectories of non-psychotic disorders) has only been investigated by Lin et al. (2015) who explored positive and negative psychotic symptoms, affective symptoms, age, gender, IQ and functioning (as measured by Global Assessment of Functioning) as predictors of trajectories of non-psychotic mental disorder. They found that incidence of a non-psychotic disorder was associated with negative symptoms at baseline and that meeting criteria for BLIPS at entry was also associated with a lower risk for persistent or recurrent disorder. Being female was associated with persistent or recurrent mood disorder compared to remitted mood disorder, and also having an incident anxiety disorder compared to never having had an anxiety disorder. They also investigated the predictive effect of Global Assessment of Functioning baseline score, IQ, age and other baseline symptoms but found that these had no association with trajectory of disorder.

No other literature has explored the ability of a broad range of clinical baseline predictor variables to predict non-psychotic long-term outcomes. The only other study in addition to Lin et al. (2015) that attempted to investigate trajectory of disorder, looked at whether current presence of a DSM disorder at baseline predicted persistence or remittance of that disorder at follow-up (Conrad et al., 2017). Conrad et al. (2017) found that a prior history of anxiety depression or substance use at baseline predicted subsequent episodes of the same disorder over the longer term (10 year follow up, $n=1997$). However, they did not report on the trajectories of these disorders in participants (a mixture of psychosis, UHR, non-UHR non-psychosis help-seekers), i.e. whether disorders were continuous, incident or remitted. There is clearly a lack of investigation into a wider range of outcome trajectories and a broader selection of clinical predictors, such as positive and negative symptom scores, types of UHR intake group, and anxiety and depression scores (not just presence of a DSM disorder). This is a gap that the current study aims to address by including these baseline predictors and more trajectory outcomes.

Chapter 6

Personality Disorder Comorbidity in Psychosis

A growing area of interest in psychosis research is the influence of personality. The relationship between schizophrenia and personality disorder (PD) has frequently been debated since the conception of both sets of disorders (Newton-Howes, Tyrer, Moore, & Nur, 2007). As early as 1921, Kretschmer postulated that schizophrenia was an expression of a person's temperament, and that aspects of people's personality lay on a continuous spectrum, ranging from normal to pathological (Kretschmer, 1970). Henry Stack Sullivan proposed an alternate view of schizophrenia as a distinct illness, with related personality deterioration (Sullivan, 1927). Since then, we have solidified our conception of schizophrenia as distinct from personality (APA, 2013). However, comorbid PD is known to worsen the course of schizophrenia (Simonsen et al., 2018) and the potential link between personality, or more specifically (PD), and psychopathology cannot be ignored.

Personality disorder is currently described in the DSM as “a stable and persistent pattern of inner experience and behaviour that develops in adolescence or early adulthood, inflexible and pervasive across a broad range of situations, deviates markedly from the expectations of the individual's culture and leads to clinically significant distress or functional impairment” (APA, 2013). Individuals diagnosed with one or more PDs are more likely to experience poorer outcomes in areas of basic functioning, for example in social role functioning (Lenzenweger, Lane, Loranger, & Kessler, 2007). Disordered personality is described by personality traits that are extreme, cause clinical distress and psychosocial impairment (Newton-Howes, Clarke, & Chanen, 2015).

Personality disorders identified within the DSM are grouped into three clusters. Cluster A comprises paranoid, schizoid and schizotypal PDs, which are characterised by ‘odd or eccentric’ behaviours (Lima Santana et al., 2018). Cluster A PDs are generally considered a risk factor for development of schizophrenia (Simonsen et al., 2018). Cluster B describes antisocial, borderline and histrionic PDs, characterised mostly by emotional instability. Cluster C emphasises fearful and anxious traits, the PDs in this cluster being avoidant, dependent and obsessive-compulsive PD. These three clusters of PDs have been retained in the transition from the DSM-IV (APA, 2000) to the DSM-5 (APA, 2013), despite the removal of the multiaxial system in the DSM-5⁷. The diagnostic criteria between the two versions remains largely unchanged, keeping the discrete categorical approach to diagnosis, whereby thresholds of symptoms are used to define the presence or absence of a disorder (Ehreta & Berking, 2013). An alternative dimensional model of PDs was included in Section III: Emerging Measures and Models, of the DSM-5, describing gradations of severity of pathological personality traits and functional difficulties. This model was not included in the main body of the DSM-5 as it requires more research. The categorical view of PD remains the dominant clinical approach today and is the approach used in the current study.

The prevalence of PDs in the general population is estimated at about 10% (Coid, Yang, Tyrer, Roberts, & Ullrich, 2006; Sansone & Sansone, 2011). This prevalence is increased by approximately four times in psychiatric populations with mental disorders, with rates varying between the disorders (Newton-Howes et al., 2010). Over half of patients with mental disorders can also be diagnosed with PDs (Zimmerman, Chelminski, & Young, 2008). Those who exhibit comorbid personality disorders with their mental disorder usually experience poorer outcomes than those

⁷ PDs were categorised as Axis II disorders in the DSM-IV

without personality disorder (Bahorik & Eack, 2010; Newton-Howes, Tyrer, & Johnson, 2006; Stevenson, Boyce, & Byth, 2011). Disordered personality has further been shown to have an effect on efficacy of treatment and is a predictor of premature mortality (Tyrer, Reed, & Crawford, 2015). Reasons for increased mortality include increased incidence of suicide and homicide (Hiroeh, Appleby, Mortensen, & Dunn, 2001) as well as lifestyle factors, including a high prevalence of smoking, alcohol and substance abuse (Frankenburg & Zanarini, 2004). Compounding these factors may also be the conflicts that arise between health-care professionals when dealing with people who have disordered personality, which may result in miscommunication and poor quality of care (Tyrer et al., 2015). Poorer outcomes for those suffering from comorbid PDs are hardly surprising, as the ability to treat other mental health disorders would be affected by a person's disordered manner of thinking and feeling, with disordered thinking and feelings being associated with PD (Widiger, 2011).

In previous reviews of the literature, it was found that the presence of PD results in poorer outcomes for people suffering from depression (Newton-Howes, et al., 2014) and other mental disorders in general (Tyrer et al., 2015). Further to this, it was shown that treatment in standard clinical care settings was only focused on depressive disorders rather than including treatment for the personality pathology (Newton-Howes, et al., 2014). One could speculate that this clinical focus/therapeutic approach is related to the poorer outcomes experienced and highlights a need to understand the role of comorbid personality disorders. Personality disorder has also been shown to be associated with subsequent development of depression and substance misuse (Conrad et al., 2017).

There is evidence that the prevalence of schizophrenia is increased in the presence of PD (Oldham et al., 1995), possibly suggesting a negative influence of personality dysfunction on onset and course of schizophrenia. Personality disorders

are much more common in people under 30 years of age (when schizophrenia usually develops) and lessen in prevalence over time (Skodol, Johnson, Cohen, Sneed, & Crawford, 2007). The negative effects of PD on symptomatic and functional outcomes is also greater for younger adults (18-40 years) compared to older adults (41-64 years) (Stevenson et al., 2011). Stevenson et al. (2011) found that presence of PD was associated with increased rates of relapse of mental disorders and admission to hospital.

The reported prevalence of personality disorders in schizophrenia varies significantly. A review by Newton-Howes and colleagues (2008) (20 articles) revealed prevalence rates of PDs in schizophrenia ranging from 4.5% to 100%, with an average co-morbidity rate of 39.5%. These rates are similar to the 40% to 60% prevalence of PDs found in bipolar disorder and related psychoses in secondary care (Keown, Holloway, & Kuipers, 2002; Loftus & Jaeger, 2006; Mantere et al., 2006) as well as the 37% to 53% prevalence in patients attending drug and alcohol services (Bowden-Jones et al., 2004). The fact that PD prevalence rates are similar across a range of other psychiatric disorders suggests that PD may be related to psychiatric issues in general.

6.1 Personality Disorder Comorbidity with Other Psychiatric Disorders

It is not unusual for an individual who meets criteria for one PD to be diagnosed with a comorbid PD (Lenzenweger et al., 2007). Further to this, comorbid psychiatric disorder is more common in people diagnosed with PD, the most common being substance use disorders, depression and anxiety (Newton-Howes et al., 2014). Personality disorder has also been found to be more prevalent in the UHR population than in the general population, a population that has been shown to also have high rates of other psychiatric disorders (Addington et al., 2017). Conrad et al. (2017) conducted a ten-year follow-up of participants who had a mixture of UHR, psychosis,

and non-psychosis mental health disorders ($n=1997$) and found that across the board, those with a PD at baseline were more likely to experience subsequent depression and substance abuse problems (Conrad et al., 2017).

6.1.1 Separating PD from psychosis.

There has been concern about whether it is possible to separate personality from psychosis (psychoanalytic literature also refers to this as the ‘psychotic process’) (Cuesta, Gil, Artamendi, Serrano, & Peralta, 2002). For example, Kraepelin suggested that personality dysfunction is a core feature of schizophrenia and therefore impossible to accurately identify as a separate ‘disorder’ (Newton-Howes et al., 2008).

The more common view is to approach PD and psychosis as separate constructs that may influence each other over time. For example, researchers have reported on the influence of personality on psychosis in early life (Peralta, Cuesta, & de Leon, 1991), clinical presentation (Lindström, Von Knorring, & Ekselius, 2000) and outcome (McGlashan, 1986). Furthermore, PD, as defined by the revised DSM-5 (APA, 2013), is in principle sufficiently independent to be discernible in those with psychotic illnesses as a separate disorder (APA, 2013; Newton-Howes et al., 2008). Most research assessing the construct validity of PD disturbances in young people classifies PDs as discrete categorical variables (Crawford, 2001). Personality disorders are distinguished by specific thresholds of symptoms that differentiate between normal and pathological functioning and are defined as being independent of other mental disorders, and therefore able to be investigated as a separate comorbid disorder.

6.2 Personality Disorder Comorbidity in Schizophrenia and First Episode

Psychosis

Comorbid PDs are common among people diagnosed with schizophrenia (McMillan et al., 2009). The presence of PDs has implications for illness prognoses and clinical management in psychiatric disorders like depression (Newton-Howes et al., 2014), though research into comorbidity of PD in schizophrenia remains scarce (Simonsen et al., 2018). Whilst PDs are among the most frequent comorbid conditions for psychiatric disorders (Newton-Howes et al., 2008; Zimmerman et al., 2005), their prevalence and impact on psychosis is poorly studied (Newton-Howes et al., 2008; Thompson et al., 2011). Where studies have examined the relationship of PDs to psychosis, these have focused mostly on schizophrenia spectrum PDs (schizoid, schizotypal and paranoid disorders) and neglected other PDs (Rodriguez & Chavez, 2000).

Most research on PD comorbidity in psychosis has centred on people with schizophrenia. A retrospective examination of PDs in a sample of 40 people with schizophrenia revealed that 85% of the sample had premorbid PD (Rodriguez & Chavez, 2000). The authors found that 47.5% of the participants could be diagnosed with two or more concurrent PDs. The most common of these were avoidant PD (32.5%), schizoid PD (27.5%), paranoid PD (20%), dependent PD (20%) and schizotypal PD (12.5%). This illustrates that PDs not described by the schizophrenia spectrum PDs may also have a relationship with psychotic disorders. An increased risk of schizophrenia was associated with presence of a PD in a large prospective longitudinal study of men ($n=50,054$) conscripted into the Swedish Army (Lewis, David, Malmberg, & Allebeck, 2000). The authors suggested that disordered personality could represent a vulnerability to schizophrenia, with other psychiatric diagnoses being indicative of a prodromal state.

Results from a National Epidemiologic Survey of Alcohol and Related Conditions of residents in the US ($n=42,038$) revealed that of participants previously diagnosed with schizophrenia or another psychotic illness or episode ($n=386$), rates of comorbid PD were as high as 60.1% compared with 14.8% in those who had never experienced an episode (McMillan et al., 2009). The most common of these, similar to findings above, were dependent PD, followed by avoidant PD. This study was limited by cross-sectional design, and self-report of diagnosis, yet results appear consistent with findings from other studies (Fogelson et al., 2007; Lewis, David, Malmberg, & Allebeck, 2000).

Functioning and outcome in severe mental disorders rely on other precursors of psychiatric disorders, such as premorbid personality problems (Tyrer et al., 2007). Personality dysfunction may impact the course of illness in psychosis and may significantly affect behaviour or coping strategies in stressful situations (Campos et al., 2011). In practice, a diagnosis of personality disorder in conjunction with schizophrenia would be considered as a predictor of a chronic course, with significantly poorer prognosis (Newton-Howes et al., 2007).

Validation studies in adults have demonstrated consistent natural histories of PDs, refractoriness to treatment, poor social adjustment and a high risk for suicide and suicidal behaviour (Nace, Saxon, & Shore, 1983; Pfohl, Stangl, & Zimmerman, 1984; Tyrer, Casey, & Gall, 1983; Weissman, Prusoff, & Klerman, 1978). Personality disorders during adolescence are similarly associated with increased suicide and suicidal behaviour, social impairment and refractoriness to treatment (Brent et al., 1993; Johnson et al., 1999; Westen, Ludolph, Lerner, Ruffins, & Wiss, 1990).

There are fewer studies of PDs in the FEP population. A retrospective assessment of PDs in a sample of FEP patients ($n=94$) indicated that premorbid personality may shape the expression of psychosis (Cuesta et al., 2002). Results from

this study showed that premorbid personality dimensions are associated with psychopathological dimensions in FEP (Cuesta et al., 2002). Higher scores on the schizoid dimension were related to more severe negative symptomatology. A trend towards significant positive correlation between both the schizotypic and the negative dimensions was found. These results suggest that the contribution of certain personality traits to the expression of psychosis, negative symptoms in particular, should not be neglected (Cuesta et al., 2002).

Three PDs have been especially implicated in schizophrenia: schizotypal, borderline and antisocial PD. Schizotypal PD is generally considered to be a risk factor for schizophrenia (Simonsen et al., 2018) and shares some commonalities with schizophrenia (detailed further in Section 6.2.1). Antisocial PD is prevalent in people with schizophrenia and has been extensively researched in this context (Moran & Hodgins, 2004). In recent years, borderline PD has emerged as an area of interest in psychosis research, with more people diagnosed with borderline PD experiencing psychotic symptoms than previously thought (detailed in Section 6.2.2).

6.2.1 Schizotypal personality disorder.

Schizotypal PD reflects a pervasive pattern of social and interpersonal deficits, reflected by a lack of close relationships as well as perceptual distortions and eccentric behaviour that persists over the long-term (APA, 2013). Schizotypal PD shares some characteristics with schizophrenia, such as experience of illusions/delusions, thought disorder, bizarre ideas, and some deficits in social and cognitive functioning, though at a sub-threshold level that does not meet criteria for schizophrenia (Jakobsen et al., 2017). Meehl (1989) postulated the existence of a “schizotaxia” gene which would manifest as the personality disorder schizotypy under normal circumstances (non-adversive events) but could decompensate into schizophrenia under adverse circumstances such as trauma and stress. While Meehl’s

theory of a single schizotaxia gene has since been refuted for a heterogeneous polygenic view of schizophrenia (Consortium, 2014; Insel, 2010), schizotypal PD is still presumed to carry vulnerability for schizophrenia (Kwapil, 2014).

Previous studies have reported that 20% to 40% of individuals with schizotypal PD transition to psychosis, mainly schizophrenia (Asarnow, 2005; Miller et al., 2002; Parnas et al., 2011; Yung et al., 1998). A literature review including 18 studies of schizotypal PD showed that an association between schizotypal PD and schizophrenia is clearly indicated, reporting transition rates from 25% to 48% (Debbané et al., 2015). However, the authors cautioned that results may be biased, as studies including schizotypy as one of many predictors would be missed by their review. Other studies have shown that families with schizophrenia are also likely to have family members with schizotypal PD (Kendler, Thacker, & Walsh, 1996; Mata et al., 2003). A meta-analysis of family, twin and adoption studies concluded that there is evidence for genetic underpinnings for both schizotypy and schizophrenia (Nelson, Seal, Pantelis, & Phillips, 2013). Previous research has shown that schizotypal PD and schizophrenia share many genetic and neural risk factors (Kendler et al., 1993; Siever et al., 2002).

6.2.2 Borderline personality disorder.

Much research on personality disorders in psychosis populations in recent years has focused on borderline PD. Studies have shown that people with borderline PD often experience psychotic symptoms (Glaser, Van Os, Thewissen, & Myin-Germeys, 2010). In fact, the term ‘borderline’ was originally ascribed to patients on the ‘border’ between psychosis and neurosis (Stern, 1938). A review of research on psychotic symptoms in borderline PD reported rates that varied from around 20-50% (Schroeder, Fisher, & Schäfer, 2013). Both the DSM-IV and DSM-5 describe psychotic symptoms in borderline PD as relating to transient, stress-related paranoid

ideation (APA, 2000; 2013). However, some studies have found the nature of these psychotic symptoms to be more persistent than the ‘transient nature’ outlined by DSM-IV criteria (Miller et al., 1993; Slotema et al., 2012) with a strong emotional impact on people with borderline PD (Schroeder et al., 2013). Some borderline PD patients experienced their non-transient auditory hallucinations as highly distressing (Kingdon et al., 2010; Slotema et al., 2012; Yee, Korner, McSwiggan, Meares, & Stevenson, 2005). Symptoms were found to be more similar to those experienced by people with schizophrenia than previously thought. However, there is currently no consensus on the phenomenology and severity of these psychotic experiences, which can be divided into those involving paranoid ideation and perceptual abnormalities (Slotema et al., 2012).

Positive symptoms were found in 8.8% of people with borderline PD ($n=113$) (Coid et al., 2009). Delusions in borderline PD samples have been reported at rates ranging from 10% to 100% (Kingdon et al., 2010; Links, Steiner, & Mitton, 1989; Pearse et al., 2014; Yee et al., 2005). Hallucinations have been reported at rates varying from 26-54% (Chopra, 1986; Links et al., 1989). A study of 324 individuals with borderline PD revealed that 27% ($n=87$) experienced auditory hallucinations at a median rate of once a week (and at least once a month) (Niemantsverdriet et al., 2017). Most of these patients reported that their hallucinations had been experienced for long periods of time (length of time was not specified). Of these patients, 21% ($n=69$) recounted verbal hallucinations which were mostly reported as abusive to the patient and were experienced as distressing.

Persistent hallucinations have been reported in people with borderline PD, with one study reporting that 29% of their sample ($n=171$) experienced auditory hallucinations that had been present since early childhood (Yee et al., 2005). A mean history of 18 years for auditory hallucinations has been reported in other studies

(Slotema et al., 2012; Tschoeke, Steinert, Flammer, & Uhlmann, 2014). These studies have shown that the hallucinations experienced were equally as severe as those experienced by patients with schizophrenia, in addition to being persistent, rather than transitory. However, there is a paucity of studies investigating hallucinations in borderline PD, and their sample sizes often tend to be small.

Some authors have attributed the presence of psychotic symptoms in borderline PD to comorbidity with other disorders, in particular mood disorders (Benvenuti et al., 2005; Schroeder et al., 2013) substance use disorder (Dowson, Sussams, Grounds, & Taylor, 2000) and posttraumatic stress disorder (Gracie et al., 2007). Niemantsverdriet et al. (2017) found that borderline PD patients were significantly more likely to suffer from comorbid psychiatric disorders if they had experienced hallucinations. Furthermore, the severity of hallucinations was associated with the number of disorders each patient had. Posttraumatic stress disorder was found to be a prevalent comorbid diagnosis within the group of borderline PD patients who experienced hallucinations (63%, $n=17$) compared to the group not experiencing hallucinations (28%, $n=20$). However, the authors only found an association between posttraumatic stress disorder and hallucinations, but not with other comorbid psychiatric disorders.

Other authors point to comorbidity of borderline PD with psychotic disorders to explain longer lasting psychotic episodes. The majority of studies of people with borderline PD, however, have excluded individuals with psychotic disorders (Nickel, 2007; Schulz et al., 2008) or have not been explicit in providing additional information on potential comorbidities. This has limited the ability to thoroughly examine the role of psychotic symptoms in the borderline population. Irrespective of the specific cause, people suffering from both psychotic symptoms and borderline PD

represent a particularly vulnerable group who often demonstrate worse outcomes than people who experience psychotic disorders alone (Bahorik & Eack, 2010).

6.2.3 Antisocial personality disorder.

Antisocial PD is one of the most well researched comorbid PDs among people with schizophrenia (Moran & Hodgins, 2004; Mueser & Essock, 2006). It is characterised by a pervasive pattern of disregard for and violation of the rights of others that has been occurring in the person since the age of 15 years (APA, 2013). Antisocial PD has been linked to increased rates of substance abuse, in particular, drug and alcohol (Moran & Hodgins, 2004; Mueser & Essock, 2006), and a more severe course of addiction. People with antisocial PD and substance abuse problems experience greater social, physical and legal consequences of use (Cadoret, Troughton, & Widmer, 1984).

Antisocial PD has been shown to be more prevalent in the schizophrenia population than in the general population (Moran & Eack, 2004). Rates of 23% for men and 17% in women with schizophrenia (Moran & Eack, 2004), compared to rates of 1-4% in the general population have been reported (Lenzenweger, Lane, Loranger, & Kessler, 2007; Trull, Jahng, Tomko, Wood, & Sher, 2010). A study examining the effect of antisocial PD comorbid with psychotic disorders ($n=178$) revealed that those diagnosed with conduct disorder and antisocial PD were significantly more likely to have a history of violent offences (68.4%) compared to those without antisocial PD (20.7%). They also found that having comorbid antisocial PD was related to an increased risk of homelessness as well as severe substance abuse (Mueser & Essock, 2006). However, the authors concluded that these poor outcomes were more likely to be linked with having antisocial PD, rather than having a compounded effect of a comorbid disorder.

6.3 Personality Disorder Comorbidity in the UHR Population

In addition to the elevated presence of non-psychotic mental disorders in people with schizophrenia and FEP, research shows that PDs also have a high prevalence in the at risk for psychosis population. In the investigation of PDs within the UHR population, the focus has been on schizotypal PD, which has been shown to be related to transition in high risk groups and is part of the trait vulnerability group UHR criteria (Miller et al., 2002; Nordentoft et al., 2006; Yung & McGorry, 1996). However, research into the role of other PDs in the UHR population is lacking (Thompson, Nelson, Domingues, Yung, & Bechdolf, 2011).

One of the few studies that has investigated general levels of PD comorbidity in the at risk for psychosis population is by Rosen and colleagues from the PRIME group. Rosen et al. (2006) found that 48% of their “prodromal” patients ($n=29$) qualified for one or more personality disorders. The most common PD diagnosis was schizotypal PD (21%) followed by borderline PD (17%) (Rosen et al., 2006). This compares to prevalence rates of 14% and 10% in their “non-prodromal” sample, respectively ($n=29$). Rosen et al. (2006) did not find any association between comorbidity between those in the cohort that made a transition to a full threshold psychotic disorder and those who did not. However, they did not examine the non-psychotic mental disorders as possible predictors of transition to psychosis or other outcomes (Rosen et al., 2006).

Schultze-Lutter et al. (2012) also investigated the prevalence of PDs in the at risk for psychosis population, as defined by a combination of basic symptoms and UHR criteria. They compared gender- and age-matched at risk patients with ($n=50$) and without transition to psychosis ($n=50$). They found a prevalence rate of 46% with one or more PD. However, in contrast to previous research showing rates of around 14% (Ruhrmann et al., 2010) they found schizotypal PD to be rare (7%). The PDs

most commonly observed were borderline (21%), avoidant (20%) followed by antisocial PD (14%) (Schultze-Lutter et al., 2012).

A more recent study demonstrated an even higher prevalence of PDs in a high risk sample ($n=40$) (Sevilla-Llewellyn-Jones et al., 2018). They found that 75% of participants qualified for PDs, in particular depressive (56.7%), borderline PD (46.7%) and schizotypal (36.7%). This study assessed participants using the Millon Multiaxial Inventory (Millon, 1997), which captured personality traits as well as PDs. When examining clinically significant traits, the majority of their high risk sample (97.5%) had at least one, with the most common being depressive (82.5%), borderline (67.5%) and masochistic traits (57.5%). These rates were significantly higher than that seen in their comparison group of healthy controls ($n=40$, 12% with borderline traits, 10% with masochistic, zero marked with borderline traits). Presence of a PD was not associated with transition to psychosis, however, the transition rate was only 5%, too low for this potential relationship to be examined. Depressive personality traits were linked to anxiety symptoms, and there was a link between borderline and paranoid traits and depressive symptoms. The authors concluded that comorbid personality played a role in depressive and anxiety disorders in high risk individuals. These results exemplify the importance of considering the role of PDs in high risk for psychosis individuals.

However, rates of PD reported by Sevilla-Llewellyn-Jones et al. (2018) for healthy controls were also higher than those observed in the general population. Almost a third (32.5%) of healthy controls met criteria for a PD, compared to the 10% usually observed in the general population (Sansone & Sansone, 2011). The authors acknowledged higher prevalence rates of PD in their high risk population. They explained that the elevated rates in high risk individuals could have resulted from a higher number of personality traits being included in the MCMI-II compared to other

scales. The higher rates of PDs observed in the healthy volunteers was not directly addressed. Therefore, caution should be used when interpreting these potentially inflated prevalence rates.

The evidence thus far indicates inflated PD rates in the UHR population. Despite this, clinicians working in UHR clinics have often seen PDs as a comorbidity that is not specifically addressed in context of how it might affect UHR status, transition or other clinical and functional outcomes. This is in contrast to other non-psychotic disorders such as depression and anxiety, which have often been considered when examining the risk for transition or the impact on outcomes in the UHR group (Yung et al., 2007; Yung et al., 2004). Personality pathology should be addressed as a clinical issue in its own right, but its role in the UHR population marks an important relationship for investigation.

6.3.1 Borderline personality disorder in the UHR population.

Various studies have indicated a high prevalence of borderline PD in the UHR population, reporting rates ranging from 14.6% to 46.7% (Rosen et al., 2006; Schultze-Lutter et al., 2012; Sevilla-Llewellyn-Jones, 2018; Thompson et al., 2012). However, little is known about the nature of borderline PD and its relationship to at risk mental state phenomena and psychosis, with most studies focusing on reporting prevalence rates.

Thompson et al. (2012) was one of the few studies found to have assessed the prevalence of borderline PD in the UHR population and the relationship to transition. They used a case-control retrospective file audit ($n=96$), and found that the rate of borderline PD in the UHR population was relatively high (14.6%). However, they found no significant difference in borderline PD rates between those who transitioned to full threshold psychosis (18.8%) and those who did not (10.5%). As there were no previous studies examining borderline PD and transition to psychosis in the UHR

population, the authors recommended the relationship be further explored prospectively using a larger sample. Subsequent to the Thompson et al. (2011) study, Schultze-Lutter et al. (2012) also examined the relationship of borderline PD in the at risk population. In their sample, borderline PD was the most frequently observed PD ($n=50$ patients with and $n=50$ without transition to psychosis, borderline PD rates of 24% and 18% respectively, with no significant difference).

The few studies that have investigated borderline PD in the UHR population in more depth have investigated the types of psychotic symptoms seen in UHR patients with borderline PD compared with UHR patients without borderline PD. Ryan et al. (2015) found that UHR patients with borderline PD (25.2% of the sample) experienced attenuated positive psychotic symptoms that were not limited to paranoid ideation and dissociation. They found that while some differences existed in the types of symptoms experienced by UHR patients with and without borderline PD, these differences were not statistically significant. One difference that was observed between the groups was that UHR patients with borderline PD were more likely to present with non-bizarre delusions, in comparison to UHR patients without borderline PD pathology. These symptoms could also reflect that borderline PD patients experience a wider range of psychotic symptoms than previously thought, an argument consistent with previous research (Glaser, van Os, Thewissen, & Myin-Germeys, 2010; Schroeder et al., 2013; Yee et al., 2005). An alternative explanation of presence of psychotic symptoms that exceed the definitions provided for borderline PD could be due to an underlying psychosis prodrome, and thus sub-threshold psychotic symptoms in BPD could be predictive of later transition to psychosis.

In contrast to the above supposition, a review of borderline PD in psychosis did not find that the presence of psychotic symptoms in patients with borderline PD predicted transition to a psychotic disorder (Barnow et al., 2010). More recent studies

have supported this finding – Thompson et al. (2012) found increased prevalence rates of borderline PD in ultra high risk patients at the PACE clinic (14.8%, $n=102$) when conducting a file audit of records from 2004-2007 but found no link to transition to psychosis within a 24 month period. Ryan et al. (2015) similarly found no link with borderline PD to transition to psychosis. Instead, absence of depression predicted increased likelihood of transition to psychosis. The authors postulated that instead of being associated with a vulnerability to psychosis, borderline psychotic features in borderline PD patients are more varied than previously thought.

6.3.2 Schizotypal personality disorder in the UHR population.

As mentioned previously, young people with schizotypal PD have been shown to have an elevated risk of transition to a full-blown psychotic disorder. In a two and a half year follow-up, Woods et al. (2009) compared a group of young people identified as being at high risk of psychosis (as diagnosed by SIPS) to 49 young people with schizotypal PD. Of those with schizotypal PD, 36% converted to psychosis in the follow up period, with a total transition rate of 40% for the high risk sample demonstrating a similar rate of transition for both schizotypal PD participants as prodromal participants. Another similarity between the two groups was seen in terms of functioning. The authors suggest that this indicates that schizotypal PD may also present an identifiable risk syndrome for transition to psychosis and that young adults in this group may demonstrate a more gradual progression to psychosis than those meeting high risk criteria without meeting criteria for schizotypal PD.

An alternate possibility is that high risk criteria are picking up individuals with schizotypal PD who are not likely to transition to a full blown psychotic disorder. Schlosser et al.'s (2012) two year follow up of UHR participants, revealed that 50% neither transitioned to full psychosis, nor remitted from UHR status. Rather, their functioning remained poor, similar to the transitioned patients, although they

experienced less severe positive symptoms than those who had transitioned. The stable maintenance of sub-threshold positive symptoms and continued functional deficits reflected the symptoms seen in schizotypal PD. The authors reasoned that it was possible that up to 50% of their non-transitioning cases were “progressing” to schizotypal PD or a sub-threshold variant of it. In contrast to previous research that indicates that schizotypal PD increases risk of transition, Schlosser et al. (2012) observed that the rate of transition was modest.

Schultze-Lutter et al. (2012) similarly did not find a link between schizotypal PD and the transition to psychosis in their group of UHR participants ($n=100$) (Schultze-Lutter et al., 2012). They further found that schizotypal PD occurred infrequently in their sample (7%) compared to BPD (21%), avoidant PD (20%) and antisocial PD (14%).

6.3.3 Antisocial personality disorder in the UHR population.

While antisocial PD is one of the most well researched PDs in people with schizophrenia, research into this PD is greatly lacking in the UHR population. The current review is unable to report any research in antisocial PD in the UHR population beyond prevalence rates. Rates of PD in the UHR population are higher than in the general population (Moran & Hodgins, 2004). Rosen et al. (2006) found a rate of 7% of their UHR sample had antisocial PD, compared to 4% of their non-UHR controls. Schultze-Lutter et al. (2012) reported a higher prevalence of 14% in their UHR sample, second in prevalence to 21% with borderline PD and 20% with avoidant PD.

6.4 Summary of Personality Disorders

Evidence indicates that people who have comorbid personality and mental disorders exhibit poorer outcomes than people with mental disorders alone (Bahorik

et al., 2010; Newton-Howes et al., 2006; Stevenson et al., 2011). These outcomes include poorer functioning, increased clinical symptoms (Stevenson et al., 2011) as well as increased rates of relapse of mental disorders (Stevenson et al., 2011). This is relevant in the context of UHR, as the majority of people meeting UHR criteria have been shown to have comorbid mental disorders and PDs (Addington et al., 2017; Rosen et al., 2006; Schultze-Lutter et al., 2012).

Disordered personality has been shown to have a detrimental effect on coping strategies and behaviours in people with schizophrenia (Campos et al., 2011). However, despite their higher prevalence in psychiatric disorders (Newton-Howes et al., 2008; Zimmerman et al., 2005), their impact on psychosis is poorly understood (Newton-Howes et al., 2008; Thompson et al., 2011; Simonsen et al., 2018). Prevalence of PD in schizophrenia varies significantly, with rates ranging from 4.5% to 100% (Newton-Howes et al., 2008). These rates are similar to bipolar disorder and other psychiatric disorders (Loftus & Jaeger, 2006; Bowden-Jones et al., 2004), indicating that PD may be related to psychiatric disorders in general.

Schizotypal, antisocial and borderline PDs have received special attention in the context of schizophrenia, with schizotypal and borderline also being selectively researched in the context of UHR. Schizotypal PD is considered a risk factor for developing schizophrenia (Simonsen et al., 2018), with studies reporting transition rates from 25% to 48% (Debbane et al., 2015), and is represented in one of the UHR risk groups (vulnerability group) (Yung & McGorry, 1996). Individuals with schizophrenia are also likely to have family members with schizotypal PD (Mata et al., 2003) indicating that these two disorders are likely to have genetic and neural risk factors in common (Siever et al., 2002). In the context of UHR, schizotypal PD and borderline have been the most researched, though research into PDs in UHR is generally lacking (Beck et al., 2019).

Borderline PD has also received special attention in the context of psychosis. People with BPD report psychotic symptoms at rates of 20-50% (Schroeder et al., 2013). Described by the DSM to be transient and stress-related, recent research is finding psychotic symptoms in borderline PD to be more persistent (Slotema et al., 2012; Tschoeke et al., 2014), have a greater emotional impact (Schroeder et al., 2013), more frequency than previously thought (Niemantsverdriet et al., 2017) and more similar in nature to psychotic experiences in people with schizophrenia (Slotema et al., 2012). Some researchers have attributed psychotic experiences in borderline PD to comorbidity with other disorders (Schroeder et al., 2013; Benvenuti et al., 2005; Gracie et al., 2007) but there is currently no consensus on the phenomenology of these psychotic experiences (Slotema et al., 2012) and little research is being done in the context of UHR to further understanding. People who experience both psychotic symptoms and borderline PD often demonstrate worse outcomes than people who experience psychotic disorders alone (Bahorik et al., 2010), and thus constitute a vulnerable group requiring attention.

Borderline PD is one of the most prevalent PDs in the UHR population, with rates varying from 14.6-46.7% (Rosen et al., 2006; Schultze-Lutter et al., 2012; Thompson et al., 2012; Sevilla-Llewellyn-Jones et al., 2018). Most studies of borderline PD in UHR have, however, only focused on prevalence (Schultze-Lutter et al., 2012; Sevilla-Llewellyn-Jones, et al., 2018) so its relationship to UHR phenomena still remains under-explored. Given that people with borderline PD have recently been shown to experience a wider range of psychotic phenomena than previously thought (Yee et al., 2005; Schroeder et al., 2013) it is important to further investigate this syndrome in the context of UHR.

Antisocial PD is one of the most well researched comorbid PDs among people with schizophrenia (Mueser et al., 2006) with rates of 23% for men and 17% for

women with comorbid antisocial PD and schizophrenia being observed (Moran et al., 2004). However, research of antisocial PD specifically in the context of UHR is lacking and limited to reports of prevalence, which is higher in the UHR population than in the general population (Moran et al., 2004).

Presence of PDs, with the exception of schizotypal PD, have not thus far been shown to be linked to transition in the UHR population (Sevilla-Llewellyn-Jones et al., 2018). However, studies examining this relationship have reported transition rates that may be too low for a relationship to be uncovered (Sevilla-Llewellyn-Jones et al., 2018). This represents a gap in the UHR literature that deserves further exploration.

Despite the elevated prevalence of PDs in the UHR population, this area remains under-researched (Beck et al., 2019). The limited evidence shows that UHR individuals with comorbid PD at baseline are more likely to develop depression and substance abuse problems over the long term (Conrad et al., 2017) and the presence of PDs in UHR have been linked to anxiety symptoms (Sevilla-Llewellyn-Jones et al., 2018). Personality pathology is an important clinical issue in itself, but given its apparent role in people at UHR, it is imperative to further our understanding of the relationships between UHR and PD.

Chapter 7

Rationale, Aims and Hypotheses for the Current Study

7.1 Rationale for the Current Study

A better understanding of comorbid mental and personality disorders and their relationship to psychosis may improve the identification of those at highest probability of transition to psychosis within the UHR population if specific trajectories and relationships are better understood. This research will also have a bearing on the issue of whether the UHR phenotype is a pluripotential syndrome (i.e. might evolve into a range of different disorders) or is more specific to psychosis outcomes.

There is evidence to suggest that non-psychotic psychiatric disorders identified in an UHR population persist over time (Beck et al., 2019). Beck et al.'s (2019) meta-analysis found that research into non-psychotic psychiatric disorders in non-transitioned UHR participants was scarce. In the studies examining these outcomes though, more than half of non-transitioned UHR participants had non-psychotic psychiatric disorder or personality disorder at follow-up. Lin et al. (2012) found that elevated rates of non-psychotic disorders identified in an UHR population at baseline ($n=226$), persisted over the long term (between 2-14 years), with almost half of the sample experiencing a current non-psychotic disorder at follow-up. Those still classified as UHR for psychosis at follow-up presented with an even higher prevalence of non-psychotic disorders than the total sample, 65.5% experiencing a current mood disorder. Onset of an anxiety and/or SUD that had not been present at baseline occurred in almost 20% of the total sample. Subsequent studies have found similar rates of persistence (Addington et al., 2017; Beck et al., 2019; Rutigliano et al., 2016).

Beck et al.'s (2019) meta-analysis illustrates the importance of understanding the role of mental disorders in the UHR population as these disorders may persist long term, even when UHR status remits. The onset of new mental disorders needs to be considered as an outcome for patients identified as UHR. The onset and persistence of non-psychotic mental disorders in a population initially identified as UHR for psychosis may indicate whether UHR outcomes are pluripotential or specific to psychosis (Hartmann et al., 2017).

Furthermore, it is not known how presence of non-psychotic mental disorders relates to transition to psychosis in the UHR population. The few studies addressing this question have had mixed results. Salokangas et al. (2012) investigated the relationship of non-psychotic disorder diagnoses with the transition to psychosis prospectively in the at-risk population (assessed using SIPS). The researchers found that occurrence of bipolar, somatoform and depressive disorders at baseline predicted transition to psychosis. They also found that the presence of anxiety disorders was associated with a decreased likelihood of transition to psychosis. The current study will extend on Salokangas and colleagues' 18-month follow-up study by providing up to 10 years of follow-up data.

Previous research within the UHR population has focused mainly on transition to psychosis (though not in the context of comorbid mental disorders and their relationship to transition) (Beck et al., 2019). The importance of broadening this focus to other outcomes is being increasingly recognised (Armando et al., 2010). The current study aims to investigate functional outcomes related to the presence of non-psychotic mental and personality disorders in the UHR population. Improved understanding of the relationship of these disorders to functional outcomes will inform treatment options and facilitate management of mental illness in the UHR population. For example, if we find that comorbid disorders are associated with

particularly poor functional outcomes, then this may indicate a need to focus clinical attention on these disorders when they present in the context of UHR. The need to better understand the clinical features of the UHR population is recognised as a priority, given the recent inclusion of the Attenuated Psychosis Syndrome in the DSM 5 (APA, 2013). The links of clinical features at baseline to trajectories of outcomes for UHR patients has also not yet been explored. Understanding the role of clinical features in the trajectory of comorbid mental disorders will also contribute to management of outcomes for UHR patients over the longer term.

The study of personality disorders in the UHR has mostly been under-investigated, especially those disorders outside of the schizophrenia spectrum PDs. Better understanding of the role of personality pathology in psychosis would be of clinical utility, given that currently, personality disorder diagnoses in psychosis are often overlooked (Simonsen & Newton-Howes, 2018). In particular, few studies have investigated borderline PD in the UHR population, despite prevalence rates of this disorder in the UHR population being similarly high to schizophrenia spectrum PDs (14-25%) (Ryan et al., 2017; Thompson et al., 2011). The current study will improve on previous research by utilising a large sample and assessing a wide range of PDs. Another neglected area to date has been PDs as *outcomes* in the UHR population, which will be addressed in the current study.

The PACE clinic at Orygen was the first UHR clinic, established with the unique aim of assessing, managing and following up young people who may be in the prodromal phase of psychotic illness, before the expression of frank psychosis. This 6-12 year follow-up of UHR patients will lead to a better understanding of divergent outcomes related to comorbid mental and personality disorders, which may facilitate targeted interventions to either prevent transition or ameliorate distress and improve the functional outcomes experienced by these patients (McGorry et al., 2002).

7.2 Research Aims and Hypotheses of the Current Study

The purpose of this research project is to investigate the relationship between UHR status and non-psychotic mental disorders and personality disorders (as defined by DSM-IV). Specifically: What are the types and prevalence rates of non-psychotic mental disorders diagnosed at clinic entry? What is the course and stability of these disorders in UHR subjects over the longer term (i.e. do disorders remit or persist over time)? Is there onset of new non-psychotic mental disorders in UHR patients over the longer term? The trajectory of non-psychotic mental disorders in UHR participants will test the pluripotential model of UHR status, i.e., whether it is a specific risk state for psychosis outcomes, as opposed to a range of mental disorders (Figure 2). Related to the question of pluripotent outcomes, the study aims to investigate whether UHR status is persistent over the longer term and if its trajectory is related to the presence of non-psychotic mental disorders at baseline and follow-up. Clinical baseline predictors of the different trajectories of non-psychotic mental disorder will also be explored.

Further, little is known about the clinical and functional outcomes for non-transitioned UHR patients. This study aims to investigate the impact of persistent UHR status and presence of non-psychotic mental disorders at follow-up on patients' functioning. In addition, this study aims to extend the limited research currently available on a possible relationship between diagnosis of particular non-psychotic mental disorders at baseline and transition to psychosis.

As PDs disorders remain under researched in the UHR context, this study aims to establish the prevalence rates and types of PDs found in an UHR sample at long term follow up. This study will also investigate whether there is a relationship between the presence of PDs at follow up and outcomes in the UHR population

(transition to psychosis, presence of non-psychotic mental disorders and functional outcomes).

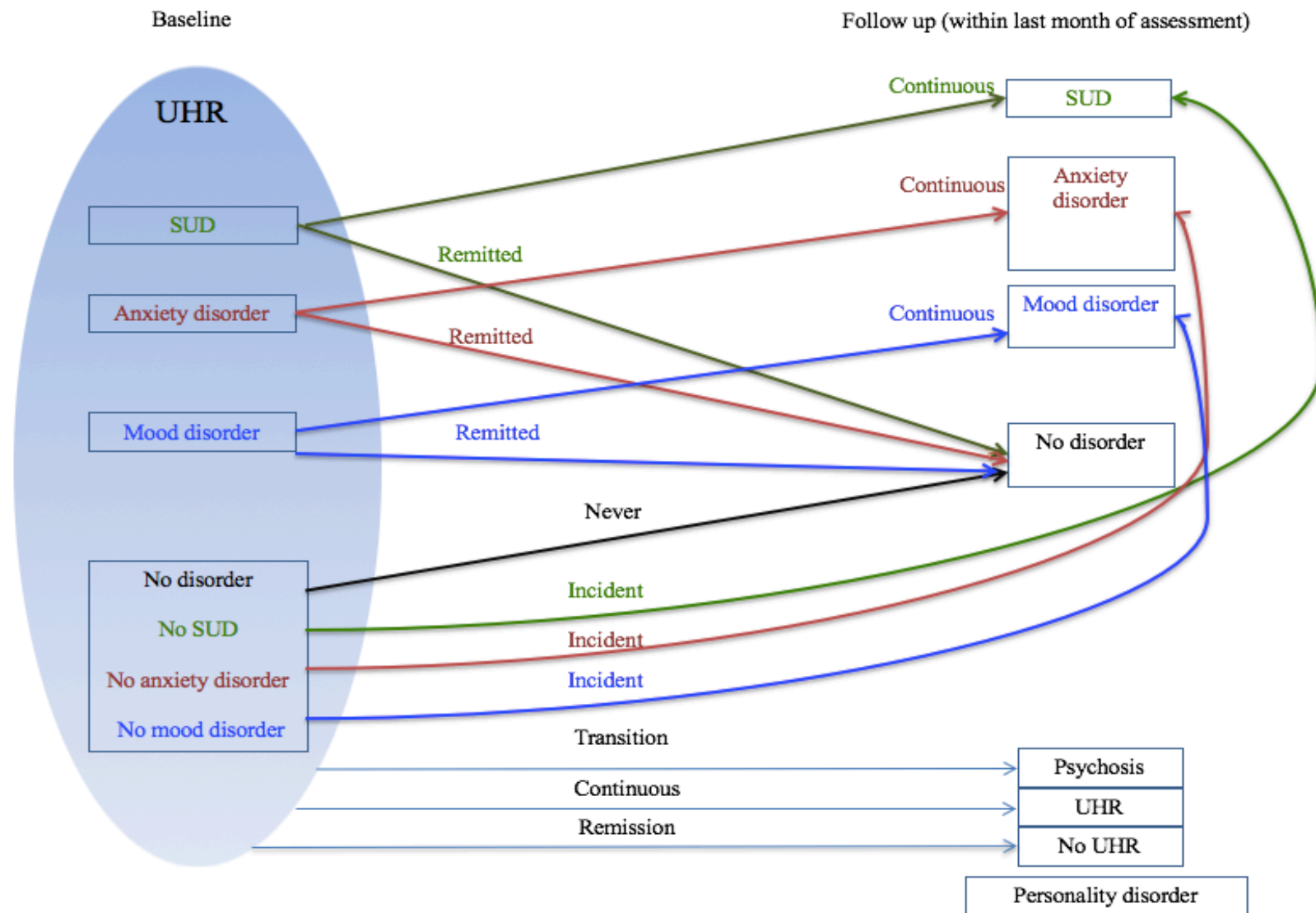


Figure 2: Potential long-term diagnostic outcomes for patients diagnosed as UHR at baseline

7.2.1 Hypotheses.

Consistent with previous studies examining non-psychotic mental disorders in a group of patients considered at risk of developing psychosis (Addington et al., 2017), it is hypothesised that the majority (approximately three-quarters or more) of the UHR sample will be diagnosed with one or more non-psychotic mental disorders at baseline. Of those diagnosed, the most common will be mood disorder, anxiety disorder and substance use disorder, based on prevalence rates reported by Beck et al. (2019). Based on Lin et al. (2015) it is predicted that around half of the sample will have a continuous non-psychotic mental disorder, and fewer than a quarter will remit from their non-psychotic mental disorder, or never experience a non-psychotic mental disorder over the follow-up period and new non-psychotic mental disorders will emerge in approximately one third of UHR patients over long term follow up.

It is hypothesised that the majority of people will have remitted from UHR status at longer term follow up, based on findings from Beck et al. (2019). Whether UHR status at follow-up is associated with presence of a non-psychotic mental disorder or poorer functioning will be approached as exploratory questions due to scarce research in this area. Also to be approached as an exploratory question is whether we can identify baseline clinical predictors of trajectories of non-psychotic disorders.

Based on findings from Rutigliano (2016), it is hypothesised that a persistent trajectory of non-psychotic disorder will be associated with poorer functional outcomes at follow-up. Due to a paucity of research on other trajectories and functional outcomes, these will be approached in an exploratory manner. Based on the findings of Salokangas et al. (2012) it is hypothesised that the strongest association between baseline non-psychotic mental disorders and transition to psychosis will be for mood disorders, and the weakest association will be for anxiety disorders.

In keeping with previous research of PDs in ‘at risk’ patients, it is hypothesised that approximately half will be diagnosed with a PD at follow-up, the most common being avoidant PD, schizotypal PD and borderline PD (Rosen et al., 2006; Schultze-Lutter et al., 2012). The presence of PDs at follow-up will be associated with transition to psychosis, based on research linking schizotypal PD to transition (Nordentoft et al., 2006). The presence of PDs at follow up in the UHR sample will be associated with presence of non-psychotic mental disorders and poorer functional outcomes, consistent with other studies on the impact of PDs in samples with non-psychotic mental disorders (Tyrer et al., 2015).

Chapter 8

Methodology

8.1 The Setting

Individuals recruited for this study were previous patients at the PACE (Personal Assessment and Crisis Evaluation) Clinic. PACE is a specialist clinical program for UHR patients (aged 15-25 years), at Orygen Youth Health. The services provided at Orygen Youth Health comprise three components: EPPIC (Early Psychosis Prevention and Intervention Centre), HYPE and Mood Clinic, aimed at servicing non-psychotic individuals, and the PACE Clinic, which targets young people at high clinical risk of psychosis. People are accepted into PACE if they meet criteria for at least one of three UHR groups (see Section 8.2).

The PACE Clinic is the ideal setting for research into mental and personality comorbidity in the UHR population. It was established in 1995, with the aim of assessing, managing and following-up young people who may be in the prodromal phase of psychotic illness, before the expression of frank psychosis. Referrals to PACE come from a variety of sources, including primary care services, drug and alcohol services, school and university counsellors, youth accommodation centres as well as from the justice system. Self-referrals from families and young individuals are also received. A brief telephone “triage” interview is used to assess a young person wishing to enter PACE. If the individual meets the “triage” criteria, they are scheduled to attend an in-person assessment to profile symptoms and determine eligibility (see Section 8.2 for eligibility criteria).

8.2 Participants

8.2.1 Sample.

The sample consisted of a previously ascertained group of 172 individuals who met UHR criteria and were recruited into research studies at the PACE Clinic at Orygen Youth Health (i.e. had at least a baseline assessment) between March 2002 and May 2006. The interval range between baseline and follow-up assessment was 6.8 - 12.1 years ($M=8.8$ years) (see Figure 3). Thirty-two (18.6%) participants were lost to follow-up (see Results section for details), however, state medical records (CMI) were systematically checked for outcome data on these cases.

8.2.2 Inclusion criteria.

Patients were eligible for the current study if they met at least one of the three defined UHR groups (Yung et al., 2003) at baseline:

1. Vulnerability Group: Person has a first degree relative diagnosed with a psychotic disorder, or the person has schizotypal personality disorder, plus a significant recent drop in functioning or chronic low functioning.
2. Attenuated Psychotic Symptoms (APS): Presence of sub-threshold psychotic symptoms that are considered below the intensity or frequency required for a diagnosis of a psychotic disorder.
3. Brief Limited Intermittent Psychotic Symptoms (BLIPS): Brief episode of frank psychotic symptoms which spontaneously resolve within seven days (i.e. without anti-psychotic medication).

Furthermore, the APS and BLIPS group require the presence of psychotic symptoms within the last 12 months.

In addition to meeting UHR for psychosis criteria, the following exclusion criteria were applied: Participants must not have experienced a full previous psychotic episode (treated or untreated), known organic cause for presentation, and not have an intellectual disability (estimated IQ <70). Participants were required to speak English as their preferred language.

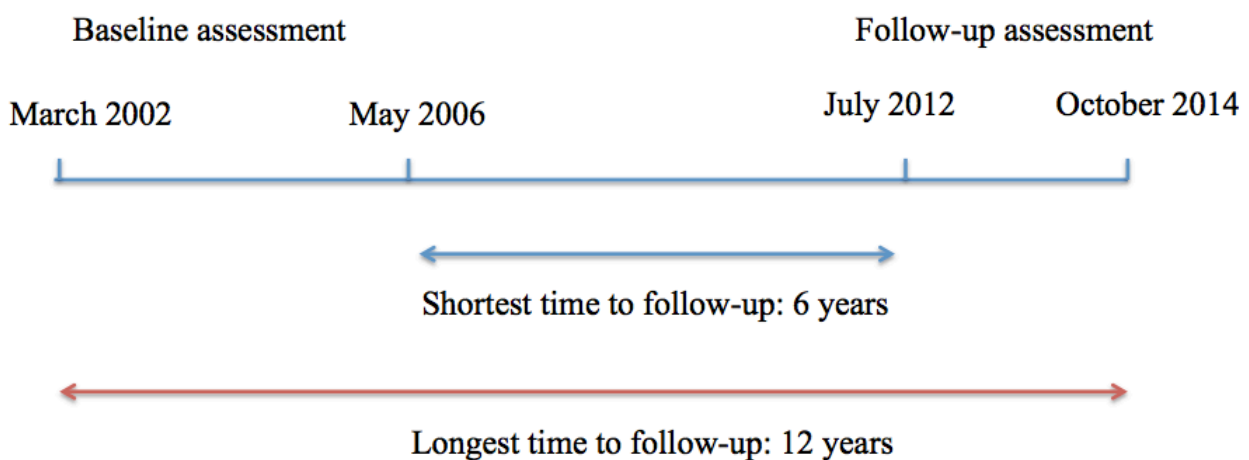


Figure 3: Recruitment timeline for follow-up assessment

8.3 Procedure

Participants who had previously been involved in studies at PACE were recontacted and assessed. The feasibility of this study was reliant on our ability to maximise our follow up rate. Every effort was made to locate and contact these individuals in order to invite them to participate in the current study.

8.3.1 Patient tracking.

All participants ($n=172$) had given informed consent for long-term follow up at the time of their baseline interview (2002-2006). If participants were no longer

contactable using the details provided at baseline, the following options were explored to determine contact information:

- 1) The National Death Index
- 2) Research files
- 3) Previous contacts
- 4) Public mental health service record systems
- 5) National Electoral Roll
- 6) Internet-based searching; and
- 7) Telephone directory

The National Death Index was used to check whether participants had deceased. No participants were reported to have deceased since baseline assessment.

The PACE research files were searched for any information on the location of the participant, and for names of family, friends or clinicians. In addition, the Client Management Interface database was utilised to obtain or cross-check the addresses of participants who had a recent registration with the Victorian public mental health system. The National Electoral roll was searched in 2012, though access was restricted in 2013. The White Pages telephone directory was also searched for the names of participants through internet search engines such as Google, MySpace and Facebook and other public networking sites.

If participants could not be located directly using the above steps, efforts were then made to locate and contact members of the participants' family, friends or clinicians and request help from them in locating the participant.

8.3.2 Contacting participants.

Once a possible location for an individual participant was determined, the participant was sent a standard letter that explained the purpose of the project and

requested that the person contact the research team, either by phone or letter (a stamped envelope addressed to the investigator was enclosed, along with a reply slip). This was believed to be the least confronting procedure for re-contacting the cohort. If the participant wished to know more about the study, the Participant Information Statement (see Appendix A2) was made available to them and the researcher attempted to respond to any concerns. Once a participant was successfully contacted, they were invited to participate in an interview at a convenient time and place, and informed consent was obtained.

If a participant did not contact the research team within two weeks of the contact letter being sent, a researcher attempted to phone them.

8.3.3 Assessment procedure.

Full assessment comprised assessment of psychopathology and functioning assessment (details of measures outlined in Section 8.4). Participants occasionally agreed to only a sub-section of the assessments. If participants did not agree to a full assessment (conducted face-to-face or via telephone or Skype) they were requested to partake in a short telephone assessment (see Appendix A3 for telephone interview questions). This allowed for at least minimal clinical and functional outcome data to be collected, even in the absence of a comprehensive assessment.

Psychopathology interviews took approximately 3-4 hours on average, with some assessments lasting as long as 8 hours in rare cases. Assessments were conducted at a location of the participant's choice, either Orygen or at their home. A small proportion of interviews were conducted over Skype or the telephone.

When participants requested or were deemed to require mental health services and were not currently linked in with services, a list of service options was provided to them in verbal and written form.

When patients were unable to be interviewed, patient files were reviewed in order to determine the presence or absence of a DSM-IV classified disorder. State public psychiatric records were also consulted to determine whether the person had any contact with public psychiatric services since last contact with PACE and, if so, whether they had been diagnosed with a DSM-IV disorder.

The process of relocating, contacting and reassessing all the participants was conducted between June 2012 and December 2013.

8.3.4 Ethical considerations.

This study was carried out according to the *National Statement on Ethical Conduct in Research Involving Humans (June 1999)* produced by the National Health and Medical Research Council of Australia. This study received ethics approval from the Behavioural and Psychiatric Research and Ethics Committees of the North Western Mental Health Program. Research participation was voluntary and participants were free to withdraw at any stage of the project, as per ethics requirements. Any information obtained in connection with this project that could identify participants was kept confidential (see Appendix A2 for details outlined in the plain language statement and consent forms).

8.4 Measures

Details of the measures are described in Section 8.4.2. Variation in measures used across the follow up period (baseline, medium term and current follow up) are listed in Table 1.

Table 1

Assessments at baseline and follow-up

	Baseline	Current study: >6 year follow up
Inclusion Criteria		
Assessment of UHR criteria	CAARMS, FIGS, GAF	
Outcomes		
Psychosis onset		CAARMS State public psychiatric records
Social functioning	GAF QLS	GAF, SOFAS QLS, LCS
Exposures		
Demographics	Age, gender, family socio-economic status	
Premorbid functioning	Average grades at school	
Duration of symptoms prior to attending PACE	CAARMS – includes section on assessing this variable	
Reason for referral to PACE	CAARMS – includes section on assessing this variable	
Service use, previous treatment	Questionnaire designed for this purpose	Questionnaire designed for this purpose, LCS
Positive psychotic symptoms	CAARMS BPRS	CAARMS BPRS
Negative symptoms	SANS	SANS
Depressive symptoms	HRSD	HRSD
Anxiety symptoms	HRSA	HRSA
Psychiatric diagnosis	SCID-IV	SCID-IV I and II

8.4.1 Demographics.

Demographics originally collected at baseline assessment were updated, including gender, age, marital status, occupational status and education.

Participants were classified as having a *full-time occupation* if they were engaged in full time employment, study or home duties. Participants undertaking more than one part-time occupation (e.g. part-time employment and part-time study) were also classified as being fully employed. *School completion* referred to participants who had completed year 12, the final pre-tertiary year of schooling in Australia.

8.4.2 Psychopathology and symptom measures.

8.4.2.1 Attenuated Psychotic Symptoms (APS).

The *Comprehensive Assessment of At-Risk Mental States* (CAARMS) is a measure developed at PACE to assess the intensity, frequency and duration of attenuated psychotic symptoms and is used to determine UHR status. Consistent with previous analyses by Yung et al. (2005) the intensity scores in this study were treated as an overall measure of psychotic symptom severity.

The CAARMS has been shown to have good to excellent reliability (Yung et al., 2005). For the purpose of the current study, the positive symptoms were analysed.

These included the following subscales:

1. Unusual Thought Content: Delusional mood and perplexity; ideas of reference; delusions of control, somatic passivity, thought insertion/withdrawal, thought broadcasting, mind reading
2. Non-Bizarre Ideas: suspiciousness/persecutory ideation; grandiose ideas, somatic ideas; delusions of guilt; nihilistic ideas; jealous ideas; religious ideas; erotomantic ideas

3. Perceptual Abnormalities: visual, auditory, olfactory, gustatory, tactile and somatic distortions or hallucinations
4. Disorganised Speech: subjective change; objective rating of circumstantiality and tangentiality

8.4.2.2 Mental disorders.

The Structured Clinical Interview for DSM-IV (SCID; First, Gibbon, Spitzer & Williams, 1996) was used to determine psychiatric diagnoses of mental disorders (defined as Axis I disorders by the DSM-IV). The SCID is a semi-structured interview that includes an introductory overview followed by modules that represent the major mental disorder diagnostic classes. These include major depressive disorders, anxiety disorders, schizophrenia spectrum disorders and substance use disorders. This allowed retrospective assessment of the period since the participant was last interviewed and includes a timeline for mapping onset of psychiatric disorders. The output of the SCID was a record of the presence or absence of each of the disorders being considered, for current episode (past month) and for lifetime occurrence. It enabled both threshold and sub-threshold forms of disorders to be rated. There are few studies of the psychometric properties of the SCID-IV. One study of inter-rater reliability and diagnostic agreement across 30 interviewees in a training study revealed very good diagnostic agreement (82%) (Ventura, Liberman, Green, Shaner & Mintz, 1998). Agreement on symptoms was also very high ($\kappa = .85$).

The Brief Psychiatric Rating Scale (BPRS) (McGorry, Goodwin, & Stuart, 1988; Ventura et al., 1993): This abridged clinician-rated measure comprises 24 items that assess psychotic symptom severity. The BPRS is grouped into four domains—positive symptoms, specifically thought disorder, negative symptoms—withdrawal, hostility, and depressive/anxious symptoms. These items are rated on a seven-point

scale, ranging from not present (1) to extremely severe (7). The BPRS has been used in schizophrenia populations and been shown to have good concurrent validity (Faustman, 1994). It also has good inter-rater reliability, with median Pearson intraclass correlation coefficient range of .67 to .88 for the overall score and individual items (Hedlund & Vieweg, 1980).

Hamilton Rating Scale for Anxiety (HRSA; Hamilton, 1959): This scale assesses anxiety via 14 items, rated on a five-point scale, which ranges from absent (0) to severe/grossly disabling (4). This scale has adequate reliability (Bruss, Gruenberg, Goldstein, & Barber, 1994) and sufficient concurrent validity (Maier, Buller, Philipp, & Heuser, 1988). However, it has poor sensitivity to detect minor changes in the severity of anxiety (Maier et al., 1988). This scale demonstrated very good internal consistency and satisfactory validity when previously tested in an adolescent sample (Clark & Donovan, 1994).

Hamilton Rating Scale for Depression (HRSD; (Hamilton, 1960): This clinician-rated scale was used to assess depressive symptoms. It comprises 24 items rating numerous features of depressive symptomatology. This scale has previously demonstrated very high inter-rater reliability, and good concurrent validity (Kørner et al., 1990). The high reliability only refers to the overall score, however; low reliability was reported at the item level (Williams, 2001).

Scale for Assessment of Negative Symptoms (SANS) (Adreasen, 1982): This clinician-rated measure comprises 24 items addressing negative symptomatology. Negative symptoms are rated on a six-point scale, ranging from none (0) to severe (5). The SANS covers five domains: affective flattening/blunting, alogia, avolition/apathy, anhedonia/asociality and attention. This scale has good inter-rater reliability (ranging from 0.86 to 0.92) for the subscales (Adreasen, 1982).

Family history of major psychiatric disorders were assessed using the widely used *Family interview for Genetic Studies* (FIGS) (Maxwell, 1992a). This was used to determine whether the participant met criteria for the family history UHR group at baseline.

8.4.2.3 Personality disorders.

Psychiatric diagnoses of personality disorders (defined as Axis II disorders by the DSM-IV) were assessed using the Structured Clinical Interview for DSM-IV Axis II (SCID-II) (First, 1997). SCID - II was administered to UHR patients at follow up only and time of onset of any personality disorder present, was estimated.

8.4.2.4 Measures of functioning.

The *Quality of Life Scale* (QLS (Heinrichs, Hanlon & Carpenter, 1984)) was administered at intake and at follow-up. This scale comprises 21 items rated on a six-point scale and was intended to measure the deficit state in schizophrenia. This instrument covers four interdependent constructs: motivation and purpose in life is examined by “intrapsychic foundations” questions, social experiences are assessed by “interpersonal relations” items, and participation in and engagement with the community, is assessed by questions relating to common objects and activities. A factor analysis performed by Shtasel et al. (1992) identified three factors in the QLS: 1) social functioning (relationships with close friends, acquaintances, social network), 2) engagement (relationships with family, sense of purpose, motivation, curiosity); and 3) occupational role functioning (degree of underemployment, satisfaction with occupation, accomplishment). It has been recommended that the total QLS score be used over the sub-scale scores as they are closely related (Bow-Thomas, Velligan, Miller, & Olsen, 1999). The QLS has good inter-rater reliability (0.92) (Bryson, Lysaker & Bell, 2002).

The *Global Assessment of Functioning* (GAF) (APA, 2000) was used to assess functioning in social, occupational and psychological domains. This measure is clinician rated on a 100 point, single item scale. Ratings of 1 to 10 indicate grossly impaired functioning, whilst ratings of 91 to 100 reflect superior functioning. The GAF has been shown to provide a valid measure of social functioning (Startup, Jackson, & Bendix, 2002). GAF scores have an inverse relationship with increasing severity of diagnosis in outpatients with schizophrenia (Bodlund, Kullgren, Ekselius, Lindström, & von Knorring, 1994). The GAF, being a single item measure, does not permit a comprehensive assessment of functioning of specific areas of life, however its advantage is the simplicity and speed with which this measure can be administered (Burns & Patrick, 2007). This measure is the most commonly used when assessing overall function in schizophrenia (Burns & Patrick, 2007).

The *Social and Occupational Functioning Assessment Scale* (SOFAS) (Goldman, Skodol & Lave, 1992) of the DSM-IV (APA, 2000) was employed to determine the level of social and occupational functioning of participants. The SOFAS is single item rated on a continuum from excellent functioning to grossly impaired functioning. This measure is similar to the GAF but unlike the GAF, it rates social and occupational functioning independently of psychiatric symptomatology. The SOFAS has been shown to have very good reliability, excellent concurrent and predictive validity, as well as good internal consistency (Russo et al., 1998).

The *Life Chart Schedule* (LCS) (Susser, Conover & Siegel, C., 1992) was used at follow-up to assess long-term symptoms, treatment, residence and work outcomes. The LCS was designed to assess the long-term course of schizophrenia, but was administered all participants in the current study, regardless of whether they had a diagnosis of schizophrenia. The LCS was administered twice, one assessing a time period of two years prior to follow up, and another assessing the entire duration

between follow-up and last assessment. LCS ratings have been shown to be reliable in all key domains (Susser et al., 2000).

8.5 Data Analysis

Data were analysed using IBM SPSS Statistics for Macintosh, Version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

8.5.1 Types of analyses.

8.5.1.1 Description of the sample (demographics and diagnoses).

Demographic variables were analysed using chi-square tests for independence for categorical variables. These included: sex, treatment provided at PACE, presence of mental disorders (at baseline and follow-up), personality disorders (at follow-up only) and type of participation at follow-up (face to face, telephone interview). Independent samples t-tests were used for continuous variables (age of participants). The likelihood of particular outcomes was determined using p -values $<.05$ and 95% confidence intervals (CI).

8.5.1.2 Group differences.

Independent samples t-tests were used to analyse continuous variables, with p -values at the level $<.05$ reported as significant. Chi-square tests for independence were used to analyse differences between groups of categorical variables, with p -values at the level $<.05$ reported as significant. Effect size (ϕ) was reported.

8.5.1.3 Clinical predictors of trajectories of mental disorders over time.

Relationships between baseline categorical clinical variables were initially investigated using Spearman's rho correlation coefficient, and relationships between continuous baseline clinical predictors using Pearson product-moment correlation coefficient. This was done as an exploratory first step, prior to logistic regression as

an assumption of logistic regression analysis is the absence of high multicollinearity between predictor variables (Tabachnick & Fidell, 2007). The examination of correlations revealed no levels of multicollinearity that violated this assumption. Correlations are presented in Appendix B.

When conducting logistic regression, the ‘enter’ method was used for each independent variable separately, in order to see how each variable contributed individually to the outcome variable. Variables which were identified to have a significant independent relationship to the dependent variable were then considered together using a stepwise selection procedure, in order to factor in their effect on each other. The β , associated degrees of freedom and p-values are reported for models. These values illustrate the ability of the model to predict the dependent variable when accounting for the effects of the independent variables on each other, and the significance of the difference between the null likelihood and the likelihood of the final model (Berwick, Cheek & Ball, 2004). In addition, OR (corresponding to $\text{Exp } \beta$) and its 95% CI are also reported, providing an estimation of the likelihood of the event. An OR with a value close to one provides an indication that the predictor does not change the likelihood of the event, with an OR less than one indicating decreased chances of the event and an OR greater than one indicating a greater likelihood of the event.

8.5.1.4 Functional outcomes (for both mental and personality disorder analyses).

To investigate functional outcomes of participants, Wilcoxon Signed Ranks Test was used for analyses consisting of two continuous variables that were not normally distributed. When the number of continuous variables exceeded two, the Kruskal-Wallis test was used. Medians, and effect size r were reported for these non-parametric analyses. For continuous variables that did not violate the assumption of

normality, analysis was conducted using ANOVA, with p -values at the level $<.05$ being reported as significant. The F-statistic, means and p -values for these tests were reported, as well as η^2 for effect size.

8.5.1.5 Transition to psychosis.

Survival analysis (Kaplan-Meier method) was used to estimate transition rates of participants since baseline. The Kaplan-Meier method was also used to investigate an association between transition and personality disorders diagnosed at follow-up, as their onset date was retrospectively assessed. In order to investigate whether having a mental disorder at baseline was associated with transition rate, Cox regression survival analysis was used. Both methods predict the probability of an event (the dependent variable, in this instance, transition to psychosis) occurring by a specified point in time (Klein & Moeschberger, 2003). These analyses require both a beginning and an end point for the purpose of calculating time to the event (Berwick et al., 2004). The initial time point was defined as entry into the PACE study (baseline assessment date). The final time point was either the date the participant transitioned to psychosis or the date of last assessment if the participant had not transitioned to psychosis. No patients had deceased, so this did not need to be accounted for. Time to event was calculated as the number of months between the start and end dates. Differences in survival curves was examined using p -values, with $p<.05$ being reported as significant. Hazard ratios with their associated 95% CI were also reported.

8.5.1.6 Persistence of UHR status.

The relationship between mental disorders at baseline and persistence of UHR status by follow-up was examined using direct logistic regression. The Chi-square values and associated degrees of freedom, as well as p -values are described for the models. The association between mental disorders at follow-up and persistent UHR

status was investigated using Chi-square tests for independence, with p - values at the level $<.05$ reported as significant. Effect size (ϕ) is also reported.

8.5.1.7 Possible confounding variables.

The UHR sample at PACE is not a naturalistic sample—these patients had received treatment at PACE upon admission with others also receiving some treatment post discharge from PACE. The provision of treatment may have influenced patient outcomes. Therefore, treatment since last assessment was assessed using the Life Chart Schedule (LCS) (Conover & Siegel, 1992) (at follow-up only).

In previous work at PACE, duration of symptoms prior to referral has been related to outcome (Nelson et al., 2013; Yung et al., 2007). Therefore, this variable was controlled for in the current analysis.

8.6 Power

Most of the research questions were addressed using descriptive statistics (prevalence rates). Power for multivariate regression analyses was determined using the $50 + 10 (k)$ rule (where k is in the number of independent variables) (Tabachnick & Fidell, 2007) and confirmed using G-Power version 3.1, based on detecting a medium effect size ($\beta \geq .20$), with critical $\alpha \leq .05$, with power of 80% (Faul, Erdfelder, Buchner, & Lang, 2009). Using this calculation, the sample size of $n=125$ enabled the use of 8 independent variables in the regression models to detect a medium effect.

With regards to prediction of transition to psychosis and functional outcome, the estimation of the rates of transition to psychosis can be expected to be between 5% to 12% of the true rates given the sample size (using Peto's formula (Peto, 1984)). Statistical tests in survival analysis, including Cox regression, are based mainly on maximum likelihood methods. Eliason (1993) suggests that a sample size of 60 is sufficient if five or fewer parameters are to be estimated. Therefore, the sample size

of $n=124$ was considered to be adequate to address the research question of prediction of transition.

8.7 Missing Values

The number of participants lost to follow-up as well as incomplete assessments resulted in some missing data. If a participant did not complete a specific measure at either time point (baseline or follow-up), these participants were not included in the analysis. No data were substituted if a participant were not able to complete an assessment. T-tests on demographic variables were conducted between those who participated and those who did not, to ensure that there were no differing characteristics between the two samples (see Chapter 9: Results).

Chapter 9

Results – Mental Disorders

Chapters 9 through to 10 display the results of this thesis, with Chapter 9 presenting results pertaining to the mental disorders hypotheses as well as a description of the sample, and Chapter 10 addressing the personality disorders hypotheses.

9.1 Description of the Sample

9.1.1 Follow-up assessment.

A total of 125 participants (72.7%) were followed up overall. Fifty-six percent ($n=97$) of the original $n=172$ sample presented for a face-to-face interview and 22% for a telephone interview (see Figure 4). These individuals completed full clinical assessments. Phone assessments involved only partial collection of psychopathology and functional outcome data, which included questions about depression, psychosis, treatment at a health service, and questions about work and living situation to ascertain functioning. Baseline differences between participants and non-participants are explored further below.

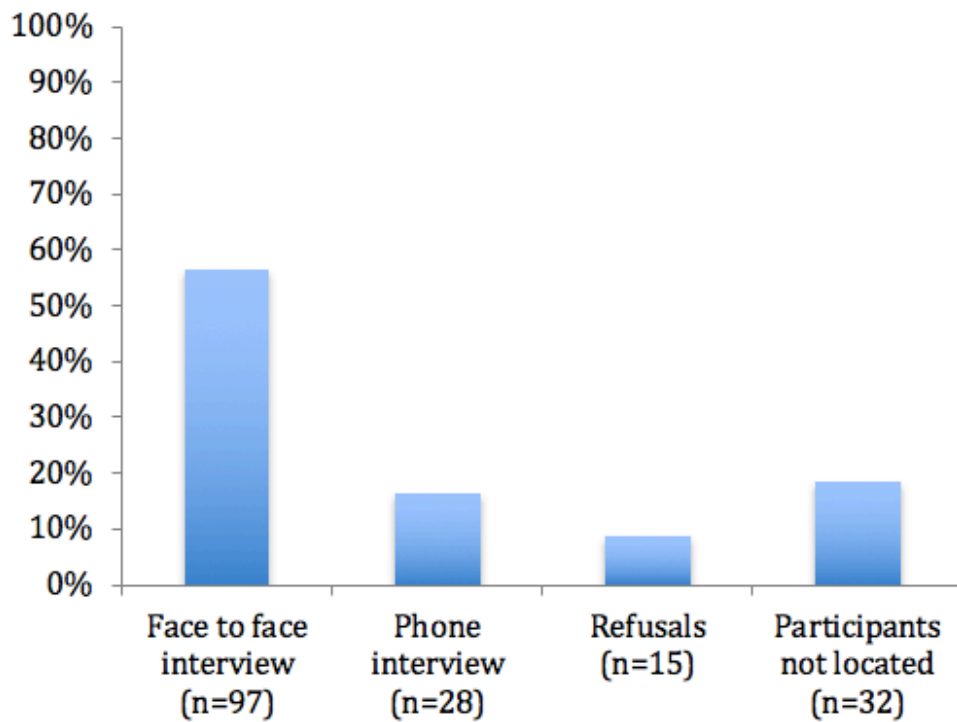


Figure 4: Rates of participation in follow-up assessment

The mean age of participants at follow-up was 26.8 years (ranging from 22 to 34 years, $SD = 2.87$ years). Mean follow-up time since baseline assessment was 8.8 years (range 6.8 to 12.1 years). There was a significant difference in age of participants based on time to follow-up, with those being followed-up after 9 years being older ($M=26.2$ years, $SD=2.86$) than those followed up between 6.8 and 9 years ($M=27.8$, $SD=2.73$) ($t(129)=-3.2$, $p<.01$). There was no difference in sex related to time to follow-up ($\chi^2(1, n=129)=.69$, $p=.72$, $\phi=.04$). There was also no relationship between time to follow-up and mental disorder ($\chi^2(1, n=126)=.20$, $p=.65$, $\phi=.04$) and personality disorder diagnosis at follow-up ($\chi^2(1, n=96)=.48$, $p=.49$, $\phi=.07$).

9.1.2 Difference in participation rates.

Just over half the followed-up sample was female ($n=73$, 58%, males $n=52$, 42%), presenting similar portions to those at baseline (females $n=97$, 56%, males

$n=75,42\%$). Sex had no effect on whether a participant presented for an interview at follow-up ($\chi^2(3, n=172)=1.30, p=.73, \phi=.09$).

An independent samples t-test was conducted to compare those who participated at follow-up and those who did not. There was no significant difference in age at baseline for those who participated at follow-up ($M=17.98$ years, $SD=2.8$) or refused/were not located for follow-up assessment ($M=17.89$ years, $SD=2.76$; $t(170)=-.17, p=.86$). There was also no difference in whether or not a participant presented for a follow-up interview if they had a mental disorder diagnosis at baseline ($\chi^2(6, n=172)=6.83, p=.33, \phi=.20$) (Appendix B1).

9.1.3 Treatment type and follow-up rates.

Type of treatment delivered while the participant was seen at PACE was not related to whether the person participated at follow up or not ($\chi^2(3, n=172)=4.37, p=.22, \phi=.16$). Treatment delivered while seen at PACE was categorised as either ‘treatment as usual’ ($n=68$) or controlled intervention ($n=104$) study treatment, as per previous research (Nelson et al., 2013).

9.1.4 Description of the sample at follow-up assessment.

The vast majority (62%) of participants had been employed (either full-time or part-time) since last assessment ($n=107$), with only 5% ($n=9$) reporting that they had not worked at all.

The majority of the sample had been employed (either full-time or part-time) for the two years prior to follow-up (Table 2). Around 16% of the sample reported that they had been unemployed for some of the time in the last two years ($n=66$), with around half of these individuals being unemployed for over one year. Of those who had been unemployed in the last two years, 70% attributed their unemployment to

problems caused by mental illness ($n=22$). Twenty-nine percent ($n=9$) said that their unemployment was not due to mental illness.

Table 2

Time spent unemployed in the last two years

Months unemployed since last assessment	N	% of sample
None at all	66	68.0%
1-3 months	2	2.1%%
4-6 months	7	7.2%
7-11 months	6	6.2%
1-2 years	16	16.5%
Total	97	100%

**Note:* Only 97 participants completed the *Life Chart Schedule- 2 Years*, from which the data in this table are drawn.

9.1.5 Intake Groups at Baseline.

As shown in Figure 5 (below), the majority of participants (88%) presented to the PACE clinic at baseline with attenuated psychotic symptoms (APS). Nineteen per cent of participants met criteria for vulnerability, with only 7% presenting with brief limited intermittent psychotic symptoms (BLIPS). Some participants met criteria for multiple intake groups, the most frequent combination being that of meeting criteria for both vulnerability and APS (9%). Only one person met criteria for all three groups.

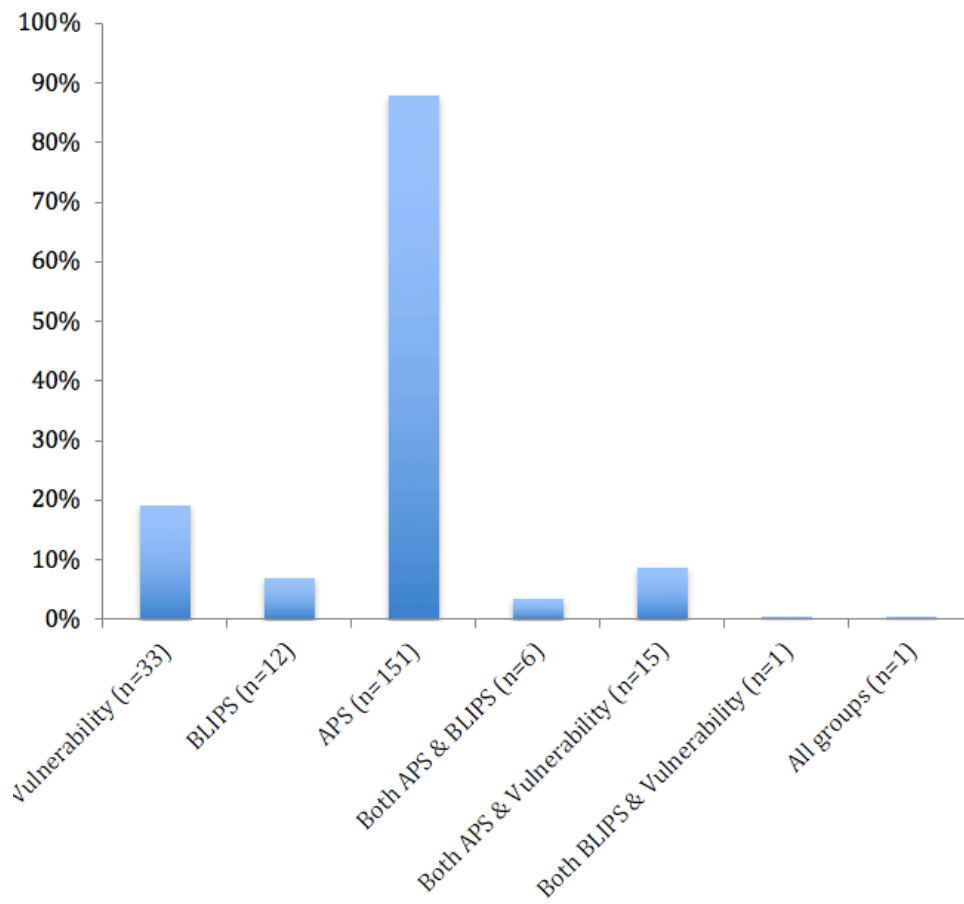


Figure 5: Intake groups at baseline

9.2 Type and Prevalence of Mental Disorders at Baseline and Follow-Up

Mental disorder diagnoses were established at baseline if the participant had presented with symptoms of the disorder within a month prior to assessment (“current diagnosis”). Only 22 participants (13%) did not meet criteria for a DSM-IV disorder at baseline, indicating that most UHR patients presented with serious clinical concerns. Mood disorder was the major concern for participants at baseline, with the vast majority of the sample meeting criteria for a diagnosis ($n=136$, 79%) (Table 3). When grouped together, anxiety disorders were the next most common disorders ($n=83$, 48%). This was followed by substance use disorder (SUD), including both substance abuse and dependence ($n=31$, 18%).

The pattern of disorders that were of major concern continued at follow-up, though at reduced prevalence. Almost half of participants did not meet criteria for a DSM-IV diagnosis at time of follow-up ($n= 61$, 48.8%). Mood disorder continued to be the most prevalent disorder reported at follow-up, with 32% of the sample having experienced the disorder within the last month ($n=40$ current diagnoses), and 28.8% ($n=36$) having experienced an episode between last assessment and follow-up assessment (classified as an ‘interval’ diagnosis) (Table 3). However, rates of mood disorder had decreased substantially since baseline (explored further in Section 9.3). There was a similar reduction in prevalence of anxiety disorders, with one-quarter of participants experiencing a current disorder ($n=32$) and only 8 (6.4%) experiencing an anxiety disorder in between baseline and follow-up. Substance use disorder rates remained fairly consistent since baseline, affecting one in five participants since baseline, with 15% participants experiencing an SUD within a month of follow-up assessment.

Table 3

Mental disorder diagnoses assessed at baseline and follow-up (disorder present within one month of assessment)

Mental disorder	Baseline		Follow-up	
	N	% of sample (n=172)	N	% of sample (n=125)
Mood Disorder*	136	79%	40	32%
Substance Use Disorder (SUD)	31	18%	19	15.2%
Panic Disorder	24	14%	12	9.6%
Social Phobia	14	8%	6	4.8%
Obsessive Compulsive Disorder (OCD)	12	7%	3	2.4%
Specific Phobia	11	6%	3	2.4%
Posttraumatic Stress Disorder (PTSD)	9	5%	2	1.6%
Generalised Anxiety Disorder (GAD)	7	4%	8	6.4%
Anxiety Not Otherwise Specified (Anxiety NOS)	6	3%	2	1.6%
Eating Disorder	5	3%	2	1.6%
Other	22	13%	9	7.2%
No Diagnosis	22	13%	61	48.8%

*Note ** A participant met criteria for mood disorder if they were diagnosed with any major depressive disorder or non-psychotic bipolar disorder. Participants may have received more than one diagnosis.

Prevalence rates for current and interval (between baseline and follow-up assessment) DSM-IV diagnoses are presented in Table 4.

Table 4

Mental disorder diagnoses between last assessment and current at follow-up

Mental disorder	Current n	% of sample (n=172)	Interval Period* N	% of sample (n=125)
Mood Disorder	40	23%	37	29.6%
Substance Use Disorder	19	11%	39	31.2%
Panic Disorder	12	7%	4	3.2%
Generalised Anxiety Disorder	8	4%	1	1%
Social Phobia	6	3%	0	0%
Psychotic Disorder	5	3%	8	6.4%
Obsessive Compulsive Disorder	3	2%	0	0%
Specific Phobia	3	2%	1	1%
Posttraumatic Stress Disorder	2	1%	3	2.4%
Anxiety Not Otherwise Specified	2	1%	1	1%
Eating Disorder	2	1%	2	1.6%
Other	9	5%	7	5.6%
No diagnosis	61	35%	66	52.8%

Note *Interval period diagnoses were defined as any disorder experienced after the last follow-up assessment, but which had resolved prior to the current follow-up assessment. Participants may have received more than one diagnosis.

Current rates of mood disorders were similar to rates experienced between baseline and follow-up assessment, however, it appeared that SUDs had mostly resolved by follow-up. This will be explored further in the section 9.3.1.

Due to the small sample size of the separate anxiety disorders diagnosed, all anxiety disorders were combined and will be reported as a group in subsequent analyses. Anxiety disorders for the purpose of this section comprise panic disorder, GAD, social phobia, specific phobia, OCD, anxiety NOS and PTSD.

Overall, mood, anxiety disorders and SUDs appear to be the main concerns for participants at both baseline and follow-up assessment. Though rates of reported mood disorders dropped, a substantial amount of the sample was still affected by mood disorder, with 32% experiencing a current mood disorder (defined as within the month prior to assessment). Grouped baseline prevalence rates are presented against current follow-up diagnoses in Figure 6.

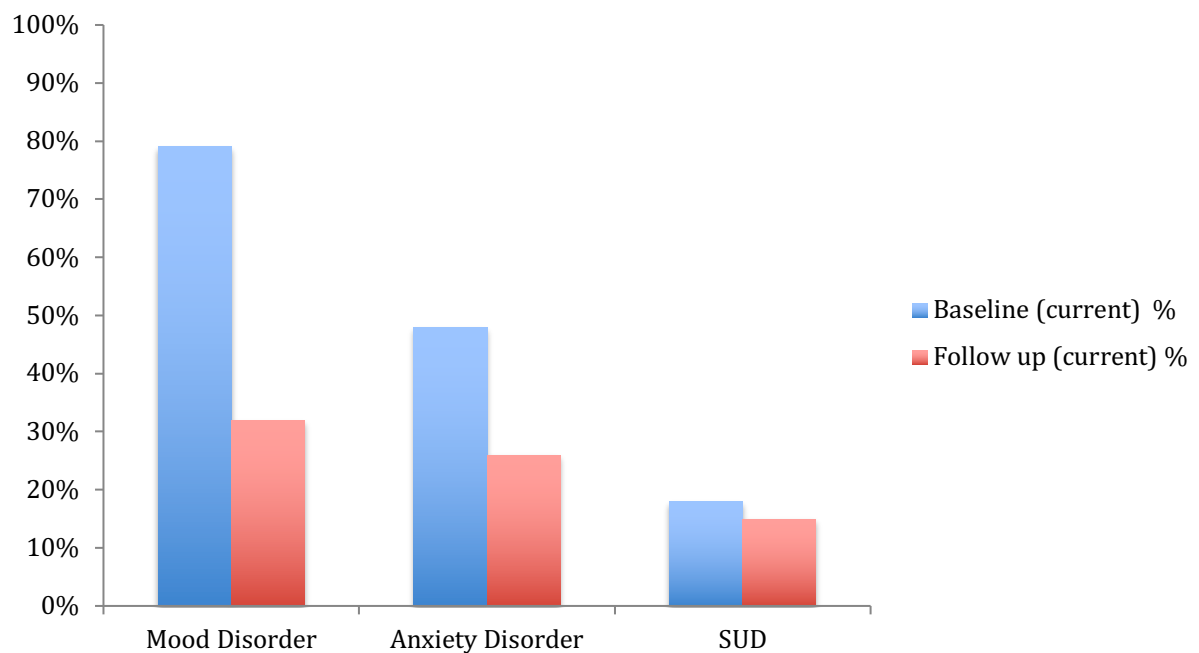


Figure 6: Prevalence of mental disorders at baseline and follow-up (current) – major groups

**Note:* "Current" means symptoms were present within the month preceding assessment

A similar pattern of results is observed for mood and anxiety disorders when DSM-IV diagnoses for lifetime disorders (i.e. a disorder experienced at any prior time in life) are included, with fewer disorders being reported at follow-up compared with

baseline. However, when disorders experienced in between assessments are included, an increase in diagnosis of SUDs from baseline is observed. The baseline prevalence of 24.8% ($n=31$) increased to 30.4% ($n=38$) experiencing SUDs at follow-up. It appears that the majority of these individuals experienced some SUD in between assessments, however, the majority of these were resolved by the time of follow-up assessment, with only 15.2% ($n=19$) still meeting criteria within one month of follow-up assessment.

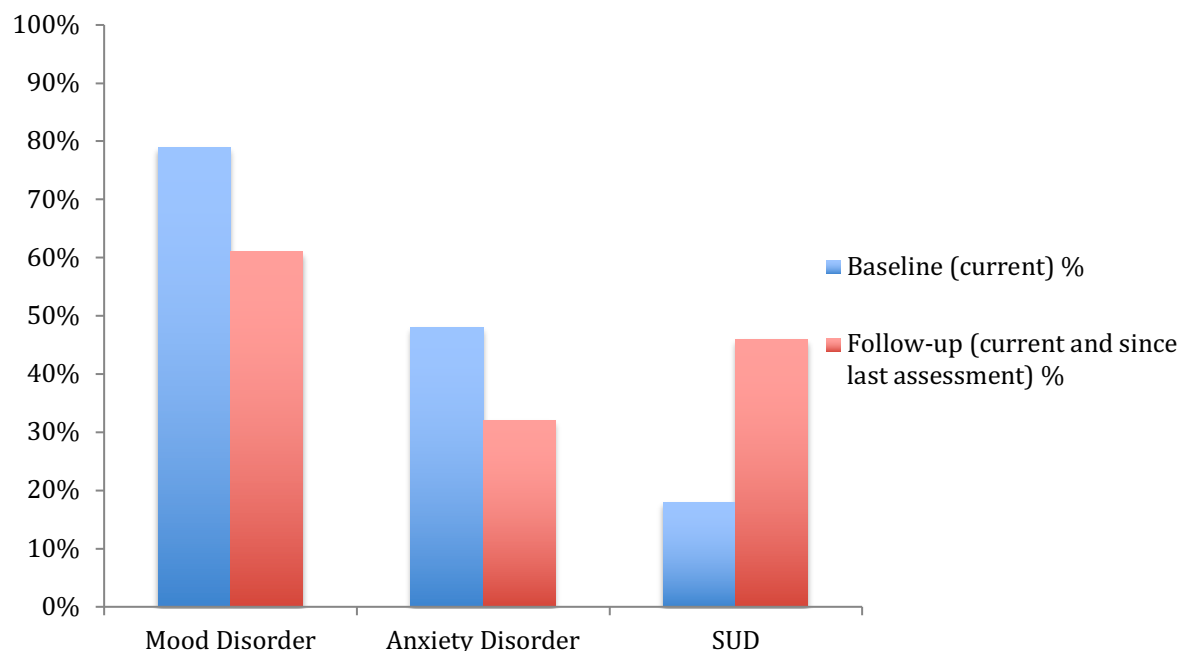


Figure 7: Prevalence of disorders at baseline compared to disorders at follow-up (both current and since last assessment combined)

*Note: "Current" means symptoms were present within the month preceding assessment

9.2.1 Effects of treatment on presence of mental disorders.

Effect of treatment was investigated to determine whether there were differences within the sample that needed to be controlled for. The majority of the sample ($n=104$, 60%) received a controlled treatment as part of an intervention trial at baseline (an intervention study that comprised three treatment groups: cognitive behavioural therapy [CBT] and medication, CBT and placebo, and supportive therapy

and placebo. See McGorry [2002] for more detailed information). This left 68 participants who received ‘treatment as usual’ at PACE. Logistic regression revealed no effect of treatment as usual versus the controlled intervention treatment on presence of mental disorders at follow-up ($\beta=0.94, p=.60$). Therefore, effect of treatment was not a variable that needed to be controlled for in this study.

People experiencing mental disorders were more likely to seek out treatment. At long-term follow-up, participants were asked if they had received treatments in addition to those they received at the PACE clinic since their previous assessment. These treatments included counselling, family meetings, medication, ECT, day treatment, traditional healing, alternative treatments, and treatment for a drug or alcohol problem. From these, the groups of medication, psychotherapy (comprising counselling and family meetings), both medication and psychotherapy, and other (comprising all other measures) were formed for analysis. Almost one-third of the sample (29.7%, $n=51$) received psychotherapy between follow-up and previous assessment, with 39% ($n=68$) not receiving any treatment (data missing for 30.8% of the sample, $n=53$). The proportion of people who were taking medication (35.5%, $n=61$) was similar to the proportion who did not take any medication (32%, $n=55$). Only 10% of the sample reported receiving “other” types of treatment between assessments ($n=17$) (Appendix B2).

Looking at participants receiving a combination of both psychotherapy and medication revealed a significant association between having a mental disorder at follow-up and receiving this combined treatment ($\chi^2(1, n=112)=11.67, p=.001, \phi=.32$) (Table 5). When looking at the potential relationship between receiving both psychotherapy and medication with having a mood disorder at follow-up, a trend toward association was found ($\chi^2(1, n=112)=3.79, p=.05, \phi=.18$). As would be expected, people were more likely to have received psychotherapy and medication if

they had been diagnosed with a mood disorder since last assessment. No significant association was found between having an SUD and having taken medication and psychotherapy since the last assessment ($\chi^2(1, n=112)=.06, p=.82, \phi=.01$) (Appendix B3). However, people receiving both medication and psychotherapy were more likely to have an anxiety disorder at follow-up ($\chi^2(1, n=112)=11.28, p=.001, \phi=.32$) (Table 5).

People who were in the baseline treatment intervention group were no less likely to have received additional treatment between baseline and follow-up than those who were in the treatment as usual group ($\chi^2(1, n=116)=.26, p=.33, \phi=.10$) (Appendix B4).

Table 5

Participants who had a mood, anxiety or overall mental disorder at follow-up (current or since last assessment) and had received both medication and psychotherapy between assessments

		Received medication and psychotherapy since last assessment		Total
		No	Yes	
Mood disorder	No	32 (46.4%)	12 (27.9%)	44
	Yes	37 (53.6%)	31 (72.1%)	68
Anxiety disorder	No	56 (81.2%)	22 (51.2%)	78
	Yes	13 (18.8%)	21 (48.8%)	34
Mental disorder (overall)	No	22 (31.9%)	2 (4.7%)	24
	Yes	47 (68.1%)	41 (95.3%)	88
Total (overall)		69	43	112

Note: Psychotherapy includes counselling and family sessions. Overall mental disorder comprised mood and anxiety disorders as well as SUD. SUD was not shown here as there was no significant association with treatment sought

9.3 Course and Stability of Baseline Non-Psychotic Mental Disorders

Over the 6-12 year follow-up period, 6% of participants ($n=8$) had not received a diagnosis of any DSM-IV disorder at either baseline or the follow-up assessment (classified as *never*). For those who were diagnosed with a mental disorder at either point, the course of their disorders was examined for three disorder groups: mood, anxiety and substance use disorders. Participants were classified as: *Remitted* if the non-psychotic mental disorder present at baseline was not present at follow-up; *Continuous* described participants whose non-psychotic mental disorder was present at both baseline and follow-up (either current at follow-up or since last assessment); participants who developed a non-psychotic mental disorder at follow-up but were not diagnosed with any non-psychotic mental disorder at baseline were classified as *Incident*.

Forty-two percent of participants were classified as *incident* over the follow-up period ($n=52$). An almost equal number of participants remitted from their disorders ($n=54$, 43.4%), or continually experienced their disorders ($n=65$, 52%). Participants may have had more than one disorder—therefore, they may have remitted from one disorder but maintained another (however, examination of change of disorder was beyond the scope of this thesis). These results are illustrated in Figure 8.

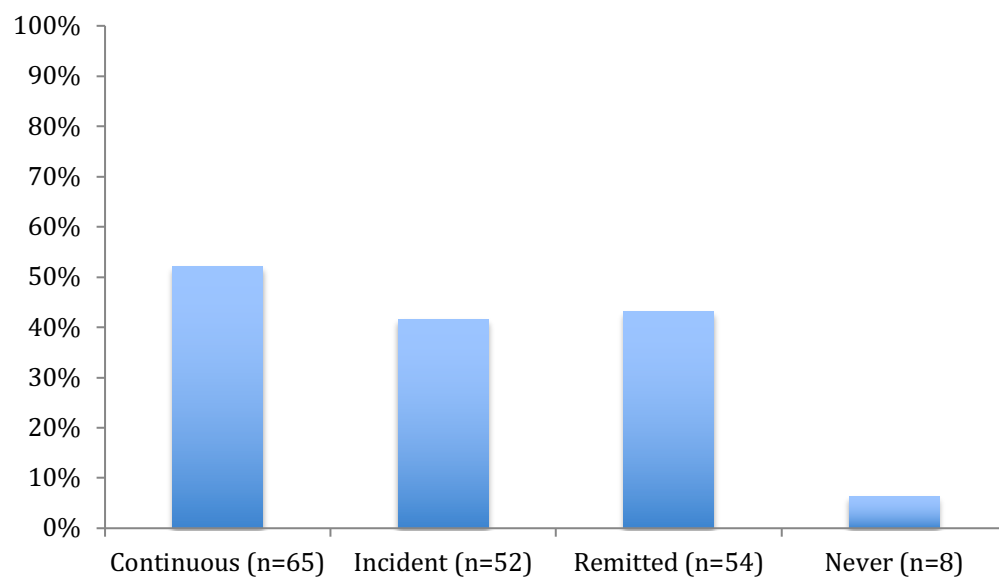


Figure 8: Trajectory of disorder – overall

9.3.1 Trajectory of mood disorder, anxiety disorder and substance use disorder over time.

Figure 9 illustrates the trajectories of the major groups of disorders: mood, anxiety and SUD over time. As can be seen, the disorder that was the most persistent for participants was mood disorder ($n=57$, 45.6%). Given the high prevalence of mood disorders at baseline, this disorder also had the highest rates of remittance ($n=39$, 31.2%). Over time, SUDs also posed a substantial problem for participants, though the prevalence was not as high as anxiety or mood disorders. Almost two-thirds of participants did not have an SUD at baseline or at follow-up ($n=80$, 64%).

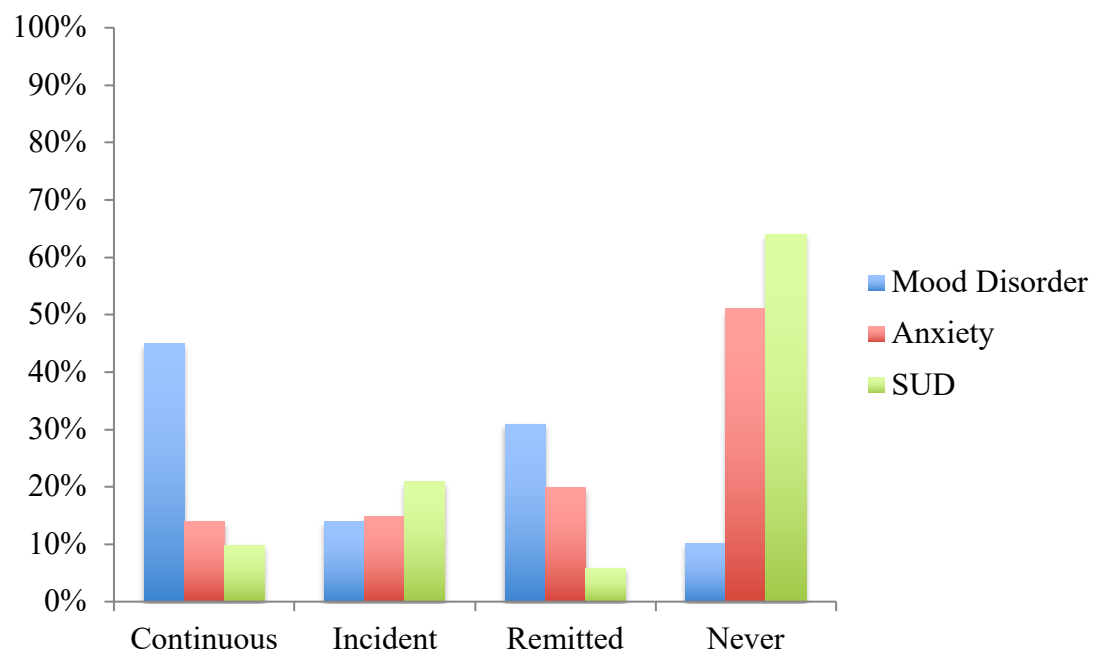


Figure 9: Over time trajectories by major group of disorder

9.3.2 Does UHR status persist over time?

Current attenuated psychotic symptoms⁸ of any severity were experienced by 71.6%⁹ ($n=73$) of the sample at follow-up, as assessed by CAARMS¹⁰. Twenty-seven per cent ($n=28$) of the sample did not present with attenuated psychotic symptoms. CAARMS data at follow up were missing for 56% ($n=70$) of the followed-up sample¹¹. Of the participants with APS, 31 (30%) had APS at a threshold (i.e. symptom severity and frequency) that fulfilled UHR criteria (i.e. 18% of the overall sample). No participants reported BLIPS. Four participants reported symptoms that indicated their transition to psychosis (all in the perceptual abnormalities category). The majority of APS reported were for non-bizarre ideas ($n=20$, 19.6%) (Table 6).

Sixty-six percent of participants had remitted from UHR status by follow-up ($n=67$). However, given the large proportion of cases with missing data, these results must be interpreted with caution.

⁸ “Current symptoms” is defined as the participant having experienced this symptom within the last month of assessment. This includes any APS, whether or not threshold for UHR status was met.

⁹ Note, $n=102$ participants completed a follow-up CAARMS assessment

¹⁰ CAARMS symptoms assessed at follow-up included perceptual abnormalities, non bizarre ideas, disorganized speech and unusual thought content

¹¹ Data were missing due to interview either being conducted via telephone or the CAARMS section of the face-to-face interview not being administered due to interviews running over time.

Table 6

Current APS in UHR range reported at follow-up

Symptom current at follow-up	APS (n)	APS % (out of 102)
Unusual thought content ¹²	11	10.8%
Non-bizarre ideas ¹³	20	19.6%
Perceptual abnormalities ¹⁴	14	13.7%
Disorganised speech ¹⁵	4	3.9%

*Note: participants may have been in more than one symptom group

9.3.3 Relationship between mental disorders at baseline and UHR status at follow-up.

Logistic regression was performed to assess whether presence of a mental disorder at baseline predicted UHR status at follow-up, but no relationship was found, $\chi^2(1, n=168)=1.19, p = .28$ (Appendix B5). Participants who had transitioned were excluded from this analysis ($n=4$). This indicated that presence of a mental disorder at baseline was not able to predict persistent UHR status.

However, a chi-square test for independence revealed a significant association between mental disorders at follow-up (current) and UHR status at follow-up, $\chi^2(1, n=168)=7.76, p = .01, \phi=.28$, with more people still meeting UHR criteria reporting presence of a mental disorder within the last month (Table 7). Therefore, people who met UHR status at follow-up were more likely to be unwell in general, experiencing both APS and non-psychotic disorder.

¹² Unusual thought content at the UHR level refers to referential ideas that certain events, objects or people have an unusual significance.

¹³ Non-bizarre ideas reflect delusions in which the content, though mistaken, is possible in real life.

¹⁴ Perceptual abnormalities reflect inconsistency between physical reality and what the person perceives.

¹⁵ Refers to somewhat vague, moderately tangential and disconnected speech in UHR participants.

Looking at the major disorder groups experienced, a significant association was found between UHR status and having a current SUD, $\chi^2(1, n=97)=6.04, p = .01$, $\phi=.25$, and an anxiety disorder at follow-up, $\chi^2(1, n=97)=5.89, p = .02$, $\phi=.25$ (see Table 7). Cell counts for the SUD analysis were low however, so results should be interpreted with caution. An association between UHR status at follow-up and having a current mood disorder approached, but did not reach, significance, $\chi^2(1, n=97)=3.79, p = .05$, $\phi=.20$. In general, these results indicate a pattern of participants without presence of mood, anxiety or SUD at follow-up to also have remitted from UHR status.

Table 7

Participants who had a mental disorder at follow-up (present within the previous month of assessment) and met UHR criteria at follow-up

		Met UHR criteria at follow-up		
		No	Yes	Total
Mood Disorder	No	51 (77.3%)	18 (58.1%)	69
	Yes	15 (22.7%)	13 (41.9%)	28
Anxiety Disorder	No	52 (78.8%)	17 (54.8%)	69
	Yes	14 (21.2%)	14 (45.2%)	28
SUD	No	61 (92.4%)	23 (74.2%)	84
	Yes	5 (7.6%)	8 (25.8%)	13
Mental Disorder (Overall)	No	37 (56.1)	8 (25.8%)	45
	Yes	29 (43.9%)	23 (74.2%)	52
Total (Overall)		66	31	97

**Note:* Percentages are calculated from column total

9.3.4 Relationship between UHR status and functional outcomes at follow-up.

One-way between groups analysis of variance revealed a significant association between UHR status and functional outcomes as measured by GAF and SOFAS, $F(2,100) = 11.81$, $p < .001$, $\eta^2 = .19$ (see Figure 10) representing a large effect (Pallant, 2011). Post-hoc comparisons using the Tukey HSD test indicated that the mean GAF score for participants who continued to meet UHR criteria at follow-up was significantly lower ($M = 62.8$, $SD = 10.37$) than for those who no longer were at UHR ($M = 72.08$, $SD = 10.01$). The lowest scores were for those who were meeting criteria for psychosis ($M = 55.00$, $SD = 17.8$), however this group only contained four participants, which may have affected comparisons and were excluded from analysis.

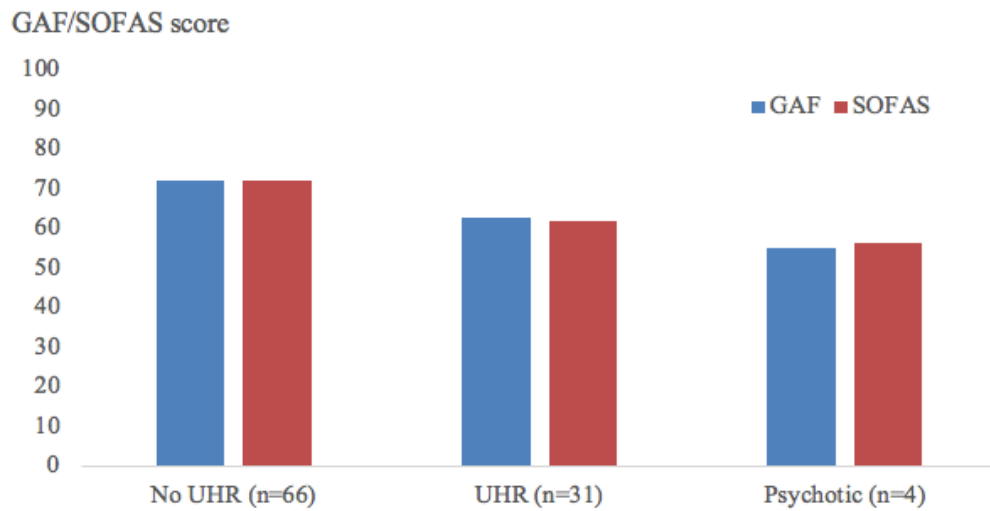


Figure 10: GAF and SOFAS score by UHR status

9.3.5 Relationship between UHR status and functional outcomes at follow-up.

A Kruskal-Wallis Test revealed a statistically significant difference in UHR status group for QLS scores, $\chi^2(2, n=90)=14.06, p = .001$. The UHR group recorded the lowest score ($Md=77.05$) compared to the non-UHR group ($Md=106$) (Figure 11). There were only three results for the psychotic group, ranging from $Md=49$ to 120, so this sample is too small to draw any conclusions from and was not included in the analysis.

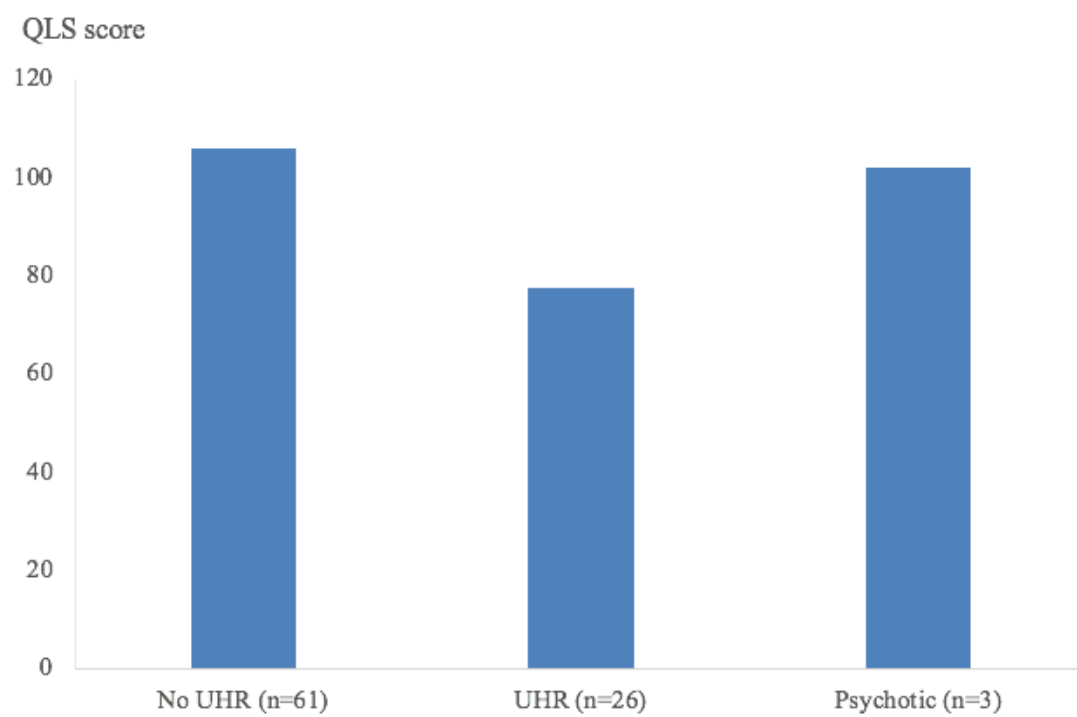


Figure 11: Quality of life score by UHR status

9.4 Baseline Clinical Predictors of Trajectories of Non-Psychotic Mental Disorders at Follow-Up

9.4.1 Relationship between baseline clinical predictors and continuous non-psychotic mental disorder at follow-up.

The relationships between the following baseline clinical variables were investigated using Spearman's rho correlation coefficient: PACE Treatment group at baseline, PACE intake groups (Vulnerability, BLIPS and APS). The relationships between the remaining baseline clinical variables were investigated using Pearson product-moment correlation coefficient: BPRS total scores, BPRS Psychotic subscale, SANS total, GAF, QLS, and HRSD¹⁶ and CAARMS (baseline)¹⁷. Age and sex were also explored as potential predictor variables but no relationship was found. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. The variable HRSD was found to have a correlation of $>.6$ with BPRS total, SANS total, and GAF (Appendix B6), and was thus excluded from further analysis; the remainder of the variables did not violate assumptions. The distributions for GAF and QLS were slightly skewed, however the sample size of these groups was large enough to not confound regression results (Tabachnick & Fidell, 2007). Correlations between independent variables that had an association with the dependent variable were small enough (all under $r = .6$, see Appendix B6) that these variables could be entered into a regression model at the next step, without having a confounding effect.

¹⁶ HRSA was not included as there was too much missing data at baseline assessment.

¹⁷ CAARMS at baseline included measures of: disorders of thought content, perceptual abnormalities, conceptual disorganization, motor disturbances, disorders of concentration, attention and memory, disorders of emotion and affect, impaired energy, impaired tolerance to normal stress.

The following baseline variables were found to have a significant correlation with continuous mental disorder at follow-up: BPRS total, Baseline Treatment Group, GAF, QLS, APS Intake Group, Impaired Tolerance to Normal Stress, and Vulnerability Intake Group. Direct logistic regression was performed to assess the individual contribution of these baseline clinical variables to the outcome variable, continuous mental disorder, at follow-up. Table 8 shows the results.

Table 8

Logistic regression results for association between continuous mental disorder and each baseline predictor individually

	B	Se (B)	Wald	Df	p-value	Odds Ratio (OR)	95.0% CI for OR	
							Lower	Upper
Baseline Treatment Group	.970	.370	6.881	1	.009**	2.638	1.278	5.447
Vulnerability Intake Group	1.080	.495	4.768	1	.029*	2.946	1.117	7.770
BLIPS Intake Group	1.559	.812	3.685	1	.055	4.755	.968	23.362
APS Intake Group	-1.418	.603	5.524	1	.019*	.242	.074	.790
BPRS total	.067	.025	7.236	1	.007**	1.069	1.018	1.123
GAF	-.062	.024	6.679	1	.010*	.940	.897	.985
QLS Total	-.024	.010	6.056	1	.014*	.976	.957	.995
Impaired Tolerance to Normal Stress	.453	.196	5.320	1	.021*	1.572	1.070	2.310

**p* value significant at the .05 level

** *p* value significant at the .01 level

In order to narrow down which variables were the strongest predictors of continuous mental disorder at follow-up, variables were considered together using a stepwise selection procedure. The stepwise regression model contained two

independent variables (BPRS Total and Baseline Treatment Group¹⁸). This model was statistically significant, $\chi^2(2, N=125)=12.24, p<.01$, indicating that the model was able to distinguish between participants who had a continuous disorder at follow-up and those who did not. As shown in Table 9 two variables made a unique statistically significant contribution to the model (BPRS Total), recording an odds ratio of 1.06 and Baseline Treatment Group, recording an odds ratio of 2.22. This indicated that if a respondent had a high BPRS Total score at baseline, they were 1.1 times more likely to have a continuous disorder by follow-up, and if they were in the intervention treatment group at baseline, they were 2.2 times more likely to have a continuous disorder by follow-up, controlling for the other variables in the model. The model as a whole explained 12.4% (Nagelkerke R square) of the variance in development of a continuous disorder, and correctly classified 64% of cases.

Individuals in the Baseline Treatment Group appeared more unwell than their treatment as usual counterparts at baseline, when looking at their BPRS Total scores (intervention group $M=49.9$, treatment as usual $M=45.49$, $t(168)=.58, p<.01$), which could explain the likelihood of this variable predicting a continuous mental disorder.

¹⁸ Treatment group: i.e. either the intervention or treatment as usual group. See McGorry (2002) for further details of treatment in these groups.

Table 9

Stepwise Logistic Regression Predicting Likelihood of Developing a Continuous mental disorder

	B	Se (B)	Wald	Df	P	Odds Ratio (OR)	95.0% CI for OR	
							Lower	Upper
BPRS Total	.054	.026	4.379	1	.036*	1.055	1.003	1.110
Baseline Treatment Group	.795	.388	4.196	1	.041*	2.215	1.035	4.741
Constant	-2.925	1.209	5.856	1	.016*	.054		

**p* value significant at the .05 level

9.4.2 Relationship between baseline clinical predictors and remission of a non-psychotic mental disorder¹⁹ at follow-up.

Possible predictive relationships between the same baseline clinical variables as above (Baseline Treatment Group, intake groups of Vulnerability, BLIPS and APS, BPRS Total and Psychotic scores, SANS, GAF, QLS, and baseline CAARMS ²⁰), as well as age and sex and having remission of a mental disorder at follow-up, were initially explored using correlations (Spearman's Rho and Pearson). There were no significant correlations (Appendix B7).

¹⁹ Remission is defined as remission by follow-up of any one of possible multiple non-psychotic mental disorders diagnosed for a given participant at baseline.

²⁰ Baseline CAARMS variables: disorders of thought content, perceptual abnormalities, conceptual disorganisation, motor disturbances, disorders of concentration, attention and memory, disorders of emotion and affect, impaired energy, and impaired tolerance to normal stress.

9.4.3 Relationship between baseline clinical predictors and development of an incident non-psychotic mental disorder at follow-up.

Pearson and Spearman's Rho correlations were performed for Baseline Treatment Group, intake groups (Vulnerability, BLIPS, APS), BPRS Total and Psychotic, SANS, GAF, QLS baseline CAARMS²¹ and this established that two independent variables (Baseline Treatment Group and Vulnerability Intake Group) had an association with Incident disorder (Appendix B8). Direct logistic regression assessed the individual contribution of these baseline clinical variables to Incident disorder at follow-up. Table 10 shows the results, with each of these predictor variables showing a significant relationship to incident disorder.

Table 10

Logistic regression results for association between development of an incident mental disorder and each baseline predictor individually

	B	se(B)	Wald	df	p-value	Odds Ratio (OR)	95.0% CI for OR	
							Lower	Upper
Baseline Treatment Group	-.845	.370	5.201	1	.023*	.430	.208	.888
Vulnerability Intake Group	1.106	.543	4.149	1	.042*	3.021	1.043	8.756

*p value significant at the .05 level

The significant baseline clinical predictors were next examined using a stepwise selection procedure, in order to identify the impact these variables had on incident mental disorder when considered together. When the effect of all variables

²¹ Baseline CAARMS: disorders of thought content, perceptual abnormalities, conceptual disorganisation, motor disturbances, disorders of concentration, attention and memory, disorders of emotion and affect, impaired energy, and impaired tolerance to normal stress.

was considered, both variables made a significant contribution to prediction of incident disorder, Wald $\chi^2(1, N=125)= 11.15, p < .01$, indicating that this model could identify participants who developed an incident disorder by follow-up. Results are shown in Table 11. Baseline treatment group recorded an odds ratio of .383, which indicated participants were 2.6 times less likely to develop an incident disorder at follow-up if they were in the intervention treatment group at baseline. If a participant was in the Vulnerability group at baseline, they were 3.5 times more likely to have an incident disorder by follow-up. The model as a whole explained 11.4% (Nagelkerke R Square) of the variance in development of an incident disorder, and correctly classified 64.3% of cases.

Table 11

Stepwise logistic regression predicting likelihood of developing an incident non-psychotic mental disorder

	B	Se (B)	Wald	Df	P	Odds Ratio (OR)	95.0% CI for OR	
							Lower	Upper
Baseline treatment group	-.959	.384	6.230	1	.013*	.383	.180	.814
Vulnerability Intake group	1.264	.560	5.086	1	.024*	3.538	1.180	10.610
Constant	-.887	.531	2.788	1	.095	.412		

**p* value significant at the .05 level

9.4.4 Relationship between baseline clinical predictors and never experiencing non-psychotic mental disorder during entire follow-up period or at baseline.

A regression analysis of clinical predictors for those who never developed a non-psychotic mental disorder was not conducted due to the insufficient sample size for this group ($n=8$).

9.5 Relationship Between Presence of Mental Disorders at Baseline and/or Follow-Up, and Functional Outcomes of Participants

9.5.1 Functional outcomes over baseline and follow-up periods.

A Wilcoxon Signed Ranks Tests revealed a significant improvement on GAF scores at follow-up compared to baseline $z=-7.50, p<.01$, with a medium effect size ($r = .44$) (Pallant, 2011). The SOFAS was not conducted at baseline, so could not be compared to follow-up, however, the median SOFAS score at follow up was 70. This score indicates that most participants were experiencing some difficulty in social, occupational and/or school functioning, but were generally doing well, and had some meaningful relationships. Descriptive statistics are presented in Table 12. Wilcoxon Signed Rank Test also revealed a statistically significant increase in QLS scores reported at follow-up ($Md = 100$) compared to baseline ($Md = 81$), $z= -4.60, p <.01$, with a small to medium effect size of $r =.29$ (Pallant, 2011).

Table 12

Descriptive statistics for the Cohort's Functional Outcomes at baseline and follow-up

Variable	N	M	SD	Md	Minimum	Maximum
GAF (baseline)	172	56.96	8.16	60.00	35	75
GAF (follow-up)	124	68.81	10.86	70.00	40	91
SOFAS (follow up)	124	68.66	11.57	70.00	40	93
QLS (baseline)	171	78.26	20.69	81.00	5	115
QLS (follow up)	90	93.70	23.17	100	24	125

9.5.2 Mood disorder trajectory and functional outcomes at follow-up.

A one-way between-groups analysis of variance was conducted to explore the impact of trajectory of mood disorder on levels of functioning at follow-up, as measured by the SOFAS. As reported previously, trajectory of mood disorder was broken into the groups continuous, incident, remitted, and never. Mean SOFAS scores from each group were compared (Figure 12). There was a statistically significant difference at the $p < .05$ level in SOFAS scores for the four trajectory groups, $F(3,118) = 4.02, p = .01, \eta^2 = .09$, representing a small effect. Post-hoc comparisons using the Tukey HSD test indicated that the mean SOFAS score for those with a continuous mood disorder ($M = 65.02, SD = 11.22$) was significantly worse than the mean SOFAS score of those with a remitted mood disorder ($M = 72.76, SD = 12.69$). The mean SOFAS score for those who had an incident mood disorder was not statistically different from the other groups ($M = 68.56, SD = 7.70$). The mean SOFAS score for those who never had a mood disorder was similar to those who had remitted ($M = 72.08, SD = 8.93$) and was not statistically different to the other groups. However, there were only 12 participants in this group. Similar results were found using the GAF (Appendix B9).

SOFAS Score

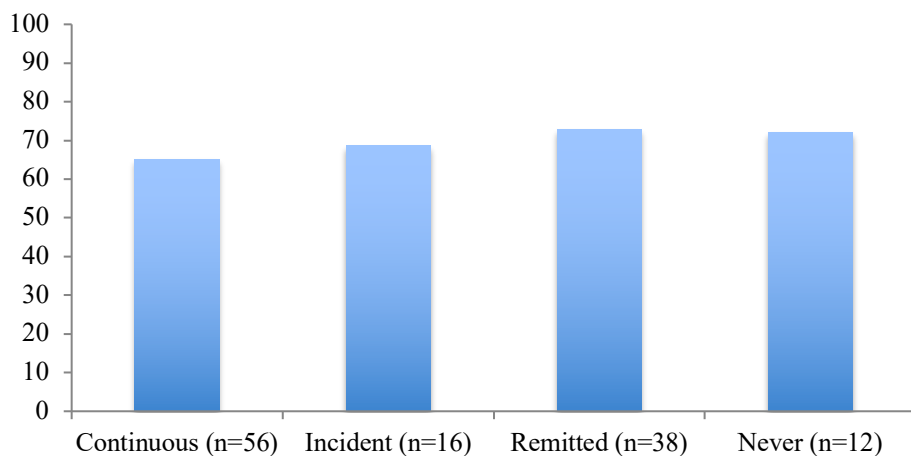


Figure 12: SOFAS score at follow-up by trajectory of mood disorder over time

9.5.3 Anxiety disorder trajectory and functional outcomes at follow-up.

Similarly, a one-way between-groups analysis of variance was conducted to explore the impact of trajectory of anxiety disorder on levels of functioning at follow-up, as measured by the SOFAS. Trajectories were plotted against SOFAS scores (Figure 13). The difference at the $p < .05$ level in SOFAS scores for the four trajectory groups was not significant: $F(3, 118) = 2.48$ $p = .07^{22}$. For the GAF results, see Appendix B10.

SOFAS Score

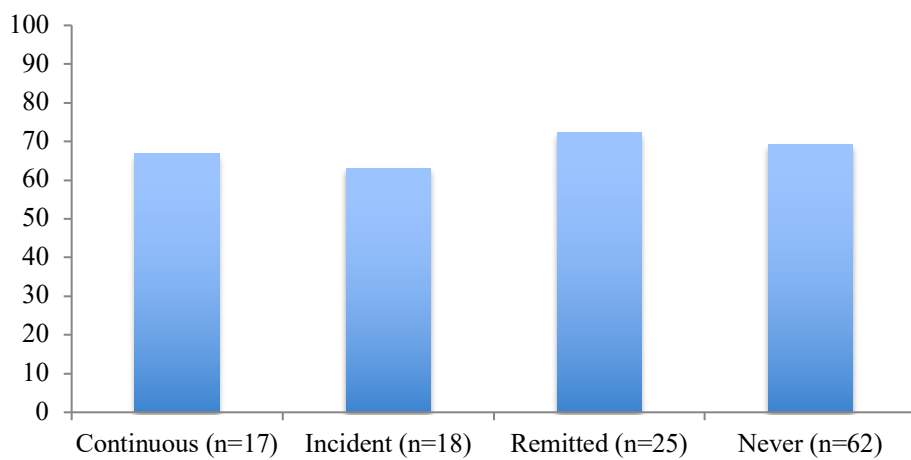


Figure 13: SOFAS score by trajectory of anxiety over time

9.5.4 Substance use disorder trajectory and functional outcomes at follow-up.

One-way between-groups analysis of variance revealed that trajectory of SUD over time had a significant impact on levels of functioning at follow-up, as measured by the SOFAS (Figure 14). There was a statistically significant difference at the $p < .05$ level in SOFAS scores for the four trajectory groups: $F(3, 118) = 4.89$, $p = .003$, $\eta^2 = .11$, representing a moderate to large effect (Pallant, 2011). Post-hoc comparisons using the Tukey HSD test indicated that the mean SOFAS score for those with an

²² The mean SOFAS scores were as follows: for those who had a remitted anxiety disorder ($M = 72.20$, $SD = 11.64$), anxiety never ($M = 69.26$, $SD = 11.53$), incident anxiety ($M = 63.00$, $SD = 12.33$), continuous anxiety ($M = 66.77$, $SD = 7.67$).

incident SUD ($M = 61.81, SD = 12.54$) was significantly different from the mean SOFAS score of those had never had an SUD ($M = 71.32, SD = 10.29$). Those with a continuous SUD had a higher average SOFAS score ($M = 67.08, SD = 12.87$) than those who had an incident SUD ($M=61.81, SD=12.54$), but this difference was not significant, possibly because the incident group was too small for comparison ($N=12$). Those who remitted from an SUD did not vary significantly from other groups ($M = 66.88, SD = 11.32$), however this group was also very small ($n=8$), which might have affected comparisons. See Appendix B11 for GAF results.

SOFAS Score

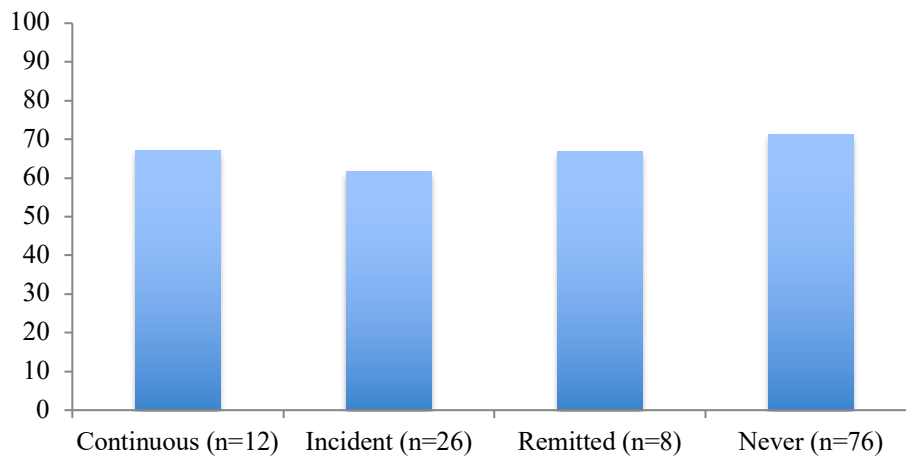


Figure 14: SOFAS score by trajectory of substance use disorder over time.

9.5.5 Mood disorder trajectory and quality of life of participants at follow-up.

A Kruskal-Wallis Test revealed a statistically significant difference in QLS across the four trajectories of mood disorder over time (continuous mood disorder, $n = 42$, incident mood disorder, $n = 11$, mood never, $n = 8$, mood remitted, $n = 28$), $\chi^2(3, n=89) = 12.38, p = .01$. The mood remitted group recorded a higher median score ($Md = 113.00$) than the other three groups. The lowest median QLS score was recorded for the continuous mood disorder group ($Md = 92$) (Figure 15).

QLS Total Score

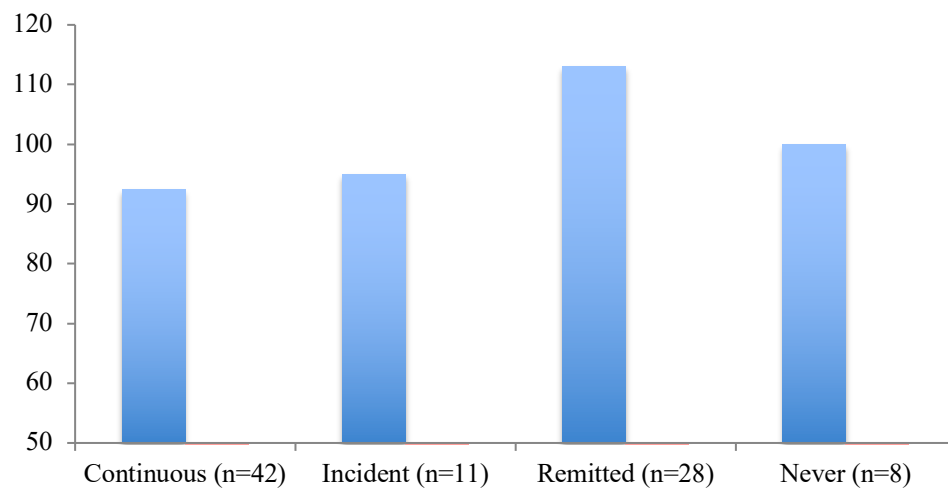


Figure 15: Quality of life total score by trajectory of mood disorder over time

9.5.6 Anxiety disorder trajectory and quality of life of participants at follow-up.

Contrary to results for mood disorder trajectory, a Kruskal-Wallis Test did not find statistically significant differences in QLS score across the four trajectories for anxiety disorders, $\chi^2(3, n=89)=4.42, p = .219$. The anxiety remitted and never groups still, however, recorded the highest median scores ($Md=108.5, 100$ respectively) than the other two groups who both scored medians of 94 (Figure 16).

QLS Total Score

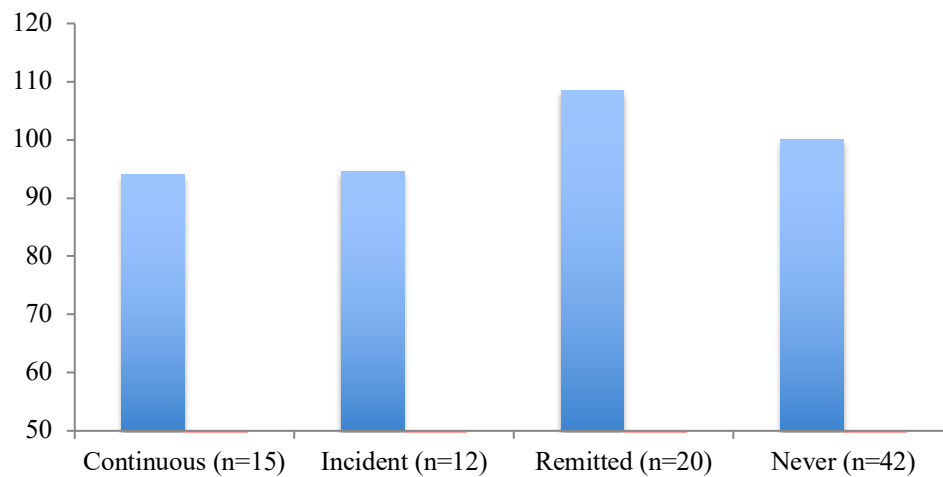


Figure 16: Quality of life total score by trajectory of anxiety disorder over time

9.5.7 Substance use disorder trajectory and quality of life of participants at follow-up.

As with mood disorder, a Kruskal-Wallis Test revealed a statistically significant difference in QLS across the four trajectories of SUD over time, $\chi^2(3, n=89)=15.38, p = .002$. The incident SUD group achieved significantly lower QLS scores than the other groups ($Md=79$) (Figure 17).

QLS Total Score

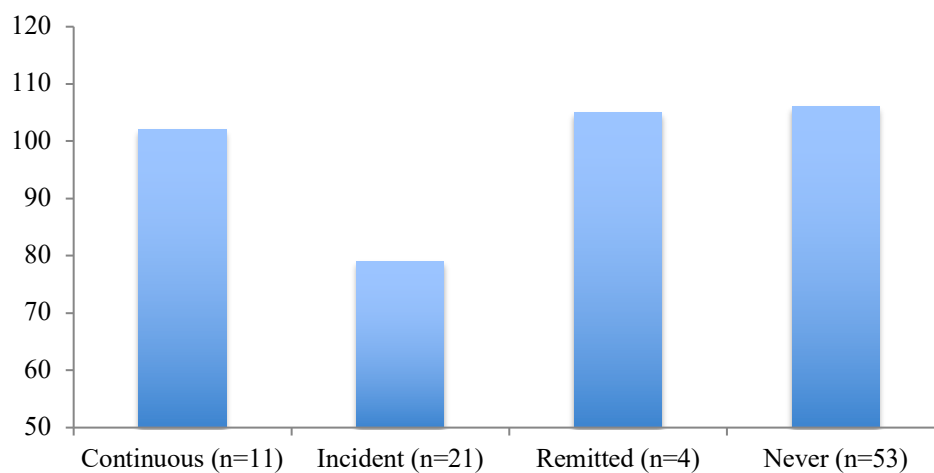


Figure 17: Quality of life total score by trajectory of substance use disorder over time

9.6 Relationship Between Mental Disorders at Baseline and Transition to Psychosis

Since assessment at baseline, 28 (16.3%) participants transitioned to psychosis. Twelve (7%) participants were lost at follow-up, leaving 132 (76.74%) participants as non-transitioned cases. Using survival analysis (Kaplan-Meier method), the estimated transition rate by 125 months is .81, SE .03. Transitions since baseline are illustrated in Figure 18. Each vertical increase in the graph illustrates a transition to psychosis and at how many months after entry at baseline this occurred. The first transition occurred within two weeks following baseline assessment, with the last transition at 87 months after baseline (number of months to transition to psychosis $\underline{M} = 23.9$ months, $SD = 26.17$).

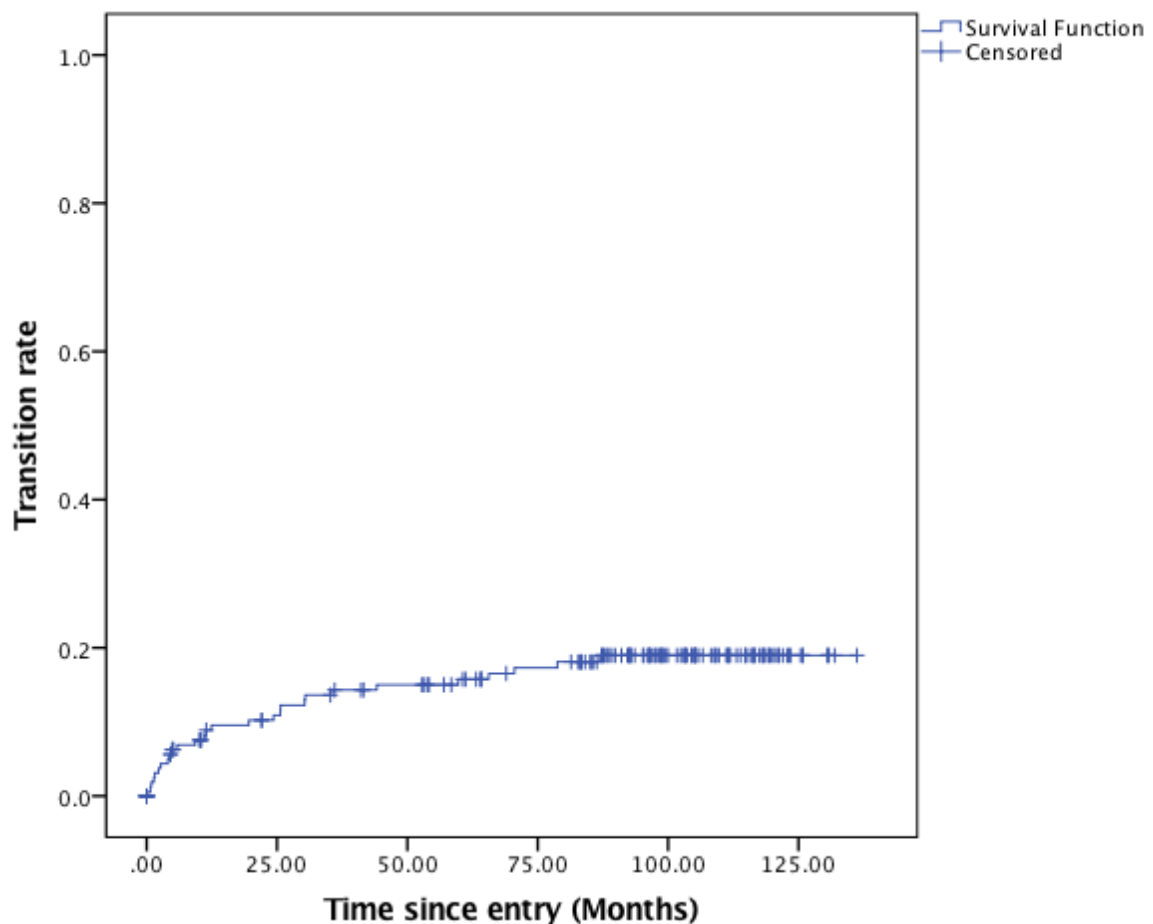


Figure 18: Survival curve showing number of months until transition to psychosis occurred

9.6.1 Transition to psychosis and mental disorders at baseline.

The association between having a mental disorder diagnosis at baseline and transition to psychosis was explored using univariate Cox regression analysis. This revealed that mental disorders had no significant association with transition to psychosis ($p=.44$, $HR=.68$, $CI95\% .26 - 1.80$). Figure 19 shows the Kaplan-Meier Survival Function of transitions for those who had a mental disorder at baseline. This graph illustrates a higher transition rate for those who did not have a mental disorder at baseline, however this group was small (five transitions in a group of 17 participants with no mental disorder at baseline), and the difference in transition rate was not statistically significant.

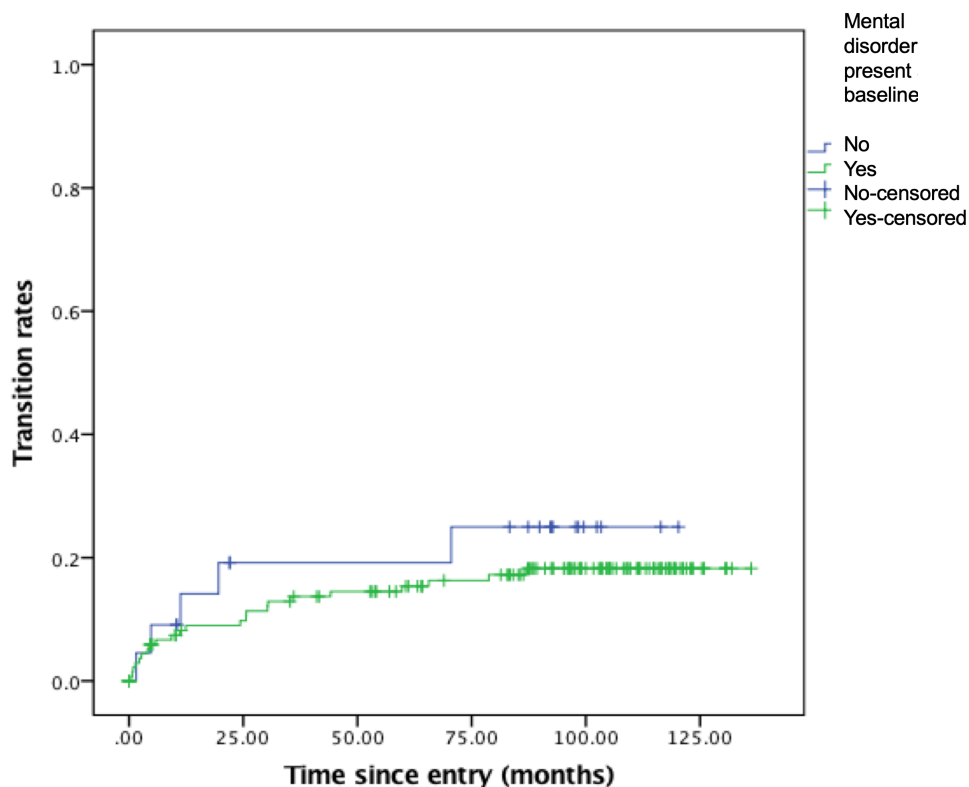


Figure 19: Transition rates in participants who had a mental disorder at baseline compared to those who did not

9.6.2 Transition to psychosis and mood disorder at baseline.

The association between mood disorder at baseline and transition to psychosis was also explored using univariate Cox regression analysis. This revealed that mood disorder had no significant association with transition ($p=.46$, HR=1.36, CI95% .60-3.10). The survival curve plotted using the Kaplan-Meier method (Figure 20) revealed a similar transition pattern to mental disorders, with those without a mood disorder showing a higher transition rate, though this difference was not significant. Given that the majority of those with a mental disorder also had a mood disorder at baseline, ($n=132$ with a mood disorder), the similarity is not surprising.

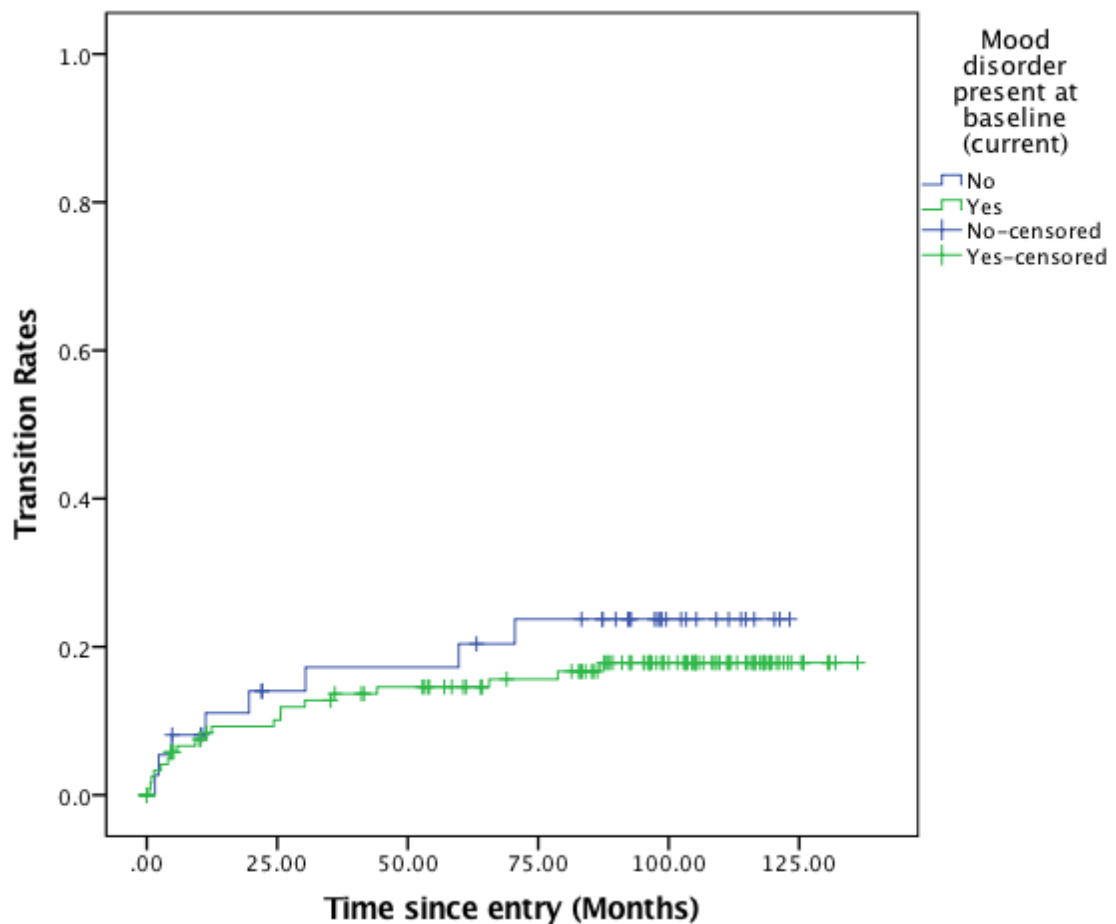


Figure 20: Transition rates in participants who had a mood disorder at baseline and those who did not

Transition to psychosis and anxiety disorder at baseline.

Anxiety disorder at baseline also showed no relationship to transition to psychosis ($p=.57$, $HR=1.26$ $CI_{95\%}$.57-2.78). Kaplan-Meier analysis (Figure 21) shows that those with no anxiety disorder at baseline had a slightly higher transition rate, however, this difference was not significant.

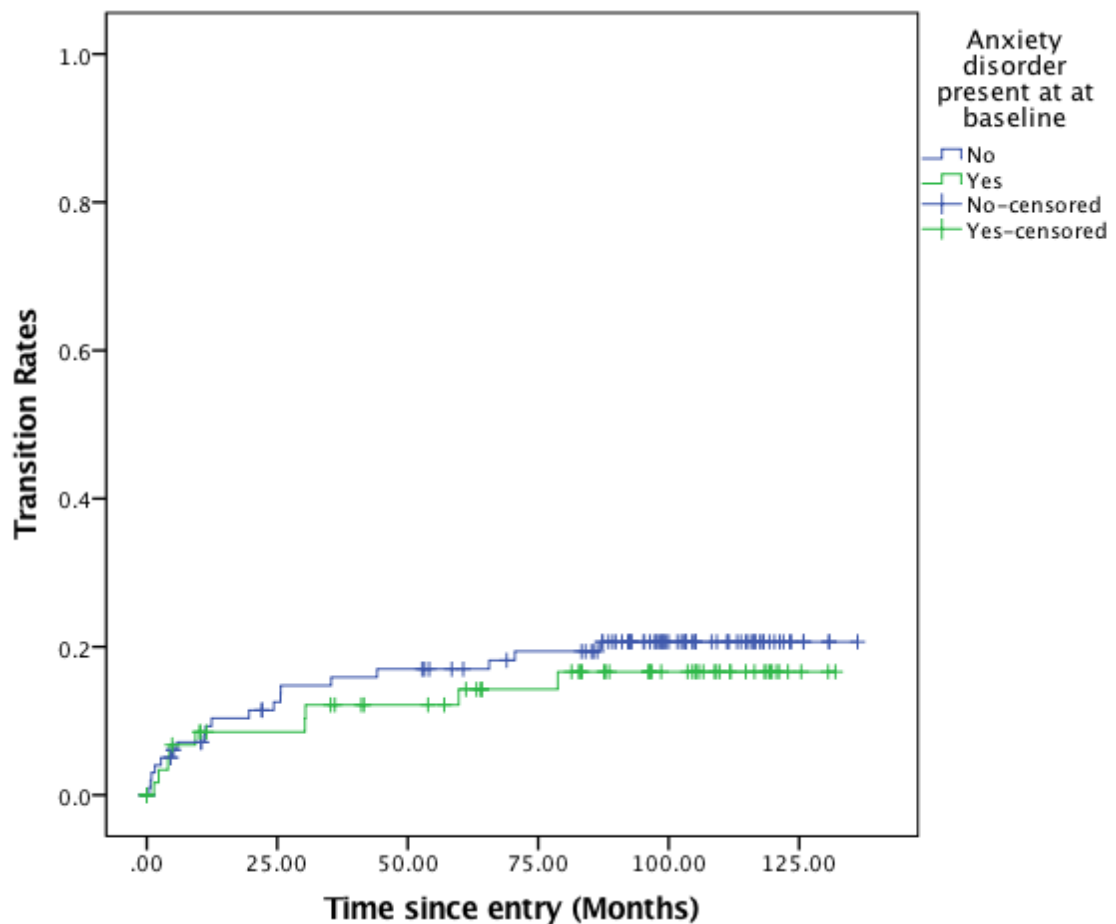


Figure 21: Transition rates in participants who had an anxiety disorder at baseline compared to those who did not

Transition to psychosis and substance use disorder at baseline.

A similar lack of association between SUD at baseline with transition to psychosis was found ($p=.89$, $HR=1.07$ $CI_{95\%}$.37-3.01). Kaplan-Meier analysis shows almost equal transition rate between those who had an SUD at baseline and those who did not (Figure 22).

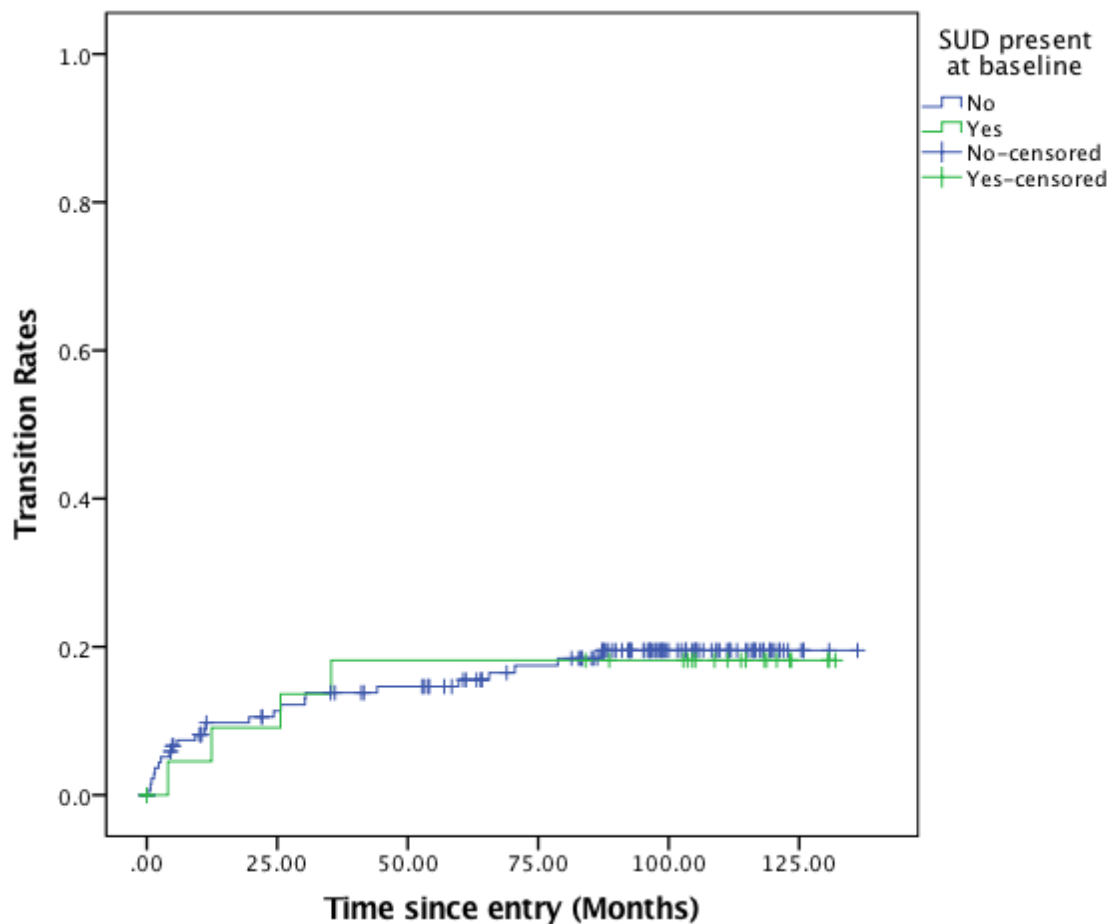


Figure 22: Transition rates in participants who had a substance use disorder at baseline compared to those who did not

9.7 Summary: Chapter 9 Mental Disorders

There was no difference in sex, age, treatment type and baseline mental disorder between participants who completed follow-up assessment and those who did not. The vast majority of the sample met criteria for a non-psychotic mental disorder at baseline (87%), the most common of these being mood, anxiety and substance use disorders. The same pattern of disorders appeared at follow-up, though prevalence rates were reduced, with almost half of the sample not meeting criteria for a mental disorder. Only 6% of participants had not received a diagnosis of mental disorder at either baseline or follow-up (Figure 23).

The most common trajectory for participants was to experience a continuous mental disorder (52%). Forty-two percent also developed a new disorder, and 43%

remitted from a disorder they had at baseline. Continuous mental disorders were associated with poorer functional outcomes as measured by the SOFAS, GAF and QLS, for mood disorders compared to those who had either never had the disorder or had remitted. People with incident SUDs were significantly more likely to have poorer functional outcomes than other SUD trajectory groups. However, there were no significant differences in functional outcomes in the anxiety disorder trajectory groups.

Thirty percent of participants continued to meet UHR criteria at follow-up, and 66% had remitted (Figure 23). Having a mental disorder at follow-up was associated with meeting UHR criteria. This association was present for disorders overall, as well as SUD and anxiety diagnoses. However, no statistically significant association between depression and UHR status was found. In addition, participants meeting UHR criteria at follow-up had significantly reduced functional outcomes as measured by the SOFAS, GAF and QLS compared to those who had remitted. Presence of a mental disorder had no relationship to transition to psychosis.

The strongest baseline clinical predictors of mental disorder trajectory included treatment group at baseline, BPRS total score, and vulnerability intake group.

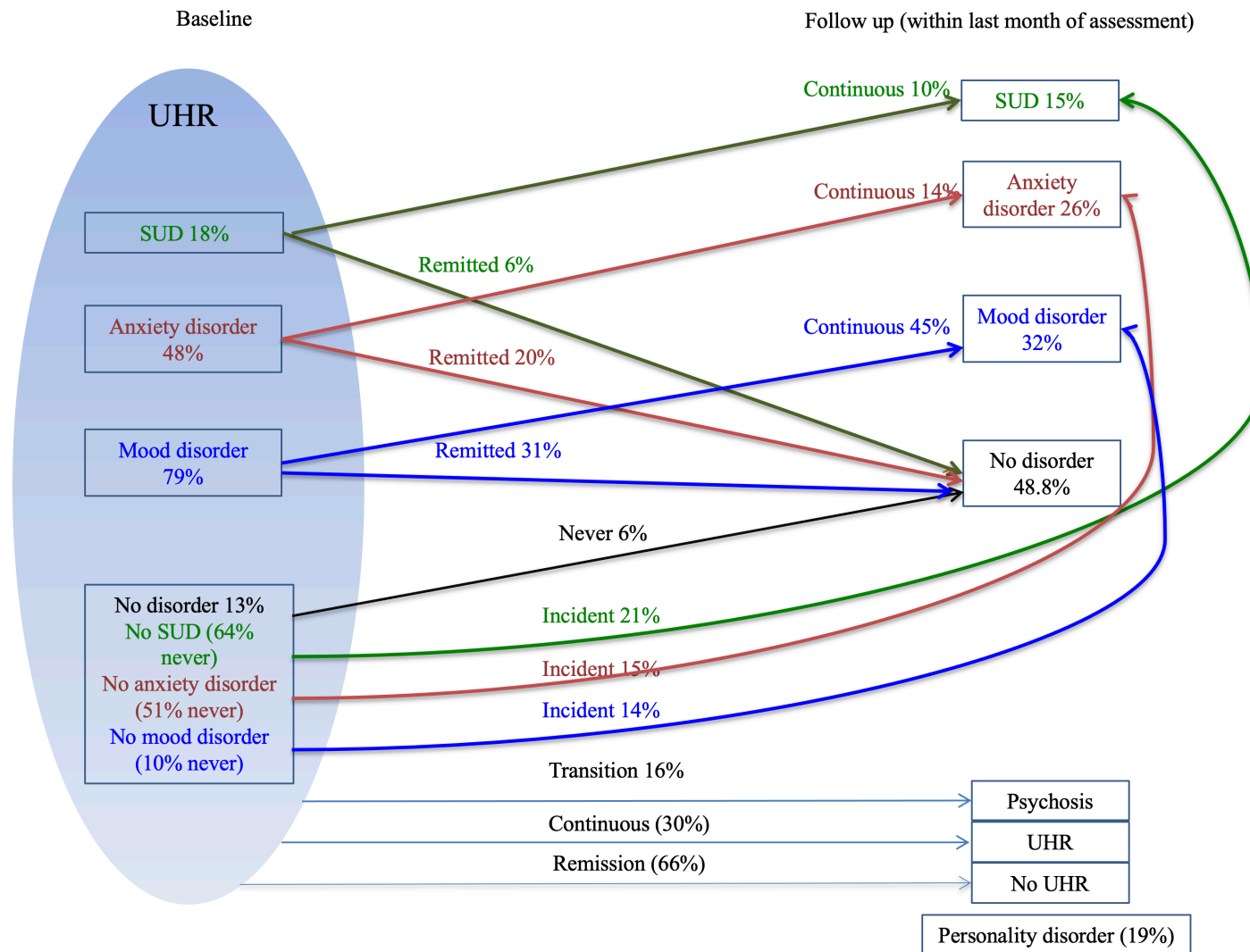


Figure 23: Prevalence rates and trajectories of mental disorders and UHR status

Chapter 10

Results -Personality Disorders

10.1 Prevalence of Personality Disorders at Follow-Up

Personality disorders (PD) were only assessed at follow-up, not at baseline, with 56% ($n=97$) of total sample completing this assessment. However, personality disorders were assessed retrospectively, with participants being asked to answer for behaviours and thoughts that had been present since their 18th birthday. Around 19% ($n=18$) of the sample assessed were diagnosed with a PD using the SCID-IV. Most of the 18 participants who had a PD only had one PD ($n=15$), two participants had two PDs and only one participant had three PDs. The most prevalent PD was borderline PD($n=11$), followed by antisocial PD ($n=4$) (Table 13).

Table 13

Prevalence rates of Personality Disorders at follow-up ($n=97$)

Personality Disorder	N	%
No diagnosis	79	81.4%
Borderline	11	11.3%
Antisocial	4	4.1%
Paranoid	3	3.1%
Obsessive compulsive	1	1%
Passive aggressive	1	1%
Schizotypal	1	1%
Schizoid	1	1%

Note: Participants may have had more than one PD diagnosed

10.2 Personality Disorder and Transition to Psychosis.

Presence of PD at follow-up associated positively with transition to psychosis ($p=.03$, HR=3.03 CI95% 1.10-8.30). In Kaplan-Meier analysis, presence of PD associated positively with transition ($p=.02$) (Figure 24). Due to the small number of participants with PD ($n=18$) no further analysis into types of PDs and their relationship with transition was conducted.

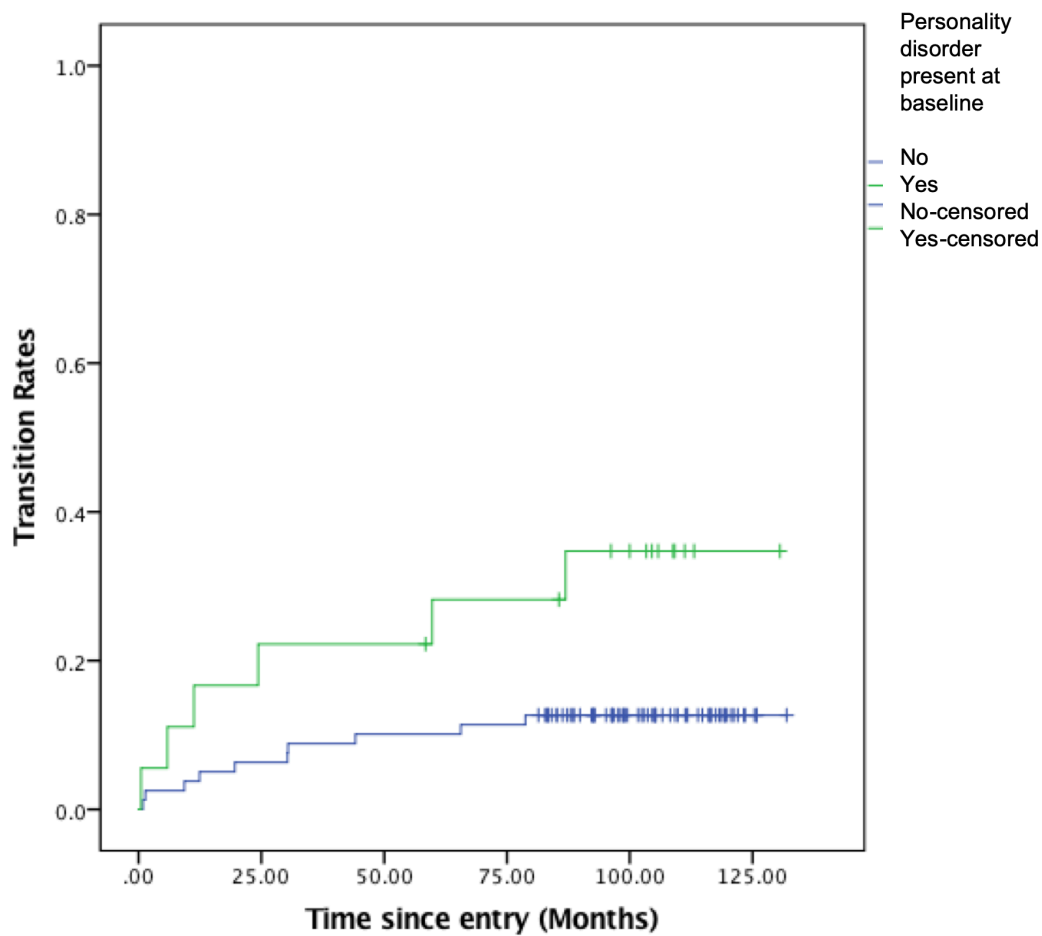


Figure 24: Transition rates comparing those with a PD to those without

Personality disorders and presence of non-psychotic mental disorders.

A chi-square test for independence indicated that participants who had a PD were significantly more likely to also have a mood disorder at follow-up, with a moderate effect, $\chi^2(1, n = 97) = 9.43, p = .002, \phi = .31$, (Pallant, 2011). See Table 14 for counts of PDs against mood disorders.

Table 14

<i>Count of mood disorders and personality disorders at follow-up (current)</i>			
Personality Disorder at Follow-up	Mood Disorder present (current at follow-up)		Total
	No	Yes	
No	60 (89.6%)	19 (63.3%)	79
Yes	7 (10.4%)	11(36.7%)	18
Total	67 (100%)	30 (100%)	97

Similar to mood disorder, those with a PD were also more likely to have an anxiety disorder at follow-up, $\chi^2(1, n= 97) = 4.81, p = .03, \phi = .22$. This effect was small but statistically significant. See Table 15 for a cross-tabulation of PD and anxiety disorders.

Table 15

<i>Count of anxiety and personality disorders at follow-up (current)</i>			
Personality Disorder at Follow-up	Anxiety Disorder present (current at follow-up)		Total
	No	Yes	
No	60 (87.0%)	19 (67.9%)	79
Yes	9 (13.0%)	9 (32.1%)	18
Total	69 (100%)	28 (100%)	97

There was also a significant association between having PD and an SUD current at follow-up, $\chi^2(1, n=97) = 12.53, p = .00, \phi = .36$. This effect was moderate. See Table 16 for a cross-tabulation of PDs and SUDS.

Table 16

<i>Count of SUDs and personality disorders at follow-up (current)</i>			
Personality Disorder at Follow-up	SUD present (current at follow-up)		Total
	No	Yes	
No	71 (80.0%)	8 (50.0%)	79
Yes	10 (12.3%)	8 (50.0%)	18
Total	81	16	97

10.3 Trajectory of Mental Disorders and Presence of Personality Disorders

The sample of participants with PDs was too small to run any further investigations into presence of PDs and trajectory of the major mental disorder groups.

10.4 Personality Disorder and Functional Outcomes.

An independent samples t-test was conducted to compare the SOFAS scores for those who had a PD at follow-up compared to those who did not. There was a significant difference, with those being diagnosed with a PD more likely to have a lower SOFAS score ($M = 57.50, SD = 10.95$) compared to those who did not ($M = 70.30, SD = 11.93$); $t(93) = 4.20, p < .01$. The magnitude in the difference of the means (mean difference = 12.80, 95% CI: 6.49 to 19.12) was large ($\eta^2 = 0.23$). This was similar for GAF scores, with those having a personality disorder also achieving a lower mean ($M = 57.19, SD = 10.32$) than those who did not ($M = 70.62, SD = 10.81$);

$t(93) = 4.71, p < .001$ (Figure 25). The effect size was also large ($\eta^2 = .19$) (Cohen, 1988).

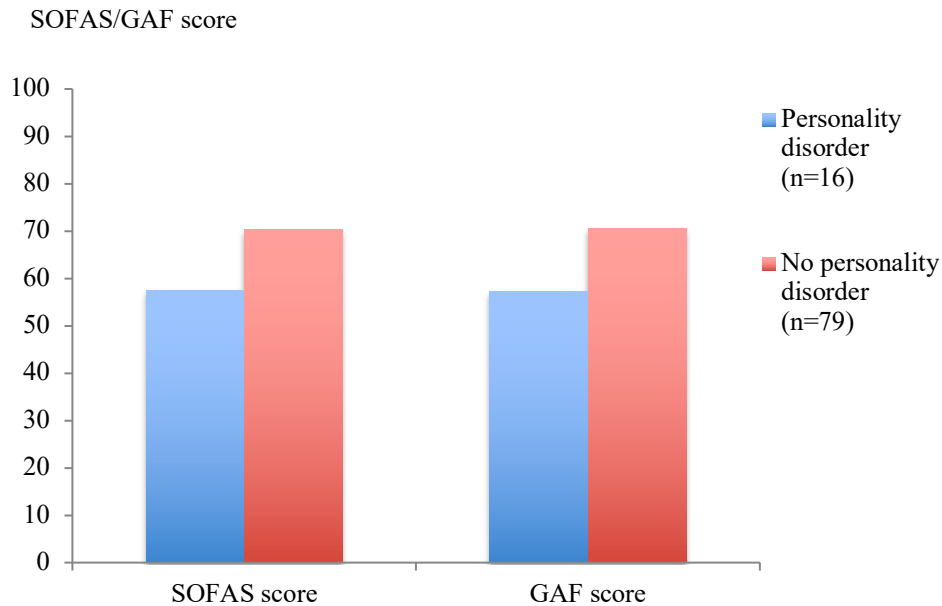


Figure 25: Personality disorders and functional outcomes – SOFAS and GAF mean scores at follow-up

10.4.1 Personality disorders and functional outcomes - quality of life

(QLS).

An independent samples t-test revealed that those diagnosed with a PD had significantly lower QLS scores at follow up ($M = 76, n = 13$), compared to those who did not ($M = 97, n = 77$), $t(88) = 3.05, p < .001$, with a medium effect size, $r = .12$ (Cohen, 1988). Median QLS scores against presence of PD are illustrated in Figure 26.

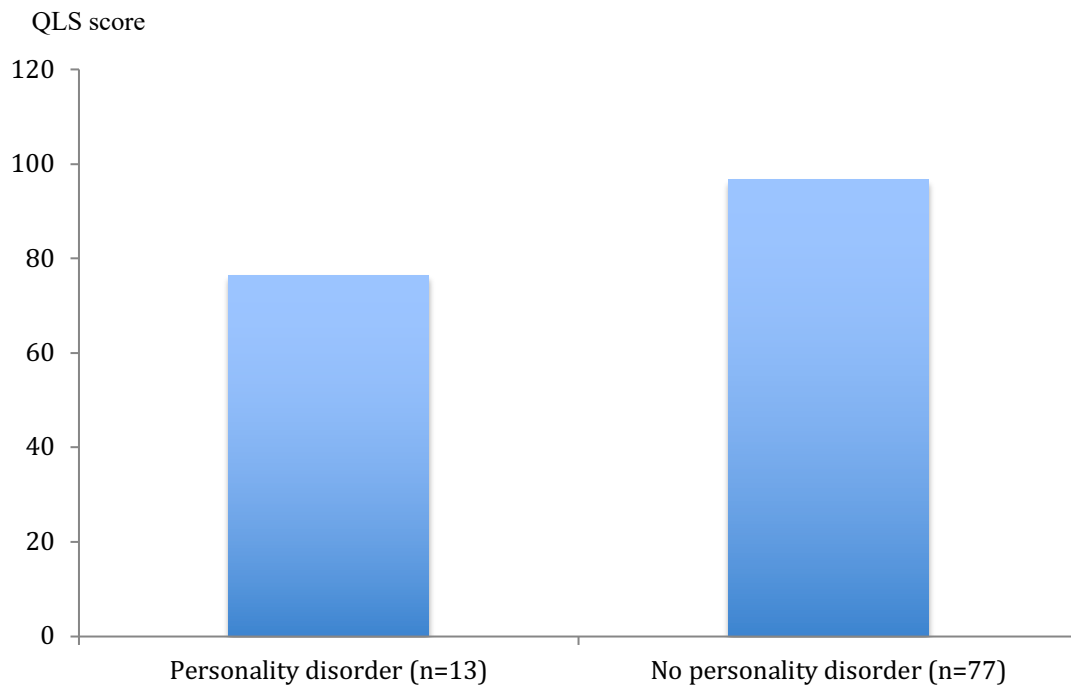


Figure 26: Personality disorders and functional outcomes QLS median scores at follow-up

10.5 Summary of Chapter 10: Personality Disorders

Nineteen percent of the sample was diagnosed with a PD at follow-up assessment, the most prevalent being borderline PD, followed by antisocial PD. Presence of PD was associated with transition to psychosis, however, caution is warranted given the small sample size. Interpretation of this relationship is also complicated by not having the exact timing of onset of the PD.

Statistically significant associations between PDs and mental disorders were also found, in particular mood disorder, anxiety disorder and SUD. Personality disorders were also related to poorer functional outcomes, as measured by GAF, SOFAS and QLS.

Chapter 11

Discussion

There were two main foci to this research project: examination of the relationship between UHR criteria and non-psychotic mental disorders and the relationship of UHR criteria to personality disorders. In particular, information about the relationship between the course of non-psychotic disorders in UHR participants was used to test the pluripotent model of UHR status (i.e. whether UHR is a specific risk state for psychosis outcomes, as opposed to a range of disorders). The findings pertaining to these research questions will be presented briefly in this section, with a more detailed discussion to follow.

11.1 Summary of Main Findings

The study demonstrated that mental disorders proved to be a significant problem for young people at UHR for psychosis both at clinic entry and over the longer term. Only 13% of participants did not have a non-psychotic mental disorder diagnosis at baseline. The number of participants without a mental disorder increased by follow-up with almost half of participants (48.8%) not meeting criteria for a diagnosis. Mood disorders remained the most prevalent, followed by anxiety disorders and SUDs at both time points.

Looking at the trajectories of these disorders over time, only 6% of the entire sample never met criteria for a mental disorder. The most common experience for participants was to have a continuous non-psychotic mental disorder (52%); of those who entered the clinic with a mental disorder, a substantial portion would continue to experience clinically significant symptoms. Over a third of those entering PACE at baseline with a non-psychotic mental disorder (43.2%) would go on to remit from their disorder over time. A similar proportion would have an incident disorder (41.6%). This demonstrates that while there were positive clinical outcomes for a

good portion of participants, the majority were experiencing significant non-psychotic mental health problems at follow-up. This lends credence to the idea that the UHR outcomes are pluripotent for a range of mental disorders and not specific for psychosis.

Some baseline clinical variables were found to predict trajectories of non-psychotic mental disorders. A model containing BPRS total and baseline treatment group was found to be a significant predictor of any continuous mental disorder. Baseline treatment group and vulnerability group were predictive of any incident disorder. No significant predictors of remission of mental disorder were found. The link between baseline predictors and those who never had a mental disorder could not be explored, as this participant group was too small.

The association between trajectory of mental disorder and functional outcomes was also explored. As predicted, participants with a continuous mental disorder had the worst functional outcomes, as measured by SOFAS, GAF and QLS. Functional outcomes were best for those who had remitted, and these participants were doing significantly better than those with a continuous disorder. Functioning of remitted participants was similar to those who had never had a disorder. Incident participants had lower functioning than the remitted and never groups, but higher than participants with a continuous disorder. Similar patterns were generally observed for specific disorder groups, with some variation – this is discussed in Section 11.6.

This research project also explored the relationship between mental disorders and transition to psychosis. Since baseline assessment, 16.3% of participants transitioned. The mean time to transition was 23.9 months. There was a higher transition rate for those who had a mental disorder at baseline compared to those who did not, but this difference was not statistically significant. The same pattern of transition was observed when looking at mood and anxiety disorders at baseline. Transition rates for people with and without a SUD at baseline were almost identical.

Persistence of UHR status was examined, with the finding that 72% of the sample were experiencing APS at follow-up, with 30% of these meeting UHR criteria based on ratings of severity and frequency. The majority of participants (66%) had remitted from UHR status by time of follow up²³. Presence of a non-psychotic mental disorder at baseline was not found to predict UHR status at follow-up. However, UHR status at follow-up was shown to be associated with presence of mental disorder at follow up. This is consistent with the notion that APS may be an indicator of severity of and risk for general psychopathology (Heinze et al., 2018). Specific disorder groups were also investigated and will be discussed in Section 11.5.

The second part of this research project involved investigation of personality disorders in UHR. Fifty-six percent of the sample completed a personality disorder assessment at follow-up. Of this group, 19% were diagnosed with a PD. The most common were borderline, antisocial and paranoid PDs. Personality disorders were associated with transition to psychosis, i.e. those who had a PD at follow up assessment were more likely to have transitioned to psychosis. In addition, people with a PD were more likely to have a mood, anxiety disorder or SUD at follow-up as well as poorer functional outcomes.

11.2 Description of the Sample

Comprehensive follow-up data were collected for the majority of the participants, with 72.7% participants being assessed. Neither age, sex, mental disorder or treatment type at baseline were related to participation rates at follow-up. The data collected for this research project are therefore likely to be reflective of the PACE cohort.

²³ APS that met UHR criteria rated high enough on severity and/or frequency measures, but not high enough to meet full psychosis threshold. See Appendix B13 for a more detailed description.

The majority of participants (68%) had been employed either full-time or part-time during the two years before follow-up assessment. Of those who had been unemployed during this time, 70% attributed their unemployment to difficulties with their mental health. This reflects that mental illness continues to present a burden for a substantial portion of people over the longer-term.

11.3 Type and Prevalence of Mental Disorders at Baseline and Follow-Up

Very few participants in the sample (13%) did not have a mental disorder diagnosis at baseline. This proportion is similar, though lower, to the hypothesis of fewer than a quarter being free from mental disorders, based on Addington et al.'s (2017) findings from their CHR participants. This prevalence is also similar to rates reported by Beck et al. (2019) in their meta-analysis. Given that the majority of this sample was in their teens at baseline, these findings are in line with the evidence that mental health disorders tend to begin at a young age (Kessler et al., 2007). Findings from this study add to evidence that patients coming into high risk for psychosis clinics experience clinically significant non-psychotic disorders in addition to attenuated psychotic symptoms.

Baseline data revealed that mood disorders were the most prevalent (79%), followed by anxiety disorders (48%) and substance use/dependence problems (18%). These results are consistent with our prediction based on findings by Beck et al., (2019). Similar patterns of disorders at baseline entry have been reported by several other studies of high risk participants, which show that over half of help-seeking UHR/CHR patients initially present with major depressive or anxiety disorders (Addington et al., 2017; Fusar-Poli et al., 2014; Salokangas et al., 2012; Velthorst et al., 2012; Yung et al., 2004).

A high prevalence of mental disorders is to be expected at baseline, given the help-seeking nature of the sample. Rates of mental disorders were higher at follow-up

than would be expected in the general population (Australian Bureau of Statistics, 2007; 2015). However, around half (48.8%) of participants did not have a mental disorder at follow-up, an improvement on baseline rates.

Mood disorders at follow-up still constituted the most prevalent diagnosis, with 32% meeting criteria, followed by 26% with anxiety disorders and 15% with SUDs. Rates for individual disorders were lower than those reported at baseline. A similar pattern was observed when disorders that developed and resolved between assessments were included in prevalence rates, with a decrease in anxiety and mood disorders still being maintained. However, when diagnoses from between assessments were included, an increase in SUDs was found. The majority of these SUDs were resolved by follow-up assessment, with only 15% still meeting criteria. These rates of disorder groups are higher than what would be expected in the general population. Australian Bureau of Statistics data report prevalence rates of around 6% for mood disorders, 14% for anxiety disorders and 5% for SUDs (Australian Bureau of Statistics, 2007²⁴).

Other studies reported somewhat higher rates at follow-up. For example, a rate of 38% for anxiety disorders was reported by Addington et al. (2017), though they reported the same prevalence of depressive disorders (32%). The follow-up by Addington et al. (2017) was performed only 24 months after baseline, compared to the mean follow-up time of 8.8 years in the current study, so this longer follow-up time may have allowed time for some disorders to resolve. Beck et al. (2019) also found that longer follow-up duration was associated with higher remission rates of mental disorders. Additional time, as well as a slightly older sample (mean age = 27 years for our sample, mean age = 19 years for Addington et al. [2017]) may have had a positive effect on reduction of anxiety disorder rates in our sample. Decrease in

²⁴ The year 2007 was the last date at which the ABS assessed a variety of mental health conditions in the general population using a validated diagnostic tool.

prevalence of mental health disorders has been shown to be associated with increasing age, with highest prevalence rates being reported in the 18-24 age bracket (Alonso et al., 2004).

11.3.1 Effects of treatment on presence of mental disorders.

Treatment type at entry to PACE was not related to presence of mental disorders at follow-up. Over the time in between assessment and follow-up, a similar proportion of participants received psychotherapy (29.7%) as those who did not (39%). The same pattern was seen for use of medication taken for mental health purposes (35.5% took medication and 32% did not). Data were missing for the other third of our sample. Participants who met criteria for a mental disorder at follow-up were more likely to have engaged in psychotherapy in between assessments, especially if they had a mood or anxiety disorder. This is not surprising given that the participants would be likely to continue seeking help if they were experiencing persistent mental health problems.

Participants with mental disorders at follow-up were also more likely to have taken medication and received psychotherapy for their mental health condition, particularly those who had been diagnosed with an anxiety or mood disorder. However, no association was found for SUD and receiving psychotherapy/medication. A lack of association with SUD seems to be consistent over treatment type, with greater variation in results for anxiety and mood disorders. It could be that treatment was sought less often in the presence of SUD. This is consistent with findings from the National Survey of Mental Health and Wellbeing (NSMHWB) which found lower rates of help-seeking amongst substance use disorders compared to anxiety and affective disorders (Reavley, Cvetkovski, Jorm, & Lubman, 2010).

11.4 Course and Stability of Baseline Non-Psychotic Mental Disorders

Only 6% of UHR participants remained free from psychiatric disorders over both the baseline and follow-up periods. However, a significant number of non-psychotic mental disorders (43.2%) had remitted by follow-up. The current study also found that many of the sample experienced continuous mental disorders (52%). Over a third of the sample (41.6%) developed incident non-psychotic mental disorders that were not present at baseline. These rates are mostly consistent with the current study's hypotheses based on Lin et al. (2015), who found that 7.3% of UHR participants remained diagnosis free over the follow-up period (between 2-14 years), 51.6% had a continuous disorder and 37.5% had an incident disorder.

The results of the current study differ from Lin et al. (2015) for remitted disorders, with Lin et al. finding a rate of 26% compared to the current study's higher rate of 43.2%. The Lin et al. (2015) follow-up covered a shorter period (mean of 6.9 years), whereas the current study's follow-up period averaged 8.8 years, perhaps allowing more time for participants to somewhat resolve psychiatric issues present at baseline. The Lin et al. (2015) follow-up was also over-represented by females, which could have created a bias towards higher rates of mood disorders and contributed to lower reports of remitted disorders, given that mood disorders were most prevalent in our sample, and being female is associated with higher risk for psychiatric disorder (Australian Bureau of Statistics, 2007). In the general population, women aged 16 to 24 had nearly twice the prevalence of mood disorders compared with men in the same age group, and nearly twice the prevalence of anxiety disorders compared to men in the 25-34 age bracket (Australian Bureau of Statistics, 2007). The current study's sample was more evenly split between males and females and this might provide some account for the higher rates of remission.

Rutigliano et al. (2016) also found high rates of persistent or recurrent mental disorders in the UHR population (61.5%). Their rate of incident disorders was higher

than the rate reported by the current study and by Lin et al. (2015), with 45.4% of their sample having developed a new disorder over the 6-year follow-up period. Their follow-up rate was low (48%), resulting in a smaller sample size of 74 participants from a baseline of 154. However, the authors did not find any significant differences between participants who dropped out and those who didn't, with the exception that participants who dropped out tended to be male. Addington et al. (2017) found a rate of around 30% for continuous disorders, which is lower than findings from the current study and Lin et al. (2015).

These findings reflect a heterogeneous sample with varied outcomes, with one consistent theme—though individual rates may vary, UHR patients continue to experience mental health conditions over the longer term, irrespective of whether they transition to psychosis. It was common even for those without a non-psychotic disorder at baseline to develop a non-psychotic disorder over time. Thus, UHR criteria appear to be useful for capturing young people at risk for developing a range of non-psychotic disorders, not just psychotic disorders. These findings are in line with Beck et al.'s (2019) observation that over the long-term, UHR individuals do not achieve full clinical remission. Beck et al.'s (2019) systematic review observed a lack of long-term trajectory data in the relevant literature, concluding that further research is required. The current study attempted to address this gap and the current findings further highlight a need to better understand the risk factors associated with development and trajectory of non-psychotic disorder in UHR samples, in addition to psychotic disorders.

11.4.1 Trajectory of mood disorder, anxiety and substance use disorder over time.

Current findings revealed that the disorder that was most continuous for participants was mood disorder (45%). This disorder also had the highest rates of remission, but given its prevalence at baseline, this is not surprising. The disorder

most likely to never be diagnosed in participants was SUD, with 64% never developing it. However, this disorder was also the highest incident disorder, with 21% of participants developing it post baseline. The tendency for self-medication in help-seeking samples may explain this finding (Harris & Edlund, 2005; Patton et al., 2002). This compares similarly to 22% of Lin et al.'s (2015) sample meeting diagnostic criteria for incident SUD.

However, Lin et al.'s (2015) rates of incident mood and anxiety disorders were higher, with rates of 32.8% and 29.5%, respectively, contrasting with rates of 14% for incident mood disorders and 15% for incident anxiety disorders in the current study. Only our rates of continuous mood disorder (45%) were similar to Lin et al. (2015) (54%), with continuous anxiety disorder (14% in the current study compared to 41%) and SUD rates also being lower in the current study (10% compared to 52%). The differences in our prevalence compared to Lin et al. (2015) could be the result of a couple of factors. As previously mentioned, the current study's longer average follow-up period may have allowed for more time for disorders to resolve (Beck et al., 2019). The current study also saw lower transition rates and a declining transition rate has been observed from earlier PACE cohorts to later ones (Hartmann et al., 2016; Yung et al., 2007). Cohorts have also differed in terms of clinical characteristics, with later cohorts showing fewer APS and less severe clinical characteristics²⁵ (Hartmann et al., 2016). Greater awareness of youth mental health also appears to have resulted in faster referral to PACE and shorter duration of untreated symptoms (Wiltink, Velthorst, Nelson, McGorry, & Yung, 2015), which is known to have a positive effect on psychotic outcomes (Marshall et al., 2005) and possibly outcomes of other non-psychotic disorders.

²⁵ See Section 11.5.1 for further discussion on changes across UHR cohorts

11.5 Persistence of UHR Status Over Time

The current study revealed that 30% of the sample still met UHR criteria with APS at follow up. This compares similarly to 28% reported by Lin et al. (2012). Persistence of APS in these participants could be reflective of an ongoing risk for psychosis, given that the prodromal period has been known to last up to ten years (Nelson et al., 2013). It is also possible that APS are a feature of severe non-psychotic disorders, as indicated in studies linking sub-threshold psychotic symptoms to concurrent depressive, anxiety and phobic symptoms (Breetvelt et al., 2010; Nelson & Yung, 2009). If APS are occurring in relation to other non-psychotic disorders, then these would be expected to resolve along with the resolution of the non-psychotic disorder. The current study did find an association between APS and non-psychotic mental disorders, which supports this possibility (discussed in more detail below).

11.5.1 Relationship between mental disorders at baseline and UHR status at follow-up.

While the current study did not find that mental disorders at baseline were able to predict UHR status at follow-up, it did reveal a significant association between presence of mental disorders at follow-up and UHR status. People who still met UHR criteria at follow-up were more likely to report presence of a mental disorder within the last month than those who did not meet UHR criteria. This finding is consistent with Lin et al.'s (2012) report of a significant association between participants with APS and presence of non-psychotic mental disorders at follow-up. The finding is also consistent with a long-term follow-up study of UHR participants showing that those with APS at follow-up had significantly higher levels of depression, anxiety and general psychopathology than those whose APS had resolved (Cropley et al., 2016). This lends support to the possibility that APS are not necessarily present as a result of a prodrome or increased risk for psychosis but can also occur as a result of severe

non-psychotic mental health disorders. While continuing APS could also be indicative of schizotypal PD, this was only diagnosed in one person in the current sample (PDs discussed further in section 11.9). This indicates that UHR criteria are capturing a wider range of emerging psychopathologies than just psychosis. This is consistent with the clinical staging model proposed by McGorry et al. (2006), whereby a number of trajectories and outcomes are possible from the initial nonspecific symptoms (reduction in functioning, depressed and anxious mood, experience of distress) that cause young people to seek help.

With regard to specific disorders, the current study revealed significant associations between UHR status at follow-up and SUD and anxiety disorders, with those currently meeting UHR criteria being more likely to also have a comorbid SUD or anxiety disorder. However, association between UHR status and mood disorders approached but did not reach significance. This compares with Lin et al.'s (2012) findings of an association between UHR status and mood disorder. In their sample, 65.5% of participants continuing UHR symptoms also experienced a concurrent mood disorder. In contrast, they did not find an association between UHR status and anxiety and substance use disorders. The difference in our findings for mood disorder could be explained by Lin et al.'s (2015) larger sample of participants with mood disorders at follow up (their $n=110$ mood disorders compared to the current study's $n=40$). This however, does not explain why the current study found an association between SUD and anxiety disorders and UHR status, when Lin et al.'s (2015) sample was similarly large for anxiety disorders and SUD.

One possibility for the current study's association between SUD and UHR status could be that SUDs have been found to have a later onset than other mental disorders (Turner, Mota, Bolten, & Sareen, 2018) and the current sample had a longer mean follow-up time than that of Lin et al. (2015). A meta-analytic review of substance use found that substance use more commonly developed following

depressive disorders and dysthymia (Turner et al., 2018). The explanation for this was that people, especially younger people, were self-medicating for other mental health problems using substances. Review of longitudinal studies further found that people who reported self-medication for mood symptoms were more likely to develop an SUD (Turner et al., 2018). This however, does not explain why the current study found a link between UHR status and anxiety disorders which are known to precede depressive disorders (Lamers et al., 2010) and thus would not be likely to have had later onset. It could, however, be that if APS persist over a longer period of time, they will be more likely to be associated with anxiety and SUD problems, whereas an association with mood disorder could appear over a shorter period.

While the specific disorders that show significant association with UHR status vary between the current study and Lin et al. (2015), results indicate that there may be a link that warrants further investigation with a larger sample of participants. Previous research has indicated a connection between experience of APS and other severe non-psychotic mental health disorders. The presence of APS has been indicated in disorders such as posttraumatic stress disorder (Sareen, Cox, Goodwin, & Asmundson, 2005) and personality disorders like borderline PD (Slotema et al., 2012).

Research into APS and other mental and personality disorders in the UHR population is scarce (personality disorders will be explored further in section 11.9). However, research from community samples suggests that psychotic symptoms may occur in instances of depression (Varghese et al., 2011) and anxiety (Varghese et al., 2011; Wigman et al., 2012). Wigman et al. (2012) found that 27% of participants ($n=3021$) in their community sample had concurrent psychotic symptoms with anxiety or depressive disorders. This compares with 14% of their sample who had anxiety or depressive disorders without psychotic symptoms. Presence of psychotic symptoms in these disorders was correlated with younger age and being male.

Presence of psychotic symptoms within anxiety/depressive disorders led to poorer outcomes over their ten-year follow-up period. Purcell et al. (2015) found that 38% of youth attending a general mental health service reported APS that were likely to meet UHR criteria. Other studies have found that psychotic symptoms have been linked to affective dysregulation (van Rossum et al., 2011; Varghese et al., 2011).

While it is possible that participants could be in a continued prodromal state, the high proportion of attenuated psychotic symptoms in affective disorders in these studies compared to the low prevalence of psychotic disorders in the population makes this explanation seem unlikely. The high proportion of individuals meeting criteria for affective disorders on entry to high risk for psychosis services in addition to their APS, and relatively low transition rate also indicates that at the very least an interaction between affective dysregulation and reality distortion that does not necessarily lead to full blown psychosis (Addington et al., 2017; Velthorst et al., 2009). In fact, sub-threshold psychotic symptoms have been shown to predict a more general range of non-psychotic disorders (Rössler & Angst, 2011). Shared genetic liabilities between psychotic and affective disorders have also been established in population-based studies (Lichtenstein et al., 2009; Weiser, van Os, & Davidson, 2005). The persistent UHR status in the current study being associated with presence of non-psychotic disorders contributes evidence to pluripotential outcomes for people meeting UHR criteria on entry to service. Sub-threshold psychotic symptoms may not only indicate psychosis outcomes but be indicative of broader non-psychotic psychopathology. Consistent with this argument, UHR criteria have been shown to capture individuals with common mental disorders, such as mood, anxiety and SUD, with additional sub-threshold psychotic symptoms (McGorry & Nelson, 2016; Phillips et al., 2005; Rosen et al., 2006).

It may be that recent high-risk cohorts are demonstrating more pluripotent outcomes than earlier high risk cohorts. There has been a decline in transition rates

over the years, from initial rates of around 40% (Yung et al., 2003) to 15% in more recent years (Nelson et al., 2013; Simon & Umbricht, 2010), indicating a possible change in the specificity of psychosis prediction of UHR criteria. A “dilution effect”, whereby people are identified as meeting UHR criteria but have lower actual risk (Yung et al., 2007) in UHR samples has been argued, perhaps resulting in an increase of “false-positives” (Nelson et al., 2013; Wiltink et al., 2015). This has been suggested to possibly result from changed screening processes and referrals, including a shift of referrals from health professionals to non-professionals (eg family members, school staff) (Wiltink et al., 2015; Hartmann et al., 2016). Other factors that have been suggested to contribute to the dilution effect include the broadening of clinical services and screening processes, for example screening help-seeking young people without a family history of psychosis (Hartmann et al., 2016). However, it is difficult to directly assess the individual contribution of these factors to transition risk.

It may be speculated that UHR cohorts may have become more pluripotent in their outcomes due to changing UHR cohort characteristics over time, with the earlier ones showing a higher proportion of APS, a higher proportion of trait risk factor and greater conceptual disorganisation (formal thought disorder). Hartman et al. (2016) suggested that earlier and recent UHR cohorts could possibly be distinguished by two causal pathways to psychosis: affective and cognitive endophenotypes. The cognitive endophenotype is characterised by negative symptoms, a more insidious onset and chronic course (Myin-Germeys & van Os, 2007). Hartmann et al., (2016) have speculated that earlier UHR cohorts were more representative of this endophenotype, as they showed higher levels of disorganised symptoms. Alternatively, the affective causal pathway is characterised by positive symptoms, greater affective symptoms, acute onset and episodic course with greater response to neuroleptic treatment (Myin-Germeys & van Os, 2007), consistent with the greater proportion of affective disorders seen in later cohorts (Hartmann et al., 2016; Lin et al., 2015). It may be that

UHR individuals of the affective endophenotype in the later cohorts are more likely to have pluripotential outcomes. However, more research on presence of affective symptoms and long-term trajectories in UHR cohorts is needed in order to examine this hypothesis.

Investigation of intake clinical characteristics showed that while earlier cohorts have differed from later cohorts, this does not fully account for the reduction in transition rates (Hartmann et al., 2016). Therefore, it is difficult to determine with certainty if UHR outcomes have become more pluripotent over time, with further investigation into long-term trajectories needed. However, given the observation of persistent non-psychotic mental illness in the UHR population, the current study offers some evidence that instead of representing a specific psychosis-risk state, UHR status could possibly represent sub-groups of various levels of risk and trajectories and that these patterns of risk and trajectories have changed over time, alongside changing UHR populations.

Van Os and Guloksuz (2017) argue that psychotic experiences are a marker for the severity of mental disorders rather than specifically indicating an at-risk state for psychotic disorders. They posit that psychosis may develop because of the severity of psychopathology being experienced by an individual, and that this psychopathology may be expressed across a variety of dimensions (eg, affective, cognitive, psychotic experiences). Thus, the baseline severity of multidimensional symptoms is what predicts the outcome, rather than a binary risk criterion for psychosis per se. This could explain the association the current study found between APS and mental disorders. Psychopathology in general may result from a single, common underlying psychopathology dimension, termed the “p-factor” by Caspi et al. (2014), rather than particular factors indicating risk for specific disorders. In this model, a person scoring high on the p-factor would be more liable to develop any type of mental disorder. This could also explain why research has thus far failed to reveal

biomarkers, causes and treatments specific to particular disorders, and why APS do not necessarily predict the onset of psychosis.

Van Os and Guloksuz (2017) tried to demonstrate that UHR criteria were not useful as a tool for prediction of psychosis. They claimed that a focus on prevention of transition to psychosis had resulted in no demonstrable effect on functional outcomes, citing a meta-analysis of high-risk intervention studies (Schmidt et al., 2015). However, the same meta-analysis also showed a significant improvement in reduction of transition to psychosis. Other studies have also shown improvement in functional outcomes as a result of intervention in UHR samples (McGorry et al., 2017; Stafford, Jackson, Mayo-Wilson, Morrison, & Kendall, 2013; van der Gaag et al., 2013). Therefore, consideration of the UHR state, and attention to the outcome of transition certainly still has its place in treatment of young people meeting both UHR criteria and presenting with a range of symptoms and disorders, irrespective of what the relationship between UHR status and APS and psychotic or non-psychotic disorders may be.

Polari et al. (2018) identified seventeen clinical trajectories in a UHR sample, exemplifying the pluripotential outcomes for people meeting UHR criteria. Within these trajectories, they classified participants as having favourable outcomes (43%) if they remitted from their UHR state and unfavourable (57%) if participants relapsed back into UHR status after recovery, sustained UHR status, had recurrence of UHR status after remission and before recovery or transitioned to psychosis. This type of conceptualisation has broader implications for care than the traditional transition to psychosis approach. Further, the role of these trajectories in non-psychotic disorders could help us to understand the development of these disorders, and non-transition outcomes.

The diverse array of outcomes for young people experiencing distress and APS indicates the need for a broader risk identification approach. The recognition of

this need prompted the development of the Clinical High at Risk Mental State (CHARMS) approach. This approach is based on the Clinical Staging Model but incorporates a range of different outcome trajectories (McGorry et al., 2018). This model will be further discussed in section 11.11.

11.6 Baseline Clinical Predictors of Trajectories of Non-Psychotic Mental Disorders

This research aim was approached in an exploratory manner, due to a lack of research on baseline clinical predictors of trajectories of mental disorders in a UHR population. Investigation of remission of a mental disorder revealed no significant associations with baseline clinical variables, but significant predictive relationships were found for continuous and incident mental disorders.

The current study found that there was a small but significant effect of having a high score on Brief Psychiatric Rating Scale (BPRS), being part of the baseline treatment group and having a continuous mental disorder. Given that a high score on BPRS indicates poor general symptomatology, it is not surprising that this was linked to experience of a continuous mental disorder. It was initially surprising to find that participants in the baseline treatment group (intervention condition) were twice as likely to experience a continuous mental disorder than if they'd been in the treatment as usual group. However, the current sample is a subset of that examined by Phillips et al. (2009) who observed a significantly higher proportion of DSM-IV diagnoses in the intervention group than their control/treatment as usual group at baseline. They also noted significantly higher scores on general psychopathology measures in the intervention group compared to treatment as usual. This indicates that the intervention group was more unwell at baseline, and therefore perhaps more likely to go on to experience a continuous disorder. In order to test whether the intervention group in the current study was similarly unwell, a post-hoc test on mental disorder was run on

the baseline treatment group (Appendix B12). This showed that the intervention group at baseline had a significantly higher proportion of mental disorders than the treatment as usual group.

The baseline treatment group was also implicated in prediction of incident mental disorder. The results of this study show that participants were more likely to develop an incident disorder if they were part of the treatment (intervention) and intake groups at baseline. Given that the baseline treatment group was more unwell at baseline, it is not surprising that they were more likely to develop a new mental disorder over time. All research participants received standard care in the PACE clinics at baseline. However, some participants consented to an intervention trial (all were offered the opportunity to participate). It might be that there were some characteristics that made some people more likely to consent than others, for example, being more unwell at the time the treatment was offered. Phillips et al. (2009) suggested that the group of young people who had not agreed to intervention might have been less likely to do so because they were less symptomatic and unwilling to try what might be seen as a serious treatment approach (using medication). They also suggested that recruiting clinicians might have unintentionally been more encouraging to young people who were more symptomatic to consent to the intervention. Given the specificity of this group to the current study (i.e. that the baseline treatment group happened to be more unwell than the control group and therefore we cannot draw conclusions about the efficacy of the treatment itself), more work is required to test how generalizable the current findings are to other samples.

More interestingly, those who were in the vulnerability group were 3.5 times more likely to experience an incident disorder over the long-term. The vulnerability intake group describes participants who met UHR criteria due to a genetic link (first degree relative diagnosed with a psychotic disorder) or had a diagnosis of schizotypal PD, and either a recent decline in functioning or chronic low functioning. This finding

is consistent with the genetic links in familial high risk studies found to predict later onset of psychotic disorders (Faraone, Taylor, & Tsuang, 2002; Sullivan, 2005), bipolar disorders (Egeland et al., 2012; Goes, 2016) and depressive disorders in non-UHR samples (Weissman et al., 2016). Decreased functioning, particularly in the psychosocial domain, has also been linked to development of bipolar disorder in non-UHR samples (Hafemen et al., 2017).

The combination of a genetic liability and decreased functioning in the vulnerability intake criteria has already been linked to prediction of psychosis, hence its inclusion as one the UHR intake criteria (Yung & McGorry, 1996). However, results from the current study, and similarities to bipolar prediction baseline variables (Hafemen et al., 2017) indicate that the vulnerability intake criteria may not be specific to psychosis outcomes. This adds insight into the debate around whether staging models and associated criteria of risk should be developed across diagnostic categories (Hartmann, Nelson, Ratheen, Treen & McGorry; 2018). Research into prediction of disorders has thus far tended to be disorder specific but a recent scoping review revealed similarities in baseline predictors across psychosis, bipolar and depressive disorders, including familial risk and psychosocial functioning as examples of common predictors (Hartmann et al., 2018). The ability of the vulnerability intake group in the current study to predict non-psychotic outcome trajectories indicates that this could be a promising tool for prediction of trans-diagnostic outcomes.

Baseline clinical predictors of trajectories of non-psychotic disorder in UHR samples are virtually un-researched. The only study that these results may compare to is Lin et al.'s (2015) exploration of whether clinical symptoms, IQ, age and Global Assessment of Functioning (GAF) scores at baseline were predictive of incident, continuous disorder or remission. Lin et al. (2015) found these variables to be poor predictors of outcome overall. However, they did find that lower scores on the Scale

for Assessment of Negative Symptoms (SANS) and not meeting Brief Limited Intermittent Psychotic Symptoms (BLIPS) was associated with incidence of any disorder, and recurrence of any disorder, respectively. Lin et al. (2015) postulated that meeting BLIPS and its relationship to lower recurrence of disorder indicates that BLIPS might be specifically capturing individuals at risk of a psychotic disorder, rather than a broader range of non-psychotic disorders. The current study did not find this particular relationship, though BLIPS was included in our list of baseline predictors.

Lin et al.'s (2015) lower score on the SANS and association with recurrent disorder is somewhat similar to the current study's findings of high scores on BPRS predicting continuous non-psychotic disorder. While the SANS measures negative symptoms, and BPRS covers a range of more general psychopathology, high scores on both scales could be indicative of symptoms that are associated with depression. Lin et al. (2015) had similarly postulated that depressive symptoms could have been interpreted as negative symptoms and rated on the SANS. An alternative explanation might be however, that these individuals are still in the prodrome of psychotic disorder, as high depressive/negative scores may also be associated specifically with the prodrome rather than be indicative of disorder level depression (Yung & McGorry, 1996; Hafner et al., 2005).

Lin et al. (2015) found that being female was predictive of a persistent or recurrent mood disorder, and incident anxiety disorder. The current study examined the potential relationship of sex to trajectory of mental disorder, but this resulted in a correlation that was too low to warrant inclusion in regression analysis. The sample of the current study was also not large enough to investigate baseline clinical predictors of individual disorder groups, so we could not investigate an association between sex, mood and anxiety disorder. However, this would be interesting to investigate with a larger sample size, given the relationship of female sex with higher 12 month

prevalence of mood and anxiety disorder in the general population (Australian Bureau of Statistics, 2007).

While the current results differ in some respects to Lin et al. (2015), a similarity is that the variables we examined, though significant, were not overall strong predictors of outcome. This differs from baseline predictors of psychosis, in which certain baseline symptoms are reliably able to predict development of psychosis. This suggests that different baseline clinical variables are needed to predict outcome of non-psychotic disorders rather than those used for prediction of psychotic outcomes. Further investigation of psychosocial predictors is suggested, based on the significance of the vulnerability intake criteria, which encompasses functioning, to predict incidence of mental disorder. Environmental and neurocognitive baseline variables could also be included. A link between aggregated environmental factors has been linked to psychosis in a familial high risk (non-UHR) sample (Padmanabhan, Shah, Tandon, & Keshavan, 2017), and environmental factors have been implicated in other psychosis studies (van Os et al., 2010). Though findings pertaining to environmental factors and transition to psychosis have been mixed, further investigation of the impact of environmental factors on non-psychotic outcomes provides an opportunity for exploration. Neurocognitive factors have also been linked to the development of psychosis (Lin et al., 2011), though have not received attention within UHR samples in the context of non-psychotic outcomes.

These findings draw attention to the need to design studies that incorporate pluripotential outcomes, rather than focus on psychosis as the main outcome, such as the CHARMS study, referred to in section 11.11. Such studies will include baseline variables that can be examined with non-psychotic outcomes specifically in mind (Fowler et al., 2010) and should be expanded beyond clinical variables to include environmental and neurocognitive measures.

11.7 Trajectory of Mental Disorder and Functional Outcomes at Follow-Up

Looking at functioning of the overall group of participants, a significant improvement was seen over time. This type of improvement was not found by Rutigliano et al. (2016) in their non-transitioned sample of high risk participants. In contrast, Addington et al. (2011) showed improvement in functioning as measured by the Global Assessment of Functioning over time, similar to the current study. Their baseline scores had a mean of 52 (compared to the current study's mean of 57), and increased to a mean of 65 at follow up (compared to the current study's mean of 69). Polari et al. (2018) also observed an improvement in functioning in the majority (91%) of their UHR participants after a 12-month follow-up (Polari et al., 2018). However, Polari et al. (2018) considered an improvement in functioning to be an increase of just five points on the Social and Occupational Functioning Assessment Scale. They described the majority of their participants to have had 'unfavourable' outcomes when transition to psychosis and presence of clinical symptoms at outcome was also taken into account.

In the current study, the potential relationship between functioning and trajectory of mental disorders was investigated with specific focus on mood, anxiety and SUDs.²⁶ Mood disorders with a continuous trajectory were associated with significantly lower Global Assessment of Functioning scores at follow-up, consistent with findings from Rutigliano et al. (2016) that continuous mental disorders predicted poorest functioning. Highest scores were seen for those who had never had a mood disorder or had remitted from one, with Global Assessment of Functioning and Social

²⁶ Functioning and mental disorders overall was not explored as one participant may have experienced a variety of trajectories if they had multiple diagnoses. For example, they could have had both an incident depressive disorder and a continuous anxiety disorder—when every possible combination was considered, groupings were too small to investigate a relationship with GAF.

and Occupational Functioning Assessment scores for both of these measures being similar. Incident disorders were associated with higher functioning than continuous disorders, though not as high as remitted or never groups. Lowest scores were also provided for quality of life by those with a continuous disorder. Prolonged illness course may have a larger impact on social functioning compared to an incident disorder because disruptions to social and support networks, as well as occupational, have longer to take root —when someone initially develops a disorder, they may still have their social and occupational networks intact.

Quality of life was rated highest for those who had a remitted mood disorder, scoring higher than those who had never had a mood disorder. The difference between never and remitted mood disorder for quality of life was more pronounced than for Global Assessment of Functioning/Social and Occupational Functioning Assessment scores. It could be that participants who remitted from a mood disorder actively compare their current healthy state to previous troubles associated with mood disorder when contemplating their quality of life. This may not be reflected by the Global Assessment of Functioning and Social and Occupational Functioning Assessment scales where a single score is assigned, rather than using a combination of ratings on individual items to encompass the different areas of functioning, and thus might miss out on some of the more detailed aspects of functioning. In contrast, the Quality of Life Scale asks participants to describe a variety of areas from their life in some depth, and thus may provide a richer picture of functioning. In previous studies, mood disorders have been associated with impaired performance of social roles (Glazer, van Os, & Thewissen, 1981). Fusar-Poli et al. (2012) also found that having a comorbid diagnosis of depression and/or anxiety was associated with impaired global functioning in a UHR sample (Fusar-Poli et al., 2012).

No significant differences were seen in functioning for different anxiety disorder trajectories. However, scores for Global Assessment of Functioning and

Social and Occupational Functioning Assessment Scale were still highest for those who had either remitted or never had an anxiety disorder and were lowest for incident disorders. No significant differences were observed when quality of life was examined either. Quality of life scores for continuous and incident trajectories were very similar, compared to Global Assessment of Functioning/Social and Occupational Functioning Assessment, which had lower average scores for incident disorders. It could be that this is because the Global Assessment of Functioning and Social and Occupational Functioning Assessment scales take clinical symptoms into account and may indicate that participants with an incident anxiety disorder experienced even more difficulty adjusting to new clinical symptoms compared to those who had a continuous anxiety disorder, and may have adapted over time. When considering quality of life functioning in terms of managing social and occupational roles, those who had an incident disorder rated their quality of life more similarly to those who had a continuous disorder, with both mean scores being lower than desirable.

Trajectory of SUD was significantly associated with functioning, revealing that those with an incident SUD were worse off than those whom had never had an SUD as measured by Global Assessment of Functioning/Social and Occupational Functioning Assessment Scale and Quality of Life Scale. Scores on functioning for remitted SUD were higher than those seen in the never group for Global Assessment of Functioning/Social and Occupational Functioning assessment and similar to the never group in quality of life scores, but it is likely that the small sample size for the remitted group ($n=4$) led to them not being identified as statistically different. Overall, the picture for the SUD group showed poorest functioning for continuous and incident disorder groups. Though participants with a continuous SUD had surprisingly high scores on the Quality of Life Scale, their scores were closer to scores for the never and remitted groups, compared to the incident group. This contrasts with other evidence showing that long-term use is associated with cognitive difficulties (Tapert,

Granholm, Leedy, & Brown, 2002) and poor psychosocial outcomes such as homelessness (Caton et al., 1994), victimization (Goodman et al., 2001), violence (Swartz et al., 1988), as well as poor treatment response and suicide (Bartels, Drake, & McHugo, 1992; Drake et al., 2006). The group of people with a continuous SUD in this study was small however ($n=11$), so unlikely to be representative of other long-term substance abusers.

Overall, similar patterns between disorders were seen, with poorest scores on functioning for the incident and continuous groups in general. Results indicated that participants who had experienced a mental disorder were likely to resume functioning a level similar to their never counterparts, a promising outcome for people with current disorders to look towards.

Comorbid mental disorders have previously been shown to be associated with functioning in UHR participants at baseline (Fusar-Poli et al., 2014). These results suggest that UHR participants are suffering from mental health problems that are disabling and distressing in their own right, irrespective of whether or not the individual progresses to frank psychosis. Even though scores in functioning overall improved when mental disorders were not considered, it appears mental disorders may play a role in maintenance of poorer functional outcomes.

The current study found a further association between UHR status and functional outcomes. Participants meeting UHR criteria at follow-up performed more poorly across all our functional measures compared to participants who remitted from UHR status. This is consistent with Fusar-Poli et al.'s (2015) study, which found that high risk individuals suffer from poorer outcomes than healthy controls, irrespective of whether they had a mental disorder. They argued that high risk status involves impairment of functioning which is inherently distressing and this is not attributable solely to the presence of comorbid mental disorders. It would be interesting to further examine these findings by including UHR status as a factor in trajectory of mental

disorder and outcomes, but unfortunately, the sample from the current study was underpowered to do this. Thus far, Rutigliano et al. (2016) is the only other study that has examined trajectory of disorders and functional outcomes, also finding that continuous or recurrent mental disorders were associated with poorer outcomes.

Results indicate continuing poor functional outcome and continued mental disorders in the presence of UHR for a substantial portion of individuals at follow-up. The presence of mental disorders may hinder coping responses by UHR individuals and further impair their social and occupational function. This reinforces the need to focus on outcomes other than transition in UHR samples, a point of view that is becoming increasingly accepted in the field (Yung, 2017; Yung, Nelson, Thompson, & Wood, 2010).

11.8 Relationship Between Mental disorders at Baseline and Transition to Psychosis

The current study's transition rate of 16% is lower than the 18%-36% generally reported (Fusar-Poli et al., 2012) but is consistent with the declining transition rates seen in more recent cohorts, with rates of around 15% (Fusar-Poli et al., 2014; Hartmann et al., 2016).

There was no significant association between having a non-psychotic mental disorder at baseline and transition to psychosis though those without a mental disorder did appear to have a higher transition rate. However only five of the 17 transitioned cases did not have a mental disorder, so this group may have been too small for differences to be detected. When only the individual disorder groups of mood, anxiety and SUD were examined, a similar lack of association was found, though participants with a mood disorder appeared to have the same higher rate of transition as the overall mental disorder group.

These findings partly support the findings of Salokangas et al. (2012), who found that the strongest association with transition was for non-psychotic bipolar disorders. The current study could not investigate a separate bipolar group as this was too small and participants with non-psychotic bipolar disorder were therefore included in the overall group of mood disorders. The present study's rate of transition for mood disorders was higher than for other disorder groups, though this difference was not significant, whereas it was significant in the Salokangas et al. (2012) study. This could be explained by the fact that the current study only had 28 transitions, compared to Salokangas et al. (2012) who had 43 transitions, which would have enabled more power to distinguish differences between groups. Salokangas et al. (2012) also did not find an association for all mental diagnoses together. However, they did find a negative association between anxiety disorder and transition to psychosis, something the current study did not replicate.

Historically, the presence of anxiety and depression have been shown to be characteristic of the beginning of a psychosis prodrome (Häfner, Löffler, Maurer, Hambrecht, & Heiden, 1999) but evidence around whether the presence of these disorders can actually predict transition is controversial. In the NAPLS cohort ($n=291$) (Cannon et al., 2008) an association between history of drug abuse and transition was found, but this was not replicated in the current study, nor by Salokangas et al. (2012). Cannon et al. (2008) failed to find an association between mood or anxiety disorder and transition, consistent with the current study but conflicting with findings from Salokangas et al. (2012). Fusar-Poli et al. (2014) followed up a cohort of 509 CHR patients over an average of 3.65 years and did not find any association between presence of transition and mental disorders, specifically depression, anxiety and substance use, despite high rates of these disorders (71%) (Fusar-Poli et al., 2014).

One possible explanation for the heterogeneous relationships of mental disorders and transition is that the assumption that non-psychotic disorders and psychotic disorders exist as separate constructs that can impact on each other is flawed. As an alternative view, Fusar-Poli et al. (2014) discuss whether anxiety, depression, negative and positive and cognitive symptoms could all occur on a continuum. The disorders we see are instead a reflection of the particular combination of these symptoms (eg schizophrenia could represent the combination of high positive, negative and cognitive symptoms), rather than distinct entities. If so, it could be more difficult to disentangle the relationships between disorders, especially if symptoms are shared across disorders and there is no clear distinction between constructs (Figure 27). However, perhaps considering particular collections of symptoms could assist with predicting a later combination of other symptoms. In this view, disorders are not separate constructs that have independent impacts on each other, but rather, collections of signs and symptoms that may interact and change over time, termed Network Theory by some researchers (Isvoranu et al., 2016; van Borkulo et al., 2015). Tracking the fluctuations of these collections of symptoms over time may assist with understanding how they may develop and change. This would be a more complex and nuanced approach than tracking change at the disorder level, and may unveil more subtle patterns that current categorical study designs are unable to.

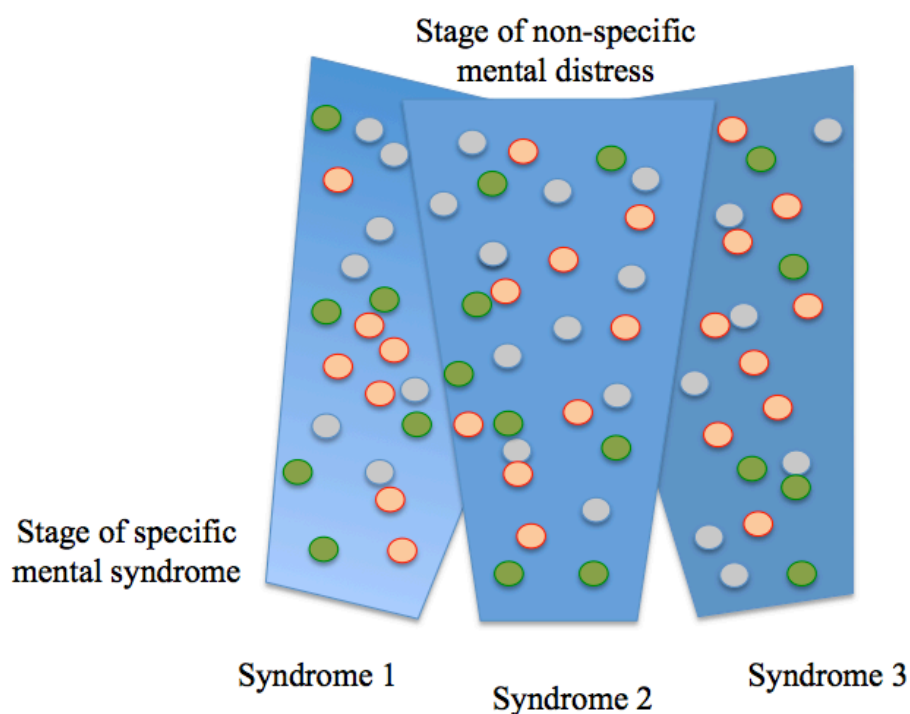


Figure 27: Continuum of symptoms evolving into specific disorders over time
(adapted from Fusar-Poli et al., 2014)

Booji et al. (2018) recently published a protocol paper on a study that will attempt to investigate fluctuation of collections of symptoms (including clinical and functional) in participants at a variety of stages of risk for psychosis. This will be one of the first studies to apply network theory to the investigation of development of psychosis, though some studies have attempted this with other psychiatric disorders (Isvoranu et al., 2016; van Borkulo et al., 2015). Though still in its infancy in psychiatry, a network approach may offer a better understanding of how psychiatric disorders develop and evolve over time, allowing for both trans-diagnostic and clinical staging of illness. Given that disorders appear to share features that exist on a continuum, it is not surprising that previous studies using traditional categorical

approaches have been unable to find a clear model of prediction of transition to psychosis.

There is also the problem of the different sampling strategies used by differing high risk cohorts, with most studies describing their selection strategies in a way that is too vague to be precisely replicated (Fusar-Poli et al., 2014). For example, some studies do not describe referral sources, nor how or what information is disseminated to these sources to encourage their referrals. The resulting variation of both transition rates and prevalence of comorbidities makes it difficult to compare the potential relationships between mental disorders and transition to psychosis between studies.

The current evidence relating non-psychotic mental disorders to transition to psychosis is mixed and contradictory. Further clarification could be gleaned if longitudinal studies better controlled for comorbid symptoms associated with the UHR state compared to being disorders in their own right. The current study attempted to do this by only including participants with mood, anxiety and substance use disorders that reached DSM-IV diagnostic threshold. However, our sample may have been underpowered to detect possible relationships. It is also possible that if the UHR state has pluripotent outcomes, that individuals entering the study with mental disorders and sub-threshold psychotic symptoms, were never truly at risk of developing a psychotic disorder, but rather their symptoms were associated with an increased risk or persistence of other non-psychotic disorders. Psychotic experiences occur in common mental disorders, such as anxiety, mood disorders and SUD as well as psychotic disorders (Van Os & Guloksuz, 2017). Thus, given that symptoms appear to exist on a continuum and across diagnostic categories, a relationship between these non-psychotic mental disorders at baseline and an outcome of transition to psychosis would be difficult to detect, if it does exist.

11.9 Personality Disorders at Follow-Up

11.9.1 Prevalence of personality disorders at follow-up.

Like Rosen et al. (2006) and Schulze-Lutter et al. (2012), the current study observed borderline PD as being the most common PD. However, the current study's rate of 19% for overall presence of PD was substantially lower than the 48% found by Rosen et al. (2006) and 46% by Schulze-Lutter et al. (2012). Differences may be due to several factors: timing of assessment, age of participants, and including recruitment of participants discussed below.

Rosen et al.'s (2006) study was cross-sectional, with participants being assessed at clinic entry. When patients first enter clinics, they are more likely to be distressed when seeking help. At this time of distress, symptoms associated with or interpreted as PD are more likely to be present than at a 6-12 year follow-up. While PDs are defined to be stable and enduring entities (APA, 2013), it can be difficult to separate personality from mental state at a single time point of measurement (Tyrer et al., 2015). Schulze-Lutter et al. (2012) also assessed their sample for PD at baseline entry, when participants were more likely to be experiencing distress. Assessment of PD at clinic entry has been shown to be vulnerable to artificial inflation due to symptoms of mental disorders, which is often the trigger for presentation to a health service (Tyrer et al., 2007). The differences in time of assessment could explain our lower rates of PD, as participants were assessed at follow-up in the current study and were thus more likely to have resolved some of the clinical issues that initially brought them into the PACE clinic. The lower rates of mental disorders observed at follow-up also supports this idea.

The mean age in the current sample was older than that of Rosen et al. (2006) and Schulze-Lutter (2012), which could also explain lower rates of PD. Evidence exists that the severity and expression of the PD changes over time, rather than

remaining stable (Lilienfeld, 2005; Seivewright, Tyrer, & Johnson, 2002). Cohen, Crawford, Johnson, & Kasen et al. (2005) found that PD symptoms declined over time from the ages of 9 to 27. Shea et al. (2002) found that PD symptoms steadily improved over a five-year period, with fewer than half their sample retaining their initial PD diagnosis after one to two years at follow-up assessment (mean age of 32.8 years). Rosen et al.'s (2006) prodromal sample had a much lower mean age of 18.4 years, compared with the mean age of 26.8 years for the current study. Given that we only assessed PD at follow-up when our patients were older, this could contribute to our lower rates of PD. The sample of participants assessed by Schultze-Lutter et al. (2012) was also younger with a mean age of 24 years, though this is much closer to the age in the current study. However, their use of self-report measures could have contributed to the effect of higher rates of disorders. Self-report measures are known to inflate diagnostic rates and be less robust than structured interviews (Tyrer et al., 2007; Widiger & Samuel, 2005). The sample used by Schultze-Lutter et al. (2012) was also not directly comparable with the current sample as the rates reported by that study included both those who had transitioned to psychosis and those who hadn't.

Rates of borderline PD in particular have been shown to decline greatly during the transition to adulthood (Skodol et al., 2005; Zanarini, Frankenburg, Hennen, Reich, & Silk, 2005). Given that borderline PD was the most common disorder in our sample and in the samples of Rosen et al. (2006) and Schultze-Lutter et al. (2012), a decline in this disorder would have affected overall rates of PDs observed.

In general, much variability exists in PD rates reported in different samples, which could be reflective of the difficulty of accurately assessing PDs (Tyrer et al., 2015). It was this difficulty that brought about the introduction of a continuous model of assessment in Section III (Emerging Measures and Models) of DSM-5 (APA, 2013). Further to this, as PD tends to be comorbid with other psychiatric disorders (Tyrer et al., 2015), prominent symptoms from the other disorder may mask the

presence of a PD (Tyrer, 2015) and contribute to variation in rates of PDs across studies.

11.9.2 Borderline PD in UHR.

Despite the differences in overall rates of PD both the current study as well as Rosen et al. (20006) and Schultze-Lutter et al. (2012) reported that borderline PD was the most common PD. There has been recent re-emergence of interest in the psychosis research community in the links between psychosis and borderline PD in particular. This interest was triggered by both the high co-occurrence of psychotic symptoms in the context of borderline PD (Glaser et al., 2010) and a growing understanding that the phenomenology of psychotic symptoms in borderline PD might not differ greatly from those experienced by people with psychotic disorders.

While borderline PD had originated as a disorder that described someone on the 'borderline' of psychosis, modern psychology established borderline PD as a separate entity to psychosis (Stern, 1938). However, Niemantsverdriet et al. (2017) demonstrated that hallucinations experienced by people with borderline PD more closely resemble hallucinations experienced by people with a full-blown psychotic disorder than previously thought (Association, 2013). The current perception of borderline PD hallucinations is that they are transient and occur only in times of stress (Association, 2013). In contrast, Niemantsverdriet et al. (2017) showed that almost half (43%) of their borderline PD sample experienced regular hallucinations that were not confined to experience of stress.

The demarcation between borderline PD and schizophrenia spectrum disorders may not be as clear as current nosology assumes (Zandersen, 2019). Both historical and current research indicates similarities between these two disorders, with borderline personality considered a variant of schizophrenia in pre-DSM-III literature (Zandersen & Parnas, 2018). In particular, the borderline criteria of identity disturbance and feelings of emptiness were originally attributed to the schizophrenia

spectrum (Zandersen & Parnas, 2018). Zanderson (2019) found that out of a sample of 30 people with BPD, 66.7% were also diagnosed (using DSM-5) with a schizophrenia spectrum disorder. Zanderson, Henriksen & Parnas (2018) go so far as to claim that it is virtually impossible to distinguish borderline PD from schizophrenia disorders (Zandersen, Henriksen, & Parnas, 2018).

There have been reports from other studies that hallucinations in borderline PD are also experienced as severe as those experienced by patients with schizophrenia (Kingdon et al., 2010; Pearse, 2014; Slotema et al., 2012). Some studies reveal that auditory verbal hallucinations in particular are phenomenologically indistinguishable in borderline PD from those experienced by people with schizophrenia (Kingdon et al., 2010; Pearse et al., 2014; Slotema et al., 2012; Tschoeke et al., 2014). People with borderline PD have reported experiencing greater distress and negative affect from their auditory verbal hallucinations than people with schizophrenia (Kingdon et al., 2010).

Borderline PD has previously been found to also have an association with affective disorders (Barnow et al., 2010; Skodol et al., 2011) and affective psychoses (Keshavan et al., 2005), though not to non-affective psychoses (Kendler et al., 1993; Rodriguez Solano & Chavez, 2000). The high prevalence in the current study's UHR sample, as well as other UHR samples provides evidence for some link between borderline PD and UHR criteria, which are aimed at picking up people at risk of all psychotic disorders, both affective and non-affective. It may be that UHR criteria are picking up people with attenuated psychotic symptoms that will only be expressed in the context of borderline PD, and not experience transition to a full-blown psychotic disorder. Given the wide range of outcomes, it follows that UHR criteria are capturing a broad range of psychiatric vulnerabilities, and not those specific to psychosis. The link between psychotic symptoms and borderline PD should not be ignored and should be factored into treatment of UHR individuals.

11.9.3 Relationship between personality disorders and transition to psychosis.

The present study found that presence of PDs was significantly related to transition to psychosis. Our findings contrast with those of Schultze-Lutter et al. (2012), who found that prevalence of PD was not associated with transition to psychosis. The only link they found to transition was for schizoid personality accentuations, and this link was described as weak. Rates of PDs did not differ between the people who converted to psychosis and who did not. However, Schultze-Lutter et al.'s use of a self-report questionnaire may have weakened their accuracy of diagnosis of PDs (Tyrer et al., 2007; Widiger & Samuel, 2005).

Sevilla-Llewellyn-Jones et al. (2018) examined a broad range of PDs and found no relationship to transition to psychosis. However, their transition rate was only 5%, limiting their power to explore this potential relationship. Thompson et al. (2012) and Ryan et al. (2015) both examined the link between BPD and transition to psychosis specifically and also found no association.

In general, research examining personality traits and later development of schizophrenia or psychosis is lacking (Simonsen & Newton-Howes, 2018). The median rate of around 40% prevalence of PD in schizophrenia does suggest some relationship between personality pathology and schizophrenia (Newton-Howes et al., 2008). It has been suggested that personality could represent vulnerability for development of psychosis or have an influencing effect on its development (Cuesta et al., 2002). An alternative explanation could be that there is some underlying trait(s) that cause personality disorder and psychosis to develop independently, rather the PD itself being a risk factor for later development of a psychotic mental disorder.

Rosen et al. (2006) had a similar rate of PDs in their control sample to their at-risk sample, which may indicate that PD is linked to severe psychiatric disorders in general, rather than psychotic disorders ($n=15/29$, 52%). Their control sample was

help seeking but did not meet the criteria for "prodrome" due to absence of attenuated psychotic symptoms.

Even though PDs may be as frequent in other non-psychotic psychiatric disorders, their high prevalence in individuals at risk of psychosis indicates that PDs should still be addressed during early intervention in UHR individuals. However, PDs are rarely given focus during early intervention, with the exception of schizotypal PD (Schultze-Lutter et al., 2012). Considering that PD affects the course of symptoms in an individual, it is unfortunate that this is often not considered to be a focus of treatment, even if a definitive link to transition has not been established in the literature.

11.9.4 Personality disorders and presence of non-psychotic mental disorders.

The results of this study show that participants with a PD were significantly more likely to also have a mood, anxiety disorder or SUD at follow up than those who did not have a personality disorder. This is consistent with the observation that around 40% of psychiatric samples have PDs comorbid with mental disorders (Newton-Howes et al., 2010).

There is a dearth of research into the relationship between PD and mental disorders in the UHR population and the psychosis population (Simonsen & Newton-Howes, 2018). However, previous research with the general clinical population has shown that if a person is diagnosed with a PD, they are also more likely to have a comorbid mental disorder (Newton-Howes et al., 2014). Beckwith, Moran and Reilly (2014) found comorbid PD prevalence estimates of between 40% and 92% in psychiatric outpatient settings. Stevenson et al. (2011) found that presence of PD was associated with increased rates of relapse of mental disorders and readmission to hospital. PD also been shown to be associated with subsequent development of depression and substance misuse (Conrad et al., 2017).

Most research of PDs in UHR has focused on prevalence rates, without a deeper investigation of the potential relationships between PD, mental disorders and UHR status. One of the few studies investigating the relationship between PD and UHR with mental disorders more deeply, proposed that particular personality profiles could play a role in comorbid mental disorders in high risk individuals (Sevilla-Llewellyn-Jones et al., 2018). The authors found that depressive personality traits (measured by the Millon Multiaxial Inventory) were associated with anxiety symptoms. They also found that borderline and paranoid traits were associated with depressive symptoms (Millon et al., 1997). This is consistent with research conducted with the non-UHR population, which shows associations between PD and anxiety disorders (Friborg, Martinussen, Kaiser, Overgard, & Rosenvinge, 2013) and depressive disorders (Hirschfeld, 1999).

Personality disorder rates of 40% to 60% in patients with bipolar and other severe psychiatric disorders further suggest that PD comorbidity may not be a problem specific to psychosis (Keown et al., 2002; Loftus & Jaeger, 2006; Mantere et al., 2006). Given the variability of PD rates in various psychiatric populations, and the variation within particular types of PDs (Newton-Howes et al., 2010), one may expect such variation between the current study and that of Rosen et al. (2006). Further to this, rates of PD vary widely in the schizophrenia population, with prevalence ranging from 4.5% to 100% (Newton-Howes et al., 2008). As stated previously, less work has been done looking at PDs specifically with the UHR population.

Tyrer (2007) has argued that personality dysfunction should be described more as a diathesis, than a disorder. Thus, people with personality dysfunction would be vulnerable towards developing other psychiatric disorders in response to certain situations. The expression of personality dysfunction would then seem to be in abeyance when the individual's environmental adjustment is optimal. According to this model, the very presence of a mental disorder would be the trigger for expression

of personality dysfunction, which would explain the 100% rate of mental disorders present in those diagnosed with PD (Tyrer, 2007). Tyrer's research was not conducted within the UHR population, however, the idea of a personality diathesis could be relevant in the UHR setting, given the pluripotentiality of outcomes for UHR individuals over time.

An alternative hypothesis is that there is an underlying characteristic that increases the likelihood of both mental and personality disorders developing. This could be an underlying genetic vulnerability, or perhaps even a personality diathesis that predisposes someone to problems that fall under both mental and personality disorder diagnostic criteria. A large Danish population study found that comorbidity in any psychiatric disorder was pervasive, and that these rates of comorbidity also persisted over the longer term (Plana-Ripoll et al., 2019). These patterns of comorbidity could reflect a latent shared risk, a hypothesis supported by findings of common genetic variants across different psychiatric illnesses (Huang et al., 2010). It could be that UHR criteria picks up individuals with a pre-disposition to experiencing psychiatric issues in general. However, this question cannot be answered with prevalence data.

11.9.5 Trajectory of mental disorders and presence of personality disorders.

Previous research with non-UHR psychiatric samples has indicated that the presence of PDs has a detrimental impact on the course of clinical symptoms and functional outcomes of individuals (Stevenson et al., 2011). There is so far no research on the trajectory of mental disorders and their relationship to personality disorders in the UHR population. Unfortunately, the sample of participants diagnosed with a PD in the current sample was too small for any further investigation into the possible links between these types of these disorders to be explored. However, previous research has shown that PDs are related to worse outcomes in mental

disorders. For example, Stevenson et al. (2011) found that PD was associated with increase relapse of mental disorders and had a negative impact on overall symptomatic outcomes. Conrad et al. (2017) found that people with PD at baseline were more likely to have incident mood or substance use problems later on. In the schizophrenia context, presence of PD is considered as a predictor of chronic course (Newton-Howes et al., 2007). Given this evidence, it is reasonable to speculate that the presence of PD would be associated with continuous and incident mental disorders in the UHR population. This potential relationship would be worth exploring with a larger sample of UHR participants.

11.9.6 Personality disorders and functional outcomes.

Participants with a personality disorder were more likely to have poorer functional outcomes than those who did not have a personality disorder. There is a lack of research into functional outcomes of people meeting UHR status and personality disorder diagnostic criteria. However, these findings are consistent with research into comorbid PD in the schizophrenia population. Bahorik & Eack (2010) found that former in-patients with schizophrenia ($n=100$) or schizoaffective disorder ($n=42$) and comorbid borderline PD had significantly less improvement in global functioning one year after being released from hospital (Bahorik et al., 2010). Patients with comorbid PD also experienced higher rates of depression and anxiety symptoms. Personality traits have been shown to be strong predictors of outcome in general psychiatric populations (Hasin et al., 2011; Tyrer, Seivewright, & Johnson, 2004). This is especially true of response to treatment of psychological disorders (Telch, Granholm, Leddy, & Brown, 2010). However, personality and personality disorders are often neglected in treatment, as clinicians tend to focus on the acute clinical symptoms that patients present with (Tyrer, Mitchard, Methuen, & Ranger, 2003).

The current study provides further support of the detrimental impact of PDs on outcome within the UHR population. Participants persistently scored significantly

lower on the Global Assessment of Functioning Scale, the Social and Occupational Functioning Assessment Scale and the Quality of Life Scale than those without a PD. Social function can be particularly affected, as personality disorder reflects an inability to form and sustain satisfactory relationships with other people (Tyrer et al., 2015). Given that relationships are a core component of the assessments used in the current study, it is not surprising that those with PDs had poorer outcomes (Seivewright, Tyrer, & Johnson, 2004). Longitudinal studies with non-UHR psychiatric samples have shown that even if behavioural items leading to a PD diagnosis improve over time, social dysfunction still persists (Seivewright et al., 2004; Skodol et al., 2005). Seivewright et al. (2004) found the domains of close and family relationships, and stress in completing tasks to be particularly affected even after a follow-up period of 12 years ($n=210$).

Given the evidence for negative impacts of comorbid PD in non-UHR psychiatric populations, it is surprising that this area remains under-researched within the UHR field. Even research of the impacts of PD on outcome in schizophrenia is lacking (Newton-Howes, Tyrer, Moore, & Nur, 2007), though what does exist suggests that comorbid PD worsens outcomes (Bahorik et al., 2010). Research of comorbid PD in the schizophrenia population has tended to focus on antisocial PD, showing increased violence from patients affected (Dingemans, Lenior, & Linszen, 1998) and some research on borderline PD (Bahorik et al., 2010). The findings from the current study indicate a need for further research of all PDs into their effect on long-term outcomes in the UHR population.

11.10 Strengths and Limitations of This Study

The findings from this study must be considered within the context of its strengths and limitations. The strengths of this study include a long-term follow-up with high follow-up rates, and a relatively large sample from one site. This study is

one of the few to investigate PD outcomes in UHR cohorts and contributes to a small but growing number of studies that investigate long-term outcomes for UHR participants beyond transition. The current study had a lower than desirable sample size for PD data, as only 56% completed the full SCID-IV-II interview at follow-up. However, missing data in longitudinal studies is common, due to participant attrition (Anstey & Hofer, 2004). The findings between PD and other outcomes (transition, functional and clinical) were significant despite the small sample size and have imperative implications for treatment. However, it is important that the current study's findings be replicated with a larger sample size as the current study was unable to investigate breakdowns between individual groups of PD. Further to this, the relatively low proportion of transitions limited further sub-categorisation of PDs and mental disorders to more fully investigate their link to psychosis.

11.10.1 Strengths and limitations of measures used.

Given that this was one of the larger samples followed up to date, this contributed to the literature on the course of non-psychotic disorders in the UHR population. Despite baseline assessment being conducted between 6 and 12 years ago, a strength was that the almost exactly the same measures were conducted at follow-up, allowing for direct comparisons of change over time to be made. The only exceptions included the Social and Occupational Functioning Assessment Scale and the SCID-IV-II being administered only at follow-up. Participant scores from the Social and Occupational Functioning Assessment Scale were, however, supplemented by scores from the Global Assessment of Functioning and Quality of Life Scale, which were administered at both baseline and follow-up time points. Diagnoses of PD were made by asking participants to describe personality characteristics that they had had since they were teenagers, though bias in recall may have influenced these results. However, previous authors have suggested that PD assessment at intake assessment is not reliable, due to traits being overshadowed by acute mental symptoms (Tyrer et al.,

2007). Therefore, assessment at follow-up may actually have provided more reliable results. It would have been beneficial to compare personality disorder diagnostic results from baseline assessment to follow-up as this would have contributed to understanding the (in)stability of PDs and the role of PDs in transition and other long-term outcomes.

Mental and personality disorder diagnoses were made using the DSM-IV-I and DSM-IV-II. Interviews were administered by trained interviewers and these measures represent the gold standard for clinical diagnosis (Furukawa, Kessler, Slade, & Andrews, 2003; Widiger & Samuel, 2005). Semi-structured interviews have been shown to be more reliable than the use of self-report measures (Tyrer et al., 2007; Widiger & Samuel, 2005). The remainder of measures used in this study have been shown to have good reliability and validity (see Methodology for details).

More specialised measures for social, role and occupational functioning in the context of UHR would have been desirable. The Quality of Life Scale (Heinrichs et al., 1984) was developed to be used in the context of schizophrenia. This measurement may thus not be appropriate for a long-term follow-up of UHR participants who may not demonstrate as severe pathology as an individual diagnosed with schizophrenia. The Global Assessment of Functioning and Social and Occupational Functioning Assessment Scale were also developed to assess functioning in a psychiatric population and may therefore not be appropriate for a UHR population exhibiting a mix of psychiatric morbidity and healthy respondents. However, there is a lack of functioning instruments designed to be used within the UHR context, with the exception of the Global Functioning: Social and Role Scale (Cornblatt et al., 2007), which was developed after the baseline assessments had been completed for the current study.

The duration of assessments was around 3-4 hours, which could have proven to be tiring for some participants. Participants who struggled with the lengthy duration

were invited back to complete their assessment on a different day. Most participants persisted to complete their assessments during one visit, however, some participants did not complete the entire battery of measurements. The main measurements affected were the SCID-II interviews with, as mentioned above, only 56% completing, and the CAARMS, with 59% missing.

11.10.2 Issues around time to follow-up.

Participants were assessed over an 18-month follow-up period but their baseline intake ranged over a much longer period (up to around 4 years). Time to follow-up from baseline ranged from 6.8 years to 12.1 years. This variation in time to follow-up may have affected analyses of trajectory of mental disorder, and thus this should be considered. However, analyses related to transition were unlikely to be affected as the minimum time to follow-up was 6.8 years. This minimised the possibility of false positives due to "lead time effect", whereby referrals to specialised services are made earlier in the illness course due to increased community awareness of the at-risk state (Nelson et al., 2013; Yung et al., 2006). Furthermore, most transitions have been shown to occur within two years (Fusar-Poli et al., 2009).

Given the lengthy period of baseline recruitment, participant characteristics may vary depending on when they entered PACE. Growing awareness of UHR criteria has been associated with an increase in referrals (Yung et al., 2007), which may also have contributed to a change in participant characteristics over time and potentially a reduction in transition rates (Hartmann et al., 2016).

Difference in treatment allocations may also have affected outcomes. The intake period for the Ris-Aus-9 study spanned 2000-2006 (covering the current study's intake period), with participants receiving a combination of cognitive or supportive therapy with placebo or risperidone for 12 months. Participants receiving intervention or treatment as usual may have differed in outcome. While treatment at

PACE was controlled for, treatments outside of PACE were beyond the control of this study. This represents a limitation of this naturalistic study.

11.10.3 Statistical limitations.

Some of the limitations of this study were statistical in nature. Due to the relatively low transition rate, the current study lacked power to conduct further analysis within diagnostic groups (for example by PD). Lack of power due to low transition rates is a common problem in recent UHR studies (McGorry et al., 2017; Morrison et al., 2012).

The current study was also underpowered to investigate the trajectory of mental disorders and presence of PDs. Given that there was a significant association between presence of mental disorders and PDs, despite the low numbers of PDs in the sample, it would have been beneficial to further investigate these potential relationships in a larger sample. The presence of PD may be linked to continuous or incident trajectories of mental disorder, and if so, would present an important target for intervention. However, the current study was unable to provide insight into this idea, as it was underpowered for the analysis required.

11.11 Research Implications

This study set out to investigate the long-term outcomes of UHR participants and test whether these outcomes were pluripotential or specific to psychosis. This study also sought to understand the relevance of outcomes to mental disorders at entry and their trajectory over time in the UHR population. Findings from this study indicate that young people at UHR for psychosis have a number of long-term outcomes other than transition to psychosis: Around one third of individuals will not transition but will continue to experience sub-threshold psychotic symptoms and experience long term clinical and functional impairment; Just under one-third of individuals will continue to experience non-psychotic clinical and functional impairment but their APS will resolve; Some individuals will resolve from both APS

and other clinical symptoms and improve functionally (just over a third). Of these individuals, some will have developed incident non-psychotic mental disorders (around 40%) and a similar proportion will have remitted from their non-psychotic mental disorders, with half experiencing a continuous course of non-psychotic mental disorder. Some individuals may also have remitted from one non-psychotic mental disorder and developed a new disorder, however change of disorder type was not explored in this thesis.

The current study has added to the evidence that non-psychotic mental disorders diagnosed in the UHR population persist over the longer term (Addington et al., 2017; Lin et al., 2015). Both the persistence and onset of new mental disorders indicate that UHR criteria are picking up individuals with outcomes that are pluripotential and not specific to psychosis.

The presence of mental disorders at baseline had no relationship to transition to psychosis in the current study. It therefore does not seem that the presence of non-psychotic mental disorders have a role in transition, but more likely that they are outcomes independently related to UHR status. There is mixed evidence about the role of non-psychotic mental disorders in transition, with some studies finding relationships (Salokangas et al., 2012) where our study did not. This indicates a need for further research and replication of results. However, the UHR population is substantially heterogeneous, which could both explain the variety of findings and makes replication difficult across samples. Despite the heterogeneity of UHR samples, one finding has been robust—that UHR individuals experience significant clinical and functional impairment over the longer term (Addington et al., 2017; Lin et al., 2015; Rosen et al., 2006).

One explanation for the variety of outcomes experienced by UHR individuals is that APS could be associated with non-psychotic psychopathology, such as depression or anxiety. Thus, these individuals were never really at risk of a full-blown

psychotic disorder. The current study provides evidence to support this notion, as UHR status at follow-up was associated with the presence of non-psychotic mental disorder at follow-up. These findings are consistent with Lin et al. (2012), who also found an association between UHR status and presence of non-psychotic mental disorders. Other studies also found that the majority UHR participants met criteria for anxiety disorders, SUDs and depressive disorders (Paolo Fusar-Poli et al., 2014; Rosen et al., 2006; Rutigliano et al., 2016). The current evidence is thus indicative of UHR criteria being useful for capturing a wide range of psychopathologies that are not exclusive to psychotic outcomes, and could be expanded to capture this range of psychopathology (Hartman et al., 2017; Heinze et al., 2018; Wigman et al., 2012). These findings are also consistent with the p-factor hypothesis, which proposes that an underlying psychopathology factor predisposes individuals to psychiatric problems in general (Caspi et al., 2014).

The finding that UHR status was associated with presence of non-psychotic mental disorder indicates that UHR criteria capture a range of exit syndromes or *pluripotent* outcomes. The APS experienced by these individuals may not just be a marker of a potential psychotic disorder, but be associated with severe non-psychotic mental disorder. This aligns with the Clinical Staging Model (McGorry, Nelson, Goldstone, & Yung, 2010), which proposes that non-specific early clinical signs and symptoms or syndromes may evolve into a variety of disorders over time.

UHR criteria were operationalised within the context of detecting psychotic disorders, despite appearing to capture a variety of outcomes. In order to address the emerging research that indicates pluripotent outcomes, Hartmann et al. (2017) adapted the UHR criteria to capture a wider range of input presentations and exit syndromes²⁷. This new set of criteria, the Clinical High at-Risk Mental State

(CHARMS) aims to not only identify people at risk of psychosis, but at risk of a range of severe psychopathology (Hartmann et al., 2017). This trans-diagnostic risk identification approach addresses treatment in regards to the signs and symptoms that are experienced across disorders, and is proposed as an alternative to comorbidity. These criteria are currently being tested through observational study but appear to be a way forward for further identifying people at risk of developing severe mental disorders. Early identification of those at risk of general psychopathology is particularly important, given that the current study demonstrated that once a participant had developed a severe mental health disorder, many of them experienced this disorder continuously.

The main trajectory experienced by the cohort in this study was of continuous non-psychotic mental disorder, with 42% of participants developing an incident disorder. These trajectories were associated with poorer functional outcomes. Other studies have also demonstrated high rates of continuous disorders (Lin et al., 2015; Rutiligiano et al., 2016), indicating the importance of addressing non-psychotic outcomes in UHR samples. Despite these UHR samples being heterogeneous across studies, the observation that is consistently made is that over the longer term, irrespective of whether they transition, they continue to experience a range of clinical and functional issues.

The current study found PD to also be a significant issue for UHR participants. Participants with PD at follow-up experienced worse outcomes than those without a PD: They had lower quality of life, poorer social and functional outcomes, were more likely to transition to psychosis and have a non-psychotic mental disorder. This area is under-researched in the UHR population but results from the current study suggest it warrants further attention. Certain PDs such as schizotypal have been linked to the development of psychotic outcomes (Nordentoft et al., 2006) but research into other PDs is scarce. Recent research suggests a

particular role of borderline PD in UHR participants, and this was also the current study's most common PD. The CHARMS criteria described above include borderline PD as one of their test exit syndromes, and so this research could provide further insight into the aetiologies of these disorders (Hartmann et al., 2017).

11.12 Clinical Implications

The findings from this study reinforce the need for at-risk clinics to maintain a focus on non-psychotic outcomes in treatment. Most UHR studies have focused on transition to psychosis as the primary concern, though more recent research has indicated the need to address long-term outcomes of those who do not transition. The majority of UHR participants do not transition but continue to experience complex social, clinical and behavioural problems as well as APS over the longer term (Lin et al., 2015). Because these individuals never became frankly psychotic, they would not have been targeted for prolonged intervention. Rather, under the UHR criteria, they would be labeled as false-positives, as they did not transition. However, given their long-term impairment, this group would benefit from longer-term treatment.

The majority of UHR individuals continue to experience clinical symptoms that meet threshold diagnostic criteria for depression, anxiety and SUD. Half of our sample had a non-psychotic mental disorder continuously over the long-term follow-up. Forty-two percent developed an incident mental disorder during this period. The trajectories of these disorders were related to worse functional outcomes for individuals, with the worst functioning observed for those who had a continuous disorder and the best functioning for those who had remitted or never experienced a non-psychotic mental disorder. The continued clinical psychopathology and associated poor functioning reinforces the need to address non-psychotic clinical symptomatology at baseline. The need for long-term monitoring is also indicated, as well as the option for re-entry into services if required.

Clinical baseline measures that were associated with mental disorder trajectories could provide indication of individuals who may need particular attention. Specific clinical baseline profiles could alert clinicians to those most at risk to chronic psychopathology. Given the implications to target individuals for treatment, it is pertinent that these tests be replicated with larger samples in order to more fully understand the relationships between baseline symptomatology of UHR individuals and the types of trajectories they may be likely to experience over the longer term.

Another important finding from the current study was the relationship of PD to UHR outcomes. Personality diagnosis is often overlooked in psychosis and UHR (Simonsen et al., 2018). However, the current study indicates that the presence of PD is associated with poor outcomes. Consideration of PD is often overshadowed by acute clinical symptomology at intake assessment but given the multitude of poor outcomes PD is associated with, assessment and treatment of PD should be given more focus. Personality is intrinsically tied to a person's experience of both psychotic and non-psychotic mental disorders, given that personality affects both their manner of thinking and feeling (Widiger, 2011). It affects response to treatment (Tyrer et al., 2015) and has been shown to be associated with suicide (Hiroeh et al., 2001). The current study expands on these findings by demonstrating PD as an outcome and its impacts on the UHR population where the focus is often on preventing transition to psychosis. PDs can be difficult to assess and treat (Tyrer et al., 2007; Tyrer et al., 2015). However, given the evidence of the widespread impacts of PD on participants in this study, it is important that personality is considered in treatment of UHR individuals.

11.13 Future Directions

The current study builds on findings from the literature that indicate non-psychotic psychopathology is experienced by the majority of UHR people over the long-term. This includes pathology related to both mental and personality disorders. It

is evident that a focus on transition as the primary outcome of UHR criteria is insufficient. UHR criteria appear to capture a wide range of pluripotential outcomes, and these must therefore all be addressed in treatment.

Further research could determine whether certain individuals are prone to transition to psychosis or to non-psychotic mental disorders. However, the evidence from this study indicates that the UHR outcomes are pluripotential and it may not be possible to distinguish pathways. There is some evidence that chronic pathology may be detected at baseline but much more research is needed on this.

The current study did not identify any strong predictors of non-psychotic outcomes, similar to Lin et al. (2015). Future attempts to identify predictors of non-psychotic outcomes could include variables this study did not examine, such as traumatic events, socio economic pressures and personality features. Current models of prediction of psychotic outcomes are much stronger. This indicates a gap in our knowledge and a need to investigate the relationship of baseline clinical variables to non-psychotic outcomes, given their prevalence in UHR samples, further. Future studies need to be designed that allow for a focus beyond prediction of psychosis. Other types of analysis, such as genetic and neurocognitive, may facilitate the identification of patterns to enable the prediction of non-psychotic outcomes in the UHR population.

This study contributes to evidence that indicates a need to look beyond transition to psychosis as the main focus in high risk research. A way forward may be through a trans-diagnostic approach at both entry to and exit from services. This will allow individually tailored treatment to address the symptoms that comprise pathology across both psychotic and non-psychotic mental disorders as well as PDs. UHR individuals are already linked in with mental health services, giving these services the opportunity to expand their focus and assist in preventing some of the

poor outcomes for people who do not transition, in addition to those who do transition.

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Appendix A1

Polari et al. (2018) grouped the 17 trajectories detailed in Table A1 into the following: recovery (35.7%), remission (7.5%), any recurrence (20%), no remission (17.3%), relapse (4.0%) and transition to psychosis (15.8%). Favourable trajectories were seen in 43.2% of cases and unfavourable (psychotic and non-psychotic) In 57.1%.

Table A1

Clinical UHR status of patients in the initial 12 months.

	Trajectory number	Baseline	M3	M6	M9	M12	Count	%
Recovery	1	1	1	0	0	0	27	13.4
	2	1	0	0	0	0	45	22.3
Remission	3	1	1	1	0	0	8	4.0
	4	1	1	1	1	0	7	3.5
No remission	5	1	1	1	1	1	35	17.3
Any Recurrence	6	1	0	1	0	0	5	2.5
	7	1	1	0	1	0	3	1.5
	8	1	0	0	1	0	4	2.0
	9	1	0	1	1	0	1	0.5
	10	1	1	1	0	1	6	3.0
	11	1	1	0	1	1	4	2.0
	12	1	1	0	0	1	7	3.5
	13	1	0	1	1	1	3	1.5
	14	1	0	1	0	1	2	1.0
	15	1	0	0	1	1	5	2.5
Relapse	16	1	0	0	0	1	8	4.0
Transition	17	1	Transition within this period				32	15.8

For each time-point, UHR status of participants was assessed and attributed a binary value corresponding to: 1 = meeting UHR criteria or 0 = not meeting UHR criteria with better functioning compared to baseline. The various permutations led to the identification of 17 different trajectories and the table below shows the number and percentage of patients following each trajectory.

*Note: this table has been reproduced from Polari et al. (2018)

Appendix A2

35 Poplar Road, Parkville 3052
Locked Bag 10, Parkville 3052
Phone: 9342 2800



PARTICIPANT INFORMATION AND CONSENT FORM (PICF)

Version 2, Date: 13 MARCH 2012

Orygen Youth Health Research Centre

Full Project Title: **Rates of Psychosis Onset in a High Risk Population**

Principal Researchers: Prof Alison Yung, Dr Barnaby Nelson, Prof Stephen Wood

Additional Researchers: Ms Emily Li, Ms Anneliese Spiteri-Staines

This Participant Information and Consent Form is 8 pages long. Please make sure you have all the pages.

1. Introduction

You are invited to take part in this research project. This is because you have previously been involved in a research study at the PACE clinic, Orygen Youth Health. The main aim of the research project is to establish the long term outcomes of young people who have been identified as being at increased risk of a psychotic disorder.

This Participant Information and Consent Form tells you about the research project. It explains the procedures involved. Knowing what is involved will help you decide if you want to take part in the research or not.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or healthcare worker.

Participation in this research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing this consent section you are telling us that you:

- understand what you have read
- consent to take part in the research project
- consent to participate in the research processes that are described
- consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research project?

The Personal Assessment and Crisis Evaluation (PACE) Clinic at Orygen Youth Health evaluates and treats young people with “at risk mental states”. Specifically, young people are seen at the clinic if they are identified as being at increased risk of a psychotic disorder. The aim of this project is to recontact young people who have previously attended the PACE Clinic and to find out more about the outcomes for young people with at risk mental states. In this project we aim to identify the range of outcomes and the factors that predict them. This is important because it may help health care workers to identify young people who are at highest risk for psychotic disorders and adapt treatments for this group. You are invited to participate in this project because you have previously participated in a research study at PACE.

Overall, 174 young people who participated in research at the PACE Clinic between 2002 and 2006 will be invited to take part in the current project.

This research has been initiated by the principal investigator, Professor Alison Yung. Prof Yung is employed at both Orygen Youth Health and Orygen Youth Health Research Centre.

The research has been funded by a National Health and Medical Research Council (NHMRC) Project Grant.

The results of this research will be used by the researcher Ms Anneliese Spiteri-Staines to obtain a PhD degree.

3. What does participation in this research project involve?

In this study we are interested in your mental health and general well being and finding out about your work, relationships and social activities. This information will be gained either by an interview with the researcher or by you completing a questionnaire. The specific parts to the study are detailed below. While we would like you to participate in all parts of the study, you may consent to some parts and not others.

A. Interview

We would like to conduct an interview with you to assess your mental health and general functioning since your last contact with the PACE clinic. The assessment will take approximately 2 - 3 hours to complete. It is possible to do this interview over two sessions if this is more convenient for you.

B. Brain scan

Magnetic resonance imaging (MRI) scanning provides an image of the brain's structure without the use of radiation. The procedure takes around 45 minutes during which time you will need to be lying down with your head very still. The most uncomfortable part of the scan can be the noise made by the machine. You may bring along a CD or DVD to listen/watch via the headphones provided.

C. Attention, memory and organization (cognition) tasks

We would like to assess your memory and attention and organizational skills. Previous research has shown that attention, memory and learning ability may predict outcomes. The assessments you will be asked to complete will include paper and pencil tasks (standard intelligence tasks) and touch-computer games. The paper and pencil tests and the computer assessment will take about ninety minutes each. It is possible to perform these tests over more than one session.

D. Permission to contact you for potential future research not approved herein

We would like your permission to contact you in the future if we extend our research program. Of course, the participation in such future projects will be part of a new consent procedure and will be completely voluntary.

E. Permission to use acquired data for research not described herein

We would like your permission to use the data we collect for this study (e.g. to use the data of the brain scan in the context of other current or future projects) for projects that are not described herein. You will help us to maximize the outcome of our research effort and avoid the need to reapproach you by giving us permission to do so. The data will only be used in a coded way and researchers will not have access to your personalized data.

F. Permission to access your medical records

In order to collect the information required for this research project, we will be asking for your permission to access your medical records held at this and other hospitals. Only information associated with this project will be requested. The information that will be collected will include your medical history relevant to the project, information related to your symptoms, other medications, and whether or not your family has a history of psychiatric disorders. Evidence of a family history of psychiatric disorders will only be obtained from your medical record (should any notes in your record relate to psychiatric disorders in any of your family members) and the information you provide during your initial interview. We will collect the following information should any of your family members have a psychiatric disorder: how they are related to you, what their diagnosis is, how the diagnosis was verified and any other important information you provide that gives the researchers an understanding of the extent of their psychiatric disorder.

It is entirely voluntary whether you participate in this study or not. If you decide to participate, then components A (the interview) is an essential part of the study, whereas components B-F are optional.

You will not be paid for your participation in this research, but you will be reimbursed for any of the following costs that you incur as a result of participating in the research project (e.g., travel costs). Reimbursement will be provided of the

following amounts: \$40 for the interview, \$40 for the MRI brain scan, and \$20 for the cognitive assessment.

4. What are the possible benefits?

The findings of the study may improve our understanding of the outcome of at risk mental states. This may help improve health services and treatments. We cannot guarantee, however, that you will receive any personal benefits from this project.

5. What are the possible risks?

There are no physical risks involved in participating in this study. If you feel distressed when being interviewed, please let the interviewer know. The interview materials and the types of questions asked in this project have been used in projects in the past and no adverse effects have been reported. You can choose not to answer any questions or participate in any part of the project that makes you feel uncomfortable. You may suspend or end your participation at any time should distress occur. If you become upset or distressed as a result of your participation in the research, the researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not members of the research team.

The MRI brain scan procedure is painless and safe and there are no known health risks. The MRI scanner makes loud noises while it is working and we will provide headphones or earplugs to reduce the noise to a comfortable level. Some people find being in a MRI scanner a bit unpleasant. A member of staff will be in constant contact with you while you are in the scanner and if you feel uncomfortable in any way the scan can be stopped. Before you get into the scanner the person who operates the scan will explain the procedure to you and answer your questions. There is no radiation involved and no drugs will be administered.

6. What if new information arises during this research project?

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and the researcher will discuss whether this new information affects you.

7. Do I have to take part in this research project?

Participation in any research project is voluntary. Just because you were a former patient of the PACE Clinic and were previously involved in PACE research studies does not mean that you have to take part in the current study. If you do not wish to take part you don't have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

8. What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team. If you decide to leave the project, the researchers would like to keep the personal and health information about you that has been collected. This is to help them make

sure that the results of the research can be measured properly. If you do not want them to do this, you must tell them before you join the research project.

9. Could this research project be stopped unexpectedly?

It is possible but unlikely that this research project would be stopped unexpectedly. If it does, it may be due to poor recruitment to the project.

10. How will I be informed of the results of this research project?

You will be advised of the project results via a written information sheet at the end of the study. These results will be presented as grouped, unidentifiable data. Results of individual participants will not be provided. This information sheet will be available after completion of the whole study and the data has been analysed.

11. What else do I need to know?

- **What will happen to information about me?**

The information you provide to us will be stored securely so that only the researchers involved in this project will have access to the data. It will be kept for a minimum of 20 years. If the information is destroyed, it will be destroyed in a manner that protects the privacy and confidentiality of this information. The information collected is classified as re-identifiable. This means that details that identify you have been removed from the information (by replacing this information with a code), but that it is possible to link the code back to you if necessary. Outside of the hospital where you are seen, your information will only be identified by this code.

We would also like your permission to use the data we collect for this study for projects that are not described herein. You will help us to maximize the outcome of our research effort and avoid the need to reapproach you by giving us permission to do so. The data will only be used in a coded way and researchers will not have access to your personalized data.

We would like your permission to contact you in the future if we extend our research program. Of course, the participation in such future projects will be part of a new consent procedure and will be completely voluntary.

The information you provide to us will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this, and other, health services for the purposes of this research. By signing the consent section, you authorise release of, or access to, this confidential information to the relevant study personnel.

In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. This will be achieved by presenting aggregated group data only, without any names or individual details presented.

Information about your participation in this research project may be recorded in your health records.

We would also like your permission to contact a person you nominate (e.g., a relative) to obtain information about your health if we are unable to contact you. It is completely up to you whether or not you grant permission for us to contact such a person.

- **How can I access my information?**

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information, with which you disagree, be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

- **What happens if I am injured as a result of participating in this research project?**

If you suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you if you elect to be treated as a public patient.

- **Is this research project approved?**

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of North Western Mental Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Approval for the project has been provided by the institution where the research will be carried out.

12. Consent

I have read, or have had read to me in a language that I understand, this document and I understand the purposes, procedures and risks of this research project as described within it.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Orygen Youth Health concerning my disease and treatment that is needed for this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described.

I understand that I will be given a signed copy of this document to keep.

I consent to the following aspects of the research study on the condition that I can withdraw my consent at any time:

A. Interview	Yes / No
B. Brain scan	Yes / No
C. Attention, memory and organisation (cognition) tasks	Yes / No
D. Permission to contact you for potential future research	Yes / No
E. Permission to use acquired data for research not described in this project	Yes / No
F. Staff from Orygen Youth Health accessing my medical information	Yes / No
G. Permission to contact the following relative or friend: _____	Yes/No

Participant's name (printed).....

Signature	Date

Name of witness to participant's signature (printed).....

Signature	Date

Researcher's name.....

Signature	Date

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher's name (printed)

Signature	Date

** A senior member of the research team must provide the explanation and provision of information concerning the research project. Note: All parties signing the consent section must date their own signature.*

13. Who can I contact?

Who you may need to contact will depend on the nature of your query, therefore, please note the following:

For further information or appointments:

If you want any further information concerning this project you can contact either of the following people:

Name: Dr Barnaby Nelson

Role: Principal Investigator/Study coordinator

Telephone: 9342 2800

Name: Prof Alison Yung

Role: Principal Investigator

Telephone: 9342 2800

For complaints:

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name: Angela Gray

Position: Manager Melbourne Health Human Research Ethics Committee

Telephone: 9342 3006

Appendix A3

Telephone Interview

1. Since we saw you at PACE have you had contact with a Dr or Somebody else like a psychiatrist or psychologist for mental health concerns? When was that?
2. Are you current seeing a Dr or somebody else for mental health concerns?
3. If yes to 1 or 2: What sort of treatment have you received for this?
4. *Screenener or psychosis status:* Since you left PACE have you had any ongoing strange experiences, like hearing voices or seeing things or feeling that others are trying to harm you?
5. *Screenener for depression status:* Since you left PACE has there been a period of time when you were feeling depressed or down most of the day nearly every day?
6. *Screenener for functioning:* Since we saw you at PACE have you been working or studying? What has your main occupation been? Where have you been living?

Appendix B

Appendix B1

Counts of mental disorder diagnoses at baseline and those who attended interviews at follow-up

Interview mode at follow-up		Had mental disorder diagnosis at baseline	Did not have mental disorder diagnosis at baseline	Missing	Total
Face-to-face interview	Count	86	10	1	97
	%	88.7%	10.3%	1%	100%
Phone interview	Count	20	7	1	28
	%	71.4%	25%	3.6%	100%
Refused	Count	13	2	0	15
	%	86.7%	13.3%	0	100%
Could not be located	Count	29	3	0	32
	%	90.6%	9.4%	0	100%
Total		148	22	2	172

Appendix B2

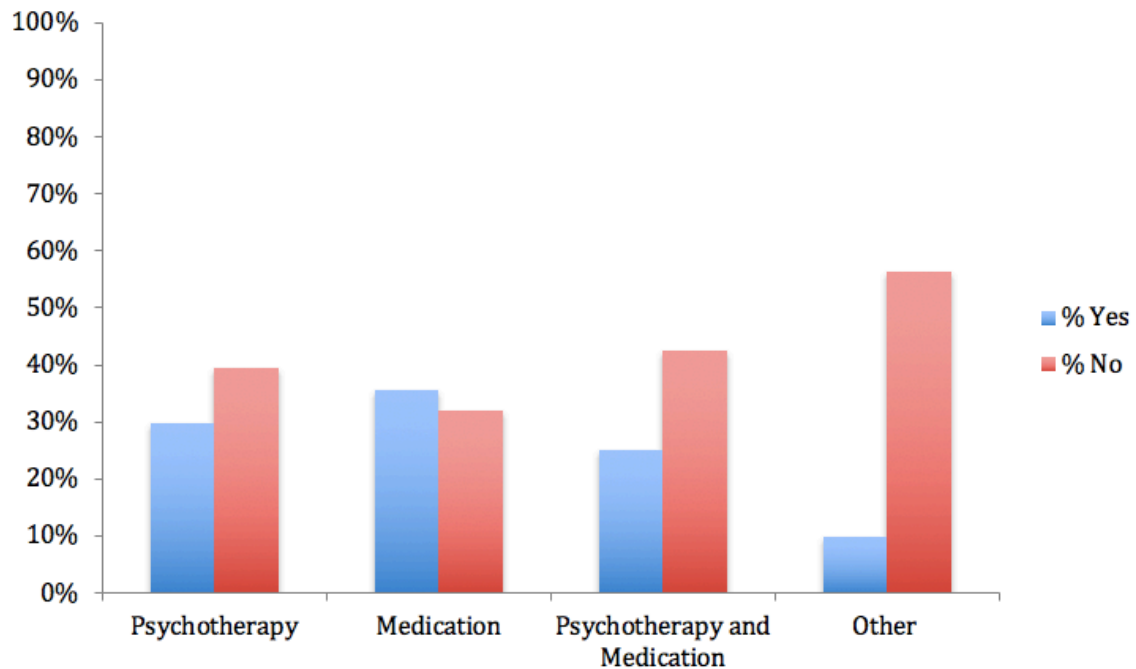


Figure B2: Treatment received by participants in between last assessment and follow up

Note: Medication includes use of any medication for mental health reasons, including antipsychotic medication. Psychotherapy includes counselling and family meetings. Other includes all other measures in the LCSE (ECT, hospitalisation, day treatment, traditional healing, alternative treatments, and treatment for a drug or alcohol problem).

Appendix B3

Table B3: Counts of participants who had an SUD disorder at follow-up (current or since last assessment) and had received both medication and psychotherapy in between assessments

			SUD at follow-up (current or since last assessment)		
			No	Yes	Total
Did the person receive medication and psychotherapy since last assessment?	No	Count	48	21	69
		%	69.6%	30.4%	100%
	Yes	Count	29	14	43
		%	67.4%	32.6	100%
Total			77	35	112

Appendix B4

Table B4: Counts of participants who received intervention or treatment as usual at baseline and had received both medication and psychotherapy in between assessments

			Baseline Intervention group		
			No	Yes	Total
Did the person receive medication and psychotherapy since last assessment?	No	Count	38	35	73
		%	52.1%	47.9%	
	Yes	Count	27	16	43
		%	62.8%	37.2%	
Total			65	51	116

Appendix B5

Table B5: Logistic regression results for association between mental disorder at baseline and UHR status at follow-up

	β	Se (β)	Wald	Df	P	Odds Ratio	95.0% CI for Odds Ratio	
							Lower	Upper
Mental disorder at baseline	-.828	.814	1.035	1	.309	.437	.089	2.155
Constant	-.676	.228	8.777	1	.003	.509		

Appendix B6

Correlations for baseline predictors of continuous disorder (next page)

		Any continuous disorder over time (includes Mood, Anxiety and SUD).	Sex	Age at baseline assessment	Pace treatment - Baseline measure	Baseline intake group Vulnerability	Baseline intake group BLIPS	Baseline intake group Attenuated psychosis	Baseline BPRS Total	Baseline SANS Total	Baseline GAF	Baseline QLS Total
Any continuous disorder over time (includes Mood, Anxiety and SUD).	Pearson Correlation	1	.043	.131	-.236**	-.200*	-.186*	.222*	.249**	.113	-.236**	-.227*
	Sig. (2-tailed)		.631	.142	.008	.025	.037	.013	.005	.208	.008	.011
	N	126	126	126	126	126	126	126	125	125	126	125
Sex	Pearson Correlation	.043	1	-.082	.040	-.018	-.035	.066	-.032	.050	-.040	.063
	Sig. (2-tailed)	.631		.283	.606	.813	.646	.390	.682	.516	.598	.413
	N	126	172	172	172	172	172	172	170	170	172	171
Age at baseline assessment	Pearson Correlation	.131	-.082	1	-.042	.147	-.037	-.013	-.002	.166*	-.219**	-.093
	Sig. (2-tailed)	.142	.283		.583	.055	.634	.869	.974	.030	.004	.227
	N	126	172	172	172	172	172	172	170	170	172	171
Pace treatment - Baseline measure	Pearson Correlation	-.236**	.040	-.042	1	.059	-.035	-.134	-.266**	-.201**	.014	.024
	Sig. (2-tailed)	.008	.606	.583		.442	.651	.079	.000	.009	.852	.755
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline intake group Vulnerability	Pearson Correlation	-.200*	-.018	.147	.059	1	-.018	-.585**	-.168*	-.007	-.012	.113
	Sig. (2-tailed)	.025	.813	.055	.442		.820	.000	.029	.932	.875	.141
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline intake group BLIPS	Pearson Correlation	-.186*	-.035	-.037	-.035	-.018	1	-.246**	.018	-.011	.125	.075
	Sig. (2-tailed)	.037	.646	.634	.651	.820		.001	.813	.883	.103	.328
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline intake group Attenuated psychosis	Pearson Correlation	.222*	.066	-.013	-.134	-.585**	-.246**	1	.226**	.126	-.161*	-.200**
	Sig. (2-tailed)	.013	.390	.869	.079	.000	.001		.003	.101	.035	.009
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline BPRS Total	Pearson Correlation	.249**	-.032	-.002	-.266**	-.168*	.018	.226**	1	.568**	-.421**	-.400**
	Sig. (2-tailed)	.005	.682	.974	.000	.029	.813	.003		.000	.000	.000
	N	125	170	170	170	170	170	170	170	170	170	170
Baseline SANS Total	Pearson Correlation	.113	.050	.166*	-.201**	-.007	-.011	.126	.568**	1	-.463**	-.561**

	Sig. (2-tailed)	.208	.516	.030	.009	.932	.883	.101	.000		.000	.000
	N	125	170	170	170	170	170	170	170	170	170	170
Baseline GAF	Pearson Correlation	-.236**	-.040	-.219**	.014	-.012	.125	-.161*	-.421**	-.463**	1	.485**
	Sig. (2-tailed)	.008	.598	.004	.852	.875	.103	.035	.000	.000		.000
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline QLS Total	Pearson Correlation	-.227*	.063	-.093	.024	.113	.075	-.200**	-.400**	-.561**	.485**	1
	Sig. (2-tailed)	.011	.413	.227	.755	.141	.328	.009	.000	.000	.000	
	N	125	171	171	171	171	171	171	170	170	171	171
Baseline Hamilton Depression Total	Pearson Correlation	.309*	.188	.185	-.043	-.103	-.105	.192	.739**	.674**	-.619**	-.453**
	Sig. (2-tailed)	.012	.088	.094	.699	.356	.347	.082	.000	.000	.000	.000
	N	66	83	83	83	83	83	83	83	83	83	83
Baseline disorders of thought content	Pearson Correlation	.043	-.047	.143	-.084	-.261**	.090	.245**	.382**	.191*	-.206**	-.006
	Sig. (2-tailed)	.636	.539	.061	.274	.001	.239	.001	.000	.012	.007	.933
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline perceptual abnormalities	Pearson Correlation	.043	.093	-.205**	.087	-.302**	.090	.359**	.199**	-.083	.001	.099
	Sig. (2-tailed)	.636	.225	.007	.254	.000	.243	.000	.009	.283	.991	.197
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline conceptual disorganisation	Pearson Correlation	.009	.029	.077	-.084	.112	.133	-.013	.294**	.221**	-.102	.017
	Sig. (2-tailed)	.922	.706	.318	.273	.143	.083	.865	.000	.004	.186	.830
	N	125	171	171	171	171	171	171	169	169	171	170
Baseline motor disturbances	Pearson Correlation	.176	.028	-.008	-.011	-.061	-.123	.121	.311**	.178*	-.113	-.187*
	Sig. (2-tailed)	.051	.717	.922	.890	.431	.112	.118	.000	.021	.142	.015
	N	124	169	169	169	169	169	169	169	169	169	169
Baseline disorders of concentration, attention and memory	Pearson Correlation	.053	.128	.118	.036	.111	-.048	-.071	.293**	.357**	-.123	-.087
	Sig. (2-tailed)	.560	.096	.126	.641	.148	.537	.357	.000	.000	.110	.261
	N	125	170	170	170	170	170	170	170	170	170	170
Baseline disorders of emotion and affect	Pearson Correlation	.092	-.002	.172*	-.248**	.061	.014	.112	.399**	.525**	-.236**	-.155*
	Sig. (2-tailed)	.311	.980	.025	.001	.429	.860	.149	.000	.000	.002	.044
	N	124	169	169	169	169	169	169	169	169	169	169
Baseline impaired energy	Pearson Correlation	.131	.010	.061	-.035	-.078	-.131	.153*	.285**	.351**	-.313**	-.263**

Baseline impaired tolerance to normal stress	Sig. (2-tailed)	.147	.899	.430	.649	.317	.090	.048	.000	.000	.000	.001
	N	124	169	169	169	169	169	169	169	169	169	169
	Pearson Correlation	.210*	.183*	.161*	.064	-.036	-.083	.154*	.389**	.273**	-.397**	-.272**
	Sig. (2-tailed)	.019	.017	.036	.406	.646	.283	.045	.000	.000	.000	.000
	N	125	170	170	170	170	170	170	170	170	170	170

		Baseline Hamilton Depression Total	Baseline disorders of thought content	Baseline perceptual abnormalities	Baseline conceptual disorganisation	Baseline motor disturbances	Baseline disorders of concentration, attention and memory	Baseline disorders of emotion and affect	Baseline impaired energy	Baseline impaired tolerance to normal stress
Any continuous disorder over time (includes Mood, Anxiety and SUD).	Pearson Correlation	.309*	.043	.043	.009	.176	.053	.092	.131	.210*
	Sig. (2-tailed)	.012	.636	.636	.922	.051	.560	.311	.147	.019
	N	66	126	126	125	124	125	124	124	125
Sex	Pearson Correlation	.188	-.047	.093	.029	.028	.128	-.002	.010	.183*
	Sig. (2-tailed)	.088	.539	.225	.706	.717	.096	.980	.899	.017
	N	83	172	172	171	169	170	169	169	170
Age at baseline assessment	Pearson Correlation	.185	.143	-.205**	.077	-.008	.118	.172*	.061	.161*
	Sig. (2-tailed)	.094	.061	.007	.318	.922	.126	.025	.430	.036
	N	83	172	172	171	169	170	169	169	170
Pace treatment - Baseline measure	Pearson Correlation	-.043	-.084	.087	-.084	-.011	.036	-.248**	-.035	.064
	Sig. (2-tailed)	.699	.274	.254	.273	.890	.641	.001	.649	.406
	N	83	172	172	171	169	170	169	169	170
Baseline intake group Vulnerability	Pearson Correlation	-.103	-.261**	-.302**	.112	-.061	.111	.061	-.078	-.036
	Sig. (2-tailed)	.356	.001	.000	.143	.431	.148	.429	.317	.646
	N	83	172	172	171	169	170	169	169	170
Baseline intake group BLIPS	Pearson Correlation	-.105	.090	.090	.133	-.123	-.048	.014	-.131	-.083
	Sig. (2-tailed)	.347	.239	.243	.083	.112	.537	.860	.090	.283
	N	83	172	172	171	169	170	169	169	170
Baseline intake group Attenuated psychosis	Pearson Correlation	.192	.245**	.359**	-.013	.121	-.071	.112	.153*	.154*
	Sig. (2-tailed)	.082	.001	.000	.865	.118	.357	.149	.048	.045
	N	83	172	172	171	169	170	169	169	170
Baseline BPRS Total	Pearson Correlation	.739**	.382**	.199**	.294**	.311**	.293**	.399**	.285**	.389**
	Sig. (2-tailed)	.000	.000	.009	.000	.000	.000	.000	.000	.000
	N	83	170	170	169	169	170	169	169	170
Baseline SANS Total	Pearson Correlation	.674**	.191*	-.083	.221**	.178*	.357**	.525**	.351**	.273**
	Sig. (2-tailed)	.000	.012	.283	.004	.021	.000	.000	.000	.000
	N	83	170	170	169	169	170	169	169	170
Baseline GAF	Pearson Correlation	-.619**	-.206**	.001	-.102	-.113	-.123	-.236**	-.313**	-.397**
	Sig. (2-tailed)	.000	.007	.991	.186	.142	.110	.002	.000	.000

	N	83	172	172	171	169	170	169	169	170
Baseline QLS Total	Pearson Correlation	-.453**	-.006	.099	.017	-.187*	-.087	-.155*	-.263**	-.272**
	Sig. (2-tailed)	.000	.933	.197	.830	.015	.261	.044	.001	.000
	N	83	171	171	170	169	170	169	169	170
Baseline Hamilton Depression Total	Pearson Correlation	1	.401**	-.002	.142	.335**	.390**	.480**	.564**	.553**
	Sig. (2-tailed)		.000	.986	.205	.002	.000	.000	.000	.000
	N	83	83	83	82	82	83	82	82	83
Baseline Disorders of thought content	Pearson Correlation	.401**	1	.257**	.163*	.056	.241**	.318**	.180*	.056
	Sig. (2-tailed)	.000		.001	.033	.468	.002	.000	.019	.468
	N	83	172	172	171	169	170	169	169	170
Baseline Perceptual abnormalities	Pearson Correlation	-.002	.257**	1	-.011	.074	-.001	.013	.049	.204**
	Sig. (2-tailed)	.986	.001		.891	.339	.993	.868	.531	.008
	N	83	172	172	171	169	170	169	169	170
Baseline Conceptual disorganisation	Pearson Correlation	.142	.163*	-.011	1	.215**	.387**	.169*	.068	.096
	Sig. (2-tailed)	.205	.033	.891		.005	.000	.028	.381	.216
	N	82	171	171	171	169	169	169	169	169
Baseline Motor disturbances	Pearson Correlation	.335**	.056	.074	.215**	1	.187*	.192*	.129	.158*
	Sig. (2-tailed)	.002	.468	.339	.005		.015	.013	.095	.041
	N	82	169	169	169	169	169	169	169	169
Baseline Disorders of concentration, attention and memory	Pearson Correlation	.390**	.241**	-.001	.387**	.187*	1	.259**	.199**	.221**
	Sig. (2-tailed)	.000	.002	.993	.000	.015		.001	.009	.004
	N	83	170	170	169	169	170	169	169	170
Baseline Disorders of emotion and affect	Pearson Correlation	.480**	.318**	.013	.169*	.192*	.259**	1	.228**	.099
	Sig. (2-tailed)	.000	.000	.868	.028	.013	.001		.003	.201
	N	82	169	169	169	169	169	169	169	169
Baseline Impaired energy	Pearson Correlation	.564**	.180*	.049	.068	.129	.199**	.228**	1	.420**
	Sig. (2-tailed)	.000	.019	.531	.381	.095	.009	.003		.000
	N	82	169	169	169	169	169	169	169	169
Baseline Impaired tolerance to normal stress	Pearson Correlation	.553**	.056	.204**	.096	.158*	.221**	.099	.420**	1
	Sig. (2-tailed)	.000	.468	.008	.216	.041	.004	.201	.000	

N	83	170	170	169	169	170	169	169	170

** . Correlation is significant at the 0.01 level (2-tailed).

* . Correlation is significant at the 0.05 level (2-tailed).

Nonparametric Correlations

		Any continuous disorder over time (includes Mood, Anxiety and SUD).		Sex	Age at baseline assessment	Pace treatment - Baseline measure	Baseline intake group Vulnerability	Baseline intake group BLIPS	Baseline intake group psychosis	Baseline BPRS Total	Baseline SANS Total	Baseline GAF
Spearman's rho	Any continuous	Correlation Coefficient	1.000	.043	.134	-.236**	-.200*	-.186*	.222*	.253**	.092	-.227*
	disorder over time	Sig. (2-tailed)	.	.631	.133	.008	.025	.037	.013	.004	.309	.011
	(includes Mood, Anxiety and SUD).	N	126	126	126	126	126	126	126	125	125	126
	Sex	Correlation Coefficient	.043	1.000	-.082	.040	-.018	-.035	.066	-.030	.032	-.052
		Sig. (2-tailed)	.631	.	.286	.606	.813	.646	.390	.695	.681	.501
		N	126	172	172	172	172	172	172	170	170	172
	Age at baseline assessment	Correlation Coefficient	.134	-.082	1.000	-.020	.111	-.029	.012	.037	.204**	-.226**
		Sig. (2-tailed)	.133	.286	.	.798	.149	.710	.875	.629	.008	.003
		N	126	172	172	172	172	172	172	170	170	172
	Pace treatment - Baseline measure	Correlation Coefficient	-.236**	.040	-.020	1.000	.059	-.035	-.134	-.272**	-.256**	-.006
		Sig. (2-tailed)	.008	.606	.798	.	.442	.651	.079	.000	.001	.934
		N	126	172	172	172	172	172	172	170	170	172
	Baseline intake group Vulnerability	Correlation Coefficient	-.200*	-.018	.111	.059	1.000	-.018	-.585**	-.155*	-.030	.015
		Sig. (2-tailed)	.025	.813	.149	.442	.	.820	.000	.043	.694	.849
		N	126	172	172	172	172	172	172	170	170	172
	Baseline intake group BLIPS	Correlation Coefficient	-.186*	-.035	-.029	-.035	-.018	1.000	-.246**	.011	.005	.135
		Sig. (2-tailed)	.037	.646	.710	.651	.820	.	.001	.885	.945	.078
		N	126	172	172	172	172	172	172	170	170	172
	Baseline intake group Attenuated psychosis	Correlation Coefficient	.222*	.066	.012	-.134	-.585**	-.246**	1.000	.226**	.131	-.161*
		Sig. (2-tailed)	.013	.390	.875	.079	.000	.001	.	.003	.089	.035
		N	126	172	172	172	172	172	172	170	170	172
	Baseline BPRS Total	Correlation Coefficient	.253**	-.030	.037	-.272**	-.155*	.011	.226**	1.000	.568**	-.414**
		Sig. (2-tailed)	.004	.695	.629	.000	.043	.885	.003	.	.000	.000
		N	125	170	170	170	170	170	170	170	170	170
	Baseline SANS Total	Correlation Coefficient	.092	.032	.204**	-.256**	-.030	.005	.131	.568**	1.000	-.419**
		Sig. (2-tailed)	.309	.681	.008	.001	.694	.945	.089	.000	.	.000

	N	125	170	170	170	170	170	170	170	170	170
Baseline GAF	Correlation Coefficient	-.227*	-.052	-.226**	-.006	.015	.135	-.161*	-.414**	-.419**	1.000
	Sig. (2-tailed)	.011	.501	.003	.934	.849	.078	.035	.000	.000	.
	N	126	172	172	172	172	172	172	170	170	172
Baseline QLS Total	Correlation Coefficient	-.227*	.054	-.124	.033	.112	.075	-.210**	-.365**	-.541**	.458**
	Sig. (2-tailed)	.011	.481	.106	.670	.144	.329	.006	.000	.000	.000
	N	125	171	171	171	171	171	171	170	170	171
Baseline Hamilton	Correlation Coefficient	.310*	.193	.252*	-.024	-.096	-.119	.184	.734**	.662**	-.614**
Depression Total	Sig. (2-tailed)	.011	.080	.022	.828	.388	.285	.096	.000	.000	.000
	N	66	83	83	83	83	83	83	83	83	83
Baseline Disorders of	Correlation Coefficient	.051	-.062	.159*	-.077	-.248**	.050	.238**	.372**	.215**	-.194*
thought content	Sig. (2-tailed)	.568	.420	.037	.314	.001	.514	.002	.000	.005	.011
	N	126	172	172	172	172	172	172	170	170	172
Baseline Perceptual	Correlation Coefficient	.029	.088	-.209**	.075	-.254**	.090	.292**	.157*	-.117	.028
abnormalities	Sig. (2-tailed)	.749	.249	.006	.326	.001	.240	.000	.041	.129	.719
	N	126	172	172	172	172	172	172	170	170	172
Baseline Conceptual	Correlation Coefficient	.019	.026	.103	-.084	.108	.123	-.005	.306**	.235**	-.098
disorganisation	Sig. (2-tailed)	.836	.737	.181	.277	.161	.108	.951	.000	.002	.201
	N	125	171	171	171	171	171	171	169	169	171
Baseline Motor	Correlation Coefficient	.150	.013	.016	-.035	-.048	-.127	.097	.285**	.165*	-.073
disturbances	Sig. (2-tailed)	.095	.864	.835	.650	.536	.100	.210	.000	.032	.347
	N	124	169	169	169	169	169	169	169	169	169
Baseline Disorders of	Correlation Coefficient	.097	.077	.151*	.033	.095	-.041	-.049	.330**	.394**	-.123
concentration,	Sig. (2-tailed)	.284	.319	.050	.665	.218	.596	.528	.000	.000	.110
attention and memory	N	125	170	170	170	170	170	170	170	170	170
Baseline Disorders of	Correlation Coefficient	.090	.000	.192*	-.230**	.063	.014	.123	.415**	.533**	-.235**
emotion and affect	Sig. (2-tailed)	.318	.996	.012	.003	.416	.858	.110	.000	.000	.002
	N	124	169	169	169	169	169	169	169	169	169
Baseline Impaired	Correlation Coefficient	.152	.034	.106	-.029	-.059	-.162*	.150	.313**	.350**	-.367**
energy	Sig. (2-tailed)	.091	.658	.168	.709	.445	.035	.052	.000	.000	.000

	N	124	169	169	169	169	169	169	169	169	169
Baseline Impaired	Correlation Coefficient	.213*	.184*	.165*	.089	-.031	-.112	.147	.377**	.253**	-.405**
tolerance to normal	Sig. (2-tailed)	.017	.016	.032	.247	.691	.147	.055	.000	.001	.000
stress	N	125	170	170	170	170	170	170	170	170	170

			Baseline QLS Total	Baseline Hamilton Depression Total	Baseline disorders of thought content	Baseline perceptual abnormalities	Baseline conceptual disorganisation	Baseline motor disturbances	Baseline disorders of concentration, attention and memory	Baseline disorders of emotion and affect	Baseline impaired energy	Baseline impaired tolerance to normal stress
Spearman's rho	Any continuous disorder over time (includes Mood, Anxiety and SUD).	Correlation Coefficient	-.227*	.310*	.051	.029	.019	.150	.097	.090	.152	.213*
		Sig. (2-tailed)	.011	.011	.568	.749	.836	.095	.284	.318	.091	.017
		N	125	66	126	126	125	124	125	124	124	125
	Sex	Correlation Coefficient	.054	.193	-.062	.088	.026	.013	.077	.000	.034	.184*
		Sig. (2-tailed)	.481	.080	.420	.249	.737	.864	.319	.996	.658	.016
		N	171	83	172	172	171	169	170	169	169	170
	Age at baseline assessment	Correlation Coefficient	-.124	.252*	.159*	-.209**	.103	.016	.151*	.192*	.106	.165*
		Sig. (2-tailed)	.106	.022	.037	.006	.181	.835	.050	.012	.168	.032
		N	171	83	172	172	171	169	170	169	169	170
	Pace treatment - Baseline measure	Correlation Coefficient	.033	-.024	-.077	.075	-.084	-.035	.033	-.230**	-.029	.089
		Sig. (2-tailed)	.670	.828	.314	.326	.277	.650	.665	.003	.709	.247
		N	171	83	172	172	171	169	170	169	169	170
	Baseline intake group	Correlation Coefficient	.112	-.096	-.248**	-.254**	.108	-.048	.095	.063	-.059	-.031
		Sig. (2-tailed)	.144	.388	.001	.001	.161	.536	.218	.416	.445	.691
		N	171	83	172	172	171	169	170	169	169	170
	Baseline intake group	Correlation Coefficient	.075	-.119	.050	.090	.123	-.127	-.041	.014	-.162*	-.112
		Sig. (2-tailed)	.329	.285	.514	.240	.108	.100	.596	.858	.035	.147
		N	171	83	172	172	171	169	170	169	169	170
	Baseline intake group	Correlation Coefficient	-.210**	.184	.238**	.292**	-.005	.097	-.049	.123	.150	.147

Attenuated psychosis	Sig. (2-tailed)	.006	.096	.002	.000	.951	.210	.528	.110	.052	.055
	N	171	83	172	172	171	169	170	169	169	170
Baseline BPRS Total	Correlation Coefficient	-.365**	.734**	.372**	.157*	.306**	.285**	.330**	.415**	.313**	.377**
	Sig. (2-tailed)	.000	.000	.000	.041	.000	.000	.000	.000	.000	.000
	N	170	83	170	170	169	169	170	169	169	170
Baseline SANS Total	Correlation Coefficient	-.541**	.662**	.215**	-.117	.235**	.165*	.394**	.533**	.350**	.253**
	Sig. (2-tailed)	.000	.000	.005	.129	.002	.032	.000	.000	.000	.001
	N	170	83	170	170	169	169	170	169	169	170
Baseline GAF	Correlation Coefficient	.458**	-.614**	-.194*	.028	-.098	-.073	-.123	-.235**	-.367**	-.405**
	Sig. (2-tailed)	.000	.000	.011	.719	.201	.347	.110	.002	.000	.000
	N	171	83	172	172	171	169	170	169	169	170
Baseline QLS Total	Correlation Coefficient	1.000	-.415**	.005	.134	.006	-.171*	-.172*	-.169*	-.314**	-.293**
	Sig. (2-tailed)	.	.000	.945	.081	.934	.026	.025	.028	.000	.000
	N	171	83	171	171	170	169	170	169	169	170
Baseline Hamilton Depression Total	Correlation Coefficient	-.415**	1.000	.370**	-.091	.130	.294**	.432**	.492**	.545**	.561**
	Sig. (2-tailed)	.000	.	.001	.414	.245	.007	.000	.000	.000	.000
	N	83	83	83	83	82	82	83	82	82	83
Baseline Disorders of thought content	Correlation Coefficient	.005	.370**	1.000	.229**	.143	.050	.230**	.318**	.177*	.070
	Sig. (2-tailed)	.945	.001	.	.003	.061	.520	.003	.000	.021	.368
	N	171	83	172	172	171	169	170	169	169	170
Baseline Perceptual abnormalities	Correlation Coefficient	.134	-.091	.229**	1.000	.005	.023	.016	-.001	.038	.154*
	Sig. (2-tailed)	.081	.414	.003	.	.951	.762	.840	.990	.623	.044
	N	171	83	172	172	171	169	170	169	169	170

Baseline	Correlation										
Conceptual	Coefficient	.006	.130	.143	.005	1.000	.216**	.408**	.144	.067	.095
disorganisatio	Sig. (2-tailed)	.934	.245	.061	.951	.	.005	.000	.062	.385	.220
n	N	170	82	171	171	171	169	169	169	169	169
Baseline	Correlation										
Motor	Coefficient	-.171*	.294**	.050	.023	.216**	1.000	.208**	.184*	.117	.127
disturbances	Sig. (2-tailed)	.026	.007	.520	.762	.005	.	.007	.017	.130	.101
	N	169	82	169	169	169	169	169	169	169	169
Baseline	Correlation										
Disorders of	Coefficient	-.172*	.432**	.230**	.016	.408**	.208**	1.000	.275**	.250**	.187*
concentration,	Sig. (2-tailed)	.025	.000	.003	.840	.000	.007	.	.000	.001	.015
attention and	N	170	83	170	170	169	169	170	169	169	170
memory											
Baseline	Correlation										
Disorders of	Coefficient	-.169*	.492**	.318**	-.001	.144	.184*	.275**	1.000	.218**	.097
emotion and	Sig. (2-tailed)	.028	.000	.000	.990	.062	.017	.000	.	.004	.211
affect	N	169	82	169	169	169	169	169	169	169	169
Baseline	Correlation										
Impaired	Coefficient	-.314**	.545**	.177*	.038	.067	.117	.250**	.218**	1.000	.389**
energy	Sig. (2-tailed)	.000	.000	.021	.623	.385	.130	.001	.004	.	.000
	N	169	82	169	169	169	169	169	169	169	169
Baseline	Correlation										
Impaired	Coefficient	-.293**	.561**	.070	.154*	.095	.127	.187*	.097	.389**	1.000
tolerance to	Sig. (2-tailed)	.000	.000	.368	.044	.220	.101	.015	.211	.000	.
normal stress	N	170	83	170	170	169	169	170	169	169	170

** . Correlation is significant at the 0.01 level (2-tailed).

* . Correlation is significant at the 0.05 level (2-tailed).

Appendix B7

Correlations for baseline predictors of remitted disorders (next page)

		At least one of the major 3 disorders remitted over time (but could still have other persisting disorders)	Sex	Age at assessment	Pace treatment - Baseline measure	Baseline intake group Vulnerability	Baseline intake group BLIPS	Baseline intake group Attenuated psychosis	Baseline BPRS Total	Baseline SANS Total	Baseline GAF	Baseline QLS Total
At least one of the major 3 disorders remitted over time (but could still have other persisting disorders)	Pearson Correlation	1	-.042	.156	-.115	.047	.042	-.127	-.097	.096	.051	.034
	Sig. (2-tailed)		.642	.080	.198	.598	.638	.155	.282	.289	.572	.710
	N	126	126	126	126	126	126	126	125	125	126	125
Sex	Pearson Correlation	-.042	1	-.082	.040	-.018	-.035	.066	-.032	.050	-.040	.063
	Sig. (2-tailed)			.283	.606	.813	.646	.390	.682	.516	.598	.413
	N	126	172	172	172	172	172	172	170	170	172	171
Age at baseline assessment	Pearson Correlation	.156	-.082	1	-.042	.147	-.037	-.013	-.002	.166*	-.219**	-.093
	Sig. (2-tailed)		.283		.583	.055	.634	.869	.974	.030	.004	.227
	N	126	172	172	172	172	172	172	170	170	172	171
Pace treatment - Baseline measure	Pearson Correlation	-.115	.040	-.042	1	.059	-.035	-.134	-.266**	-.201**	.014	.024
	Sig. (2-tailed)		.606	.583		.442	.651	.079	.000	.009	.852	.755
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline intake group Vulnerability	Pearson Correlation	.047	-.018	.147	.059	1	-.018	-.585**	-.168*	-.007	-.012	.113
	Sig. (2-tailed)		.813	.055	.442		.820	.000	.029	.932	.875	.141
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline intake group BLIPS	Pearson Correlation	.042	-.035	-.037	-.035	-.018	1	-.246**	.018	-.011	.125	.075
	Sig. (2-tailed)		.646	.634	.651	.820		.001	.813	.883	.103	.328
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline intake group Attenuated psychosis	Pearson Correlation	-.127	.066	-.013	-.134	-.585**	-.246**	1	.226**	.126	-.161*	-.200**
	Sig. (2-tailed)		.390	.869	.079	.000	.001		.003	.101	.035	.009
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline BPRS Total	Pearson Correlation	-.097	-.032	-.002	-.266**	-.168*	.018	.226**	1	.568**	-.421**	-.400**
	Sig. (2-tailed)		.682	.974	.000	.029	.813	.003		.000	.000	.000
	N	125	170	170	170	170	170	170	170	170	170	170

Baseline SANS Total	Pearson Correlation	.096	.050	.166*	-.201**	-.007	-.011	.126	.568**	1	-.463**	-.561**
	Sig. (2-tailed)	.289	.516	.030	.009	.932	.883	.101	.000		.000	.000
	N	125	170	170	170	170	170	170	170	170	170	170
Baseline GAF	Pearson Correlation	.051	-.040	-.219**	.014	-.012	.125	-.161*	-.421**	-.463**	1	.485**
	Sig. (2-tailed)	.572	.598	.004	.852	.875	.103	.035	.000	.000		.000
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline QLS Total	Pearson Correlation	.034	.063	-.093	.024	.113	.075	-.200**	-.400**	-.561**	.485**	1
	Sig. (2-tailed)	.710	.413	.227	.755	.141	.328	.009	.000	.000	.000	
	N	125	171	171	171	171	171	171	170	170	171	171
Baseline disorders of thought content	Pearson Correlation	-.103	-.047	.143	-.084	-.261**	.090	.245**	.382**	.191*	-.206**	-.006
	Sig. (2-tailed)	.250	.539	.061	.274	.001	.239	.001	.000	.012	.007	.933
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline perceptual abnormalities	Pearson Correlation	-.167	.093	-.205**	.087	-.302**	.090	.359**	.199**	-.083	.001	.099
	Sig. (2-tailed)	.062	.225	.007	.254	.000	.243	.000	.009	.283	.991	.197
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline conceptual disorganisation	Pearson Correlation	.048	.029	.077	-.084	.112	.133	-.013	.294**	.221**	-.102	.017
	Sig. (2-tailed)	.592	.706	.318	.273	.143	.083	.865	.000	.004	.186	.830
	N	125	171	171	171	171	171	171	169	169	171	170
Baseline motor disturbances	Pearson Correlation	-.129	.028	-.008	-.011	-.061	-.123	.121	.311**	.178*	-.113	-.187*
	Sig. (2-tailed)	.153	.717	.922	.890	.431	.112	.118	.000	.021	.142	.015
	N	124	169	169	169	169	169	169	169	169	169	169
Baseline disorders of concentration, attention and memory	Pearson Correlation	.000	.128	.118	.036	.111	-.048	-.071	.293**	.357**	-.123	-.087
	Sig. (2-tailed)	.997	.096	.126	.641	.148	.537	.357	.000	.000	.110	.261
	N	125	170	170	170	170	170	170	170	170	170	170
Baseline disorders of emotion and affect	Pearson Correlation	.015	-.002	.172*	-.248**	.061	.014	.112	.399**	.525**	-.236**	-.155*
	Sig. (2-tailed)	.867	.980	.025	.001	.429	.860	.149	.000	.000	.002	.044
	N	124	169	169	169	169	169	169	169	169	169	169
Baseline impaired energy	Pearson Correlation	-.050	.010	.061	-.035	-.078	-.131	.153*	.285**	.351**	-.313**	-.263**
	Sig. (2-tailed)	.584	.899	.430	.649	.317	.090	.048	.000	.000	.000	.001
	N	124	169	169	169	169	169	169	169	169	169	169

Baseline impaired tolerance to normal stress	Pearson Correlation	-.120	.183*	.161*	.064	-.036	-.083	.154*	.389**	.273**	-.397**	-.272**
	Sig. (2-tailed)	.181	.017	.036	.406	.646	.283	.045	.000	.000	.000	.000
	N	125	170	170	170	170	170	170	170	170	170	170

		Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline
		disorders of	perceptual	conceptual	motor	disorders of	disorders of	impaired	
		thought	abnormalities	disorganisation	disturbances	concentration,	emotion and	impaired	tolerance to
		content				attention and	affect	energy	normal
						memory			stress
At least one of the major 3 disorders remitted over time (but could still have other persisting disorders)	Pearson Correlation	-.103	-.167	.048	-.129	.000	.015	-.050	-.120
	Sig. (2-tailed)	.250	.062	.592	.153	.997	.867	.584	.181
	N	126	126	125	124	125	124	124	125
Sex	Pearson Correlation	-.047	.093	.029	.028	.128	-.002	.010	.183*
	Sig. (2-tailed)	.539	.225	.706	.717	.096	.980	.899	.017
	N	172	172	171	169	170	169	169	170
Age at baseline assessment	Pearson Correlation	.143	-.205**	.077	-.008	.118	.172*	.061	.161*
	Sig. (2-tailed)	.061	.007	.318	.922	.126	.025	.430	.036
	N	172	172	171	169	170	169	169	170
Pace treatment - Baseline measure	Pearson Correlation	-.084	.087	-.084	-.011	.036	-.248**	-.035	.064
	Sig. (2-tailed)	.274	.254	.273	.890	.641	.001	.649	.406
	N	172	172	171	169	170	169	169	170
Baseline intake group Vulnerability	Pearson Correlation	-.261**	-.302**	.112	-.061	.111	.061	-.078	-.036
	Sig. (2-tailed)	.001	.000	.143	.431	.148	.429	.317	.646
	N	172	172	171	169	170	169	169	170
Baseline intake group BLIPS	Pearson Correlation	.090	.090	.133	-.123	-.048	.014	-.131	-.083
	Sig. (2-tailed)	.239	.243	.083	.112	.537	.860	.090	.283
	N	172	172	171	169	170	169	169	170
Baseline intake group Attenuated psychosis	Pearson Correlation	.245**	.359**	-.013	.121	-.071	.112	.153*	.154*
	Sig. (2-tailed)	.001	.000	.865	.118	.357	.149	.048	.045
	N	172	172	171	169	170	169	169	170
Baseline BPRS Total	Pearson Correlation	.382**	.199**	.294**	.311**	.293**	.399**	.285**	.389**
	Sig. (2-tailed)	.000	.009	.000	.000	.000	.000	.000	.000
	N	170	170	169	169	170	169	169	170
Baseline SANS Total	Pearson Correlation	.191*	-.083	.221**	.178*	.357**	.525**	.351**	.273**
	Sig. (2-tailed)	.012	.283	.004	.021	.000	.000	.000	.000
	N	170	170	169	169	170	169	169	170
Baseline GAF	Pearson Correlation	-.206**	.001	-.102	-.113	-.123	-.236**	-.313**	-.397**

Baseline QLS Total	Sig. (2-tailed)	.007	.991	.186	.142	.110	.002	.000	.000
	N	172	172	171	169	170	169	169	170
	Pearson Correlation	-.006	.099	.017	-.187*	-.087	-.155*	-.263**	-.272**
Baseline disorders of thought content	Sig. (2-tailed)	.933	.197	.830	.015	.261	.044	.001	.000
	N	171	171	170	169	170	169	169	170
	Pearson Correlation	1	.257**	.163*	.056	.241**	.318**	.180*	.056
Baseline perceptual abnormalities	Sig. (2-tailed)		.001	.033	.468	.002	.000	.019	.468
	N	172	172	171	169	170	169	169	170
	Pearson Correlation	.257**	1	-.011	.074	-.001	.013	.049	.204**
Baseline conceptual disorganisation	Sig. (2-tailed)	.001		.891	.339	.993	.868	.531	.008
	N	172	172	171	169	170	169	169	170
	Pearson Correlation	.163*	-.011	1	.215**	.387**	.169*	.068	.096
Baseline motor disturbances	Sig. (2-tailed)	.033	.891		.005	.000	.028	.381	.216
	N	171	171	171	169	169	169	169	169
	Pearson Correlation	.056	.074	.215**	1	.187*	.192*	.129	.158*
Baseline disorders of concentration, attention and memory	Sig. (2-tailed)	.468	.339	.005		.015	.013	.095	.041
	N	169	169	169	169	169	169	169	169
	Pearson Correlation	.241**	-.001	.387**	.187*	1	.259**	.199**	.221**
Baseline disorders of emotion and affect	Sig. (2-tailed)	.002	.993	.000	.015		.001	.009	.004
	N	170	170	169	169	170	169	169	170
	Pearson Correlation	.318**	.013	.169*	.192*	.259**	1	.228**	.099
Baseline impaired energy	Sig. (2-tailed)	.000	.868	.028	.013	.001		.003	.201
	N	169	169	169	169	169	169	169	169
	Pearson Correlation	.180*	.049	.068	.129	.199**	.228**	1	.420**
Baseline impaired tolerance to normal stress	Sig. (2-tailed)	.019	.531	.381	.095	.009	.003		.000
	N	169	169	169	169	169	169	169	169
	Pearson Correlation	.056	.204**	.096	.158*	.221**	.099	.420**	1
	Sig. (2-tailed)	.468	.008	.216	.041	.004	.201	.000	
	N	170	170	169	169	170	169	169	170

			At least one of the major 3 disorders remitted over time (but could still have other persisting disorders)									
			Sex	Age at assessment	Pace treatment - Baseline measure	Baseline intake group vulnerability	Baseline intake group BLIPS	Baseline intake group attenuated psychosis	Baseline BPRS Total	Baseline SANS Total	Baseline GAF	
Spearman's rho	At least one of the major 3 disorders remitted over time (but could still have other persisting disorders)	Correlation	1.000	-.042	.152	-.115	.047	.042	-.127	-.092	.148	.049
		Coefficient										
		Sig. (2-tailed)	.	.642	.089	.198	.598	.638	.155	.309	.100	.584
		N	126	126	126	126	126	126	126	125	125	126
	Sex	Correlation	-.042	1.000	-.082	.040	-.018	-.035	.066	-.030	.032	-.052
		Coefficient										
		Sig. (2-tailed)	.642	.	.286	.606	.813	.646	.390	.695	.681	.501
		N	126	172	172	172	172	172	172	170	170	172
	Age at baseline assessment	Correlation	.152	-.082	1.000	-.020	.111	-.029	.012	.037	.204**	-.226**
		Coefficient										
		Sig. (2-tailed)	.089	.286	.	.798	.149	.710	.875	.629	.008	.003
		N	126	172	172	172	172	172	172	170	170	172
	Pace treatment - Baseline measure	Correlation	-.115	.040	-.020	1.000	.059	-.035	-.134	-.272**	-.256**	-.006
		Coefficient										
		Sig. (2-tailed)	.198	.606	.798	.	.442	.651	.079	.000	.001	.934
		N	126	172	172	172	172	172	172	170	170	172
	Baseline intake group Vulnerability	Correlation	.047	-.018	.111	.059	1.000	-.018	-.585**	-.155*	-.030	.015
		Coefficient										
		Sig. (2-tailed)	.598	.813	.149	.442	.	.820	.000	.043	.694	.849
		N	126	172	172	172	172	172	172	170	170	172
	Baseline intake group BLIPS	Correlation	.042	-.035	-.029	-.035	-.018	1.000	-.246**	.011	.005	.135
		Coefficient										

	Sig. (2-tailed)	.638	.646	.710	.651	.820	.	.001	.885	.945	.078
	N	126	172	172	172	172	172	172	170	170	172
Baseline intake group	Correlation										
Attenuated psychosis	Coefficient	-.127	.066	.012	-.134	-.585**	-.246**	1.000	.226**	.131	-.161*
	Sig. (2-tailed)	.155	.390	.875	.079	.000	.001	.	.003	.089	.035
	N	126	172	172	172	172	172	172	170	170	172
Baseline BPRS Total	Correlation										
	Coefficient	-.092	-.030	.037	-.272**	-.155*	.011	.226**	1.000	.568**	-.414**
	Sig. (2-tailed)	.309	.695	.629	.000	.043	.885	.003	.	.000	.000
	N	125	170	170	170	170	170	170	170	170	170
Baseline SANS Total	Correlation										
	Coefficient	.148	.032	.204**	-.256**	-.030	.005	.131	.568**	1.000	-.419**
	Sig. (2-tailed)	.100	.681	.008	.001	.694	.945	.089	.000	.	.000
	N	125	170	170	170	170	170	170	170	170	170
Baseline GAF	Correlation										
	Coefficient	.049	-.052	-.226**	-.006	.015	.135	-.161*	-.414**	-.419**	1.000
	Sig. (2-tailed)	.584	.501	.003	.934	.849	.078	.035	.000	.000	.
	N	126	172	172	172	172	172	172	170	170	172
Baseline QLS Total	Correlation										
	Coefficient	-.005	.054	-.124	.033	.112	.075	-.210**	-.365**	-.541**	.458**
	Sig. (2-tailed)	.957	.481	.106	.670	.144	.329	.006	.000	.000	.000
	N	125	171	171	171	171	171	171	170	170	171
Baseline Disorders of thought content	Correlation										
	Coefficient	-.113	-.062	.159*	-.077	-.248**	.050	.238**	.372**	.215**	-.194*
	Sig. (2-tailed)	.206	.420	.037	.314	.001	.514	.002	.000	.005	.011
	N	126	172	172	172	172	172	172	170	170	172
Baseline Perceptual abnormalities	Correlation										
	Coefficient	-.136	.088	-.209**	.075	-.254**	.090	.292**	.157*	-.117	.028
	Sig. (2-tailed)	.129	.249	.006	.326	.001	.240	.000	.041	.129	.719
	N	126	172	172	172	172	172	172	170	170	172

Baseline Conceptual disorganisation	Correlation										
	Coefficient	.046	.026	.103	-.084	.108	.123	-.005	.306**	.235**	-.098
	Sig. (2-tailed)	.612	.737	.181	.277	.161	.108	.951	.000	.002	.201
	N	125	171	171	171	171	171	171	169	169	171
Baseline Motor disturbances	Correlation										
	Coefficient	-.102	.013	.016	-.035	-.048	-.127	.097	.285**	.165*	-.073
	Sig. (2-tailed)	.261	.864	.835	.650	.536	.100	.210	.000	.032	.347
	N	124	169	169	169	169	169	169	169	169	169
Baseline Disorders of concentration, attention and memory	Correlation										
	Coefficient	-.042	.077	.151*	.033	.095	-.041	-.049	.330**	.394**	-.123
	Sig. (2-tailed)	.645	.319	.050	.665	.218	.596	.528	.000	.000	.110
	N	125	170	170	170	170	170	170	170	170	170
Baseline Disorders of emotion and affect	Correlation										
	Coefficient	.019	.000	.192*	-.230**	.063	.014	.123	.415**	.533**	-.235**
	Sig. (2-tailed)	.833	.996	.012	.003	.416	.858	.110	.000	.000	.002
	N	124	169	169	169	169	169	169	169	169	169
Baseline Impaired energy	Correlation										
	Coefficient	-.087	.034	.106	-.029	-.059	-.162*	.150	.313**	.350**	-.367**
	Sig. (2-tailed)	.335	.658	.168	.709	.445	.035	.052	.000	.000	.000
	N	124	169	169	169	169	169	169	169	169	169
Baseline Impaired tolerance to normal stress	Correlation										
	Coefficient	-.117	.184*	.165*	.089	-.031	-.112	.147	.377**	.253**	-.405**
	Sig. (2-tailed)	.192	.016	.032	.247	.691	.147	.055	.000	.001	.000
	N	125	170	170	170	170	170	170	170	170	170

			Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	
			disorders	of thought	perceptual	conceptual	motor	disorders of	disorders	impaired	
			of	content	abnormalities	disorganisation	disturbances	concentration, attention and	of emotion and affect	impaired energy	
			QLS Total					memory		stress	
Spearman's rho	At least one of the major	Correlation Coefficient	-.005	-.113	-.136	.046	-.102	-.042	.019	-.087	-.117
	3 disorders remitted over	Sig. (2-tailed)	.957	.206	.129	.612	.261	.645	.833	.335	.192
	time (but could still have	N									
	other persisting		125	126	126	125	124	125	124	124	125
	disorders)										
Sex		Correlation Coefficient	.054	-.062	.088	.026	.013	.077	.000	.034	.184*
		Sig. (2-tailed)	.481	.420	.249	.737	.864	.319	.996	.658	.016
		N	171	172	172	171	169	170	169	169	170
Age at baseline assessment		Correlation Coefficient	-.124	.159*	-.209**	.103	.016	.151*	.192*	.106	.165*
		Sig. (2-tailed)	.106	.037	.006	.181	.835	.050	.012	.168	.032
		N	171	172	172	171	169	170	169	169	170
Pace treatment - Baseline measure		Correlation Coefficient	.033	-.077	.075	-.084	-.035	.033	-.230**	-.029	.089
		Sig. (2-tailed)	.670	.314	.326	.277	.650	.665	.003	.709	.247
		N	171	172	172	171	169	170	169	169	170
Baseline intake group Vulnerability		Correlation Coefficient	.112	-.248**	-.254**	.108	-.048	.095	.063	-.059	-.031
		Sig. (2-tailed)	.144	.001	.001	.161	.536	.218	.416	.445	.691
		N	171	172	172	171	169	170	169	169	170
Baseline intake group BLIPS		Correlation Coefficient	.075	.050	.090	.123	-.127	-.041	.014	-.162*	-.112
		Sig. (2-tailed)	.329	.514	.240	.108	.100	.596	.858	.035	.147
		N	171	172	172	171	169	170	169	169	170
Baseline intake group Attenuated psychosis		Correlation Coefficient	-.210**	.238**	.292**	-.005	.097	-.049	.123	.150	.147
		Sig. (2-tailed)	.006	.002	.000	.951	.210	.528	.110	.052	.055
		N	171	172	172	171	169	170	169	169	170
Baseline BPRS Total		Correlation Coefficient	-.365**	.372**	.157*	.306**	.285**	.330**	.415**	.313**	.377**
		Sig. (2-tailed)	.000	.000	.041	.000	.000	.000	.000	.000	.000
		N	170	170	170	169	169	170	169	169	170
Baseline SANS Total		Correlation Coefficient	-.541**	.215**	-.117	.235**	.165*	.394**	.533**	.350**	.253**
		Sig. (2-tailed)	.000	.005	.129	.002	.032	.000	.000	.000	.001
		N	170	170	170	169	169	170	169	169	170

Baseline GAF	Correlation Coefficient	.458**	-.194*	.028	-.098	-.073	-.123	-.235**	-.367**	-.405**
	Sig. (2-tailed)	.000	.011	.719	.201	.347	.110	.002	.000	.000
	N	171	172	172	171	169	170	169	169	170
Baseline QLS Total	Correlation Coefficient	1.000	.005	.134	.006	-.171*	-.172*	-.169*	-.314**	-.293**
	Sig. (2-tailed)	.	.945	.081	.934	.026	.025	.028	.000	.000
	N	171	171	171	170	169	170	169	169	170
Baseline disorders of thought content	Correlation Coefficient	.005	1.000	.229**	.143	.050	.230**	.318**	.177*	.070
	Sig. (2-tailed)	.945	.	.003	.061	.520	.003	.000	.021	.368
	N	171	172	172	171	169	170	169	169	170
Baseline perceptual abnormalities	Correlation Coefficient	.134	.229**	1.000	.005	.023	.016	-.001	.038	.154*
	Sig. (2-tailed)	.081	.003	.	.951	.762	.840	.990	.623	.044
	N	171	172	172	171	169	170	169	169	170
Baseline conceptual disorganisation	Correlation Coefficient	.006	.143	.005	1.000	.216**	.408**	.144	.067	.095
	Sig. (2-tailed)	.934	.061	.951	.	.005	.000	.062	.385	.220
	N	170	171	171	171	169	169	169	169	169
Baseline motor disturbances	Correlation Coefficient	-.171*	.050	.023	.216**	1.000	.208**	.184*	.117	.127
	Sig. (2-tailed)	.026	.520	.762	.005	.	.007	.017	.130	.101
	N	169	169	169	169	169	169	169	169	169
Baseline disorders of concentration, attention and memory	Correlation Coefficient	-.172*	.230**	.016	.408**	.208**	1.000	.275**	.250**	.187*
	Sig. (2-tailed)	.025	.003	.840	.000	.007	.	.000	.001	.015
	N	170	170	170	169	169	170	169	169	170
Baseline disorders of emotion and affect	Correlation Coefficient	-.169*	.318**	-.001	.144	.184*	.275**	1.000	.218**	.097
	Sig. (2-tailed)	.028	.000	.990	.062	.017	.000	.	.004	.211
	N	169	169	169	169	169	169	169	169	169
Baseline impaired energy	Correlation Coefficient	-.314**	.177*	.038	.067	.117	.250**	.218**	1.000	.389**
	Sig. (2-tailed)	.000	.021	.623	.385	.130	.001	.004	.	.000
	N	169	169	169	169	169	169	169	169	169
Baseline impaired tolerance to normal stress	Correlation Coefficient	-.293**	.070	.154*	.095	.127	.187*	.097	.389**	1.000
	Sig. (2-tailed)	.000	.368	.044	.220	.101	.015	.211	.000	.
	N	170	170	170	169	169	170	169	169	170

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Appendix B8

Correlations for baseline predictor variables of incident disorder (next page)

		Onset of any new mental disorder (calculated from the three main groups)		Sex	Age at baseline assessment	Pace treatment - baseline measure	Baseline intake group: Vulnerability	Baseline intake group: BLIPS	Baseline intake group Attenuated Psychosis	Baseline BPRS Total	Baseline SANS Total	Baseline GAF	Baseline QLS Total
Onset of any new mental disorder (calculated from the three main groups)	Pearson												
	Correlation	1		-.135	-.161	.205*	-.187*	.112	.001	-.057	-.063	.035	.051
	Sig. (2-tailed)			.132	.073	.021	.036	.213	.993	.530	.488	.699	.575
	N	126		126	126	126	126	126	126	125	125	126	125
Sex	Pearson												
	Correlation	-.135		1	-.082	.040	-.018	-.035	.066	-.032	.050	-.040	.063
	Sig. (2-tailed)	.132			.283	.606	.813	.646	.390	.682	.516	.598	.413
	N	126		172	172	172	172	172	172	170	170	172	171
Age at baseline assessment	Pearson												
	Correlation	-.161		-.082	1	-.042	.147	-.037	-.013	-.002	.166*	-.219**	-.093
	Sig. (2-tailed)	.073		.283		.583	.055	.634	.869	.974	.030	.004	.227
	N	126		172	172	172	172	172	172	170	170	172	171
Pace treatment - Baseline measure	Pearson												
	Correlation	.205*		.040	-.042	1	.059	-.035	-.134	-.266**	-.201**	.014	.024
	Sig. (2-tailed)	.021		.606	.583		.442	.651	.079	.000	.009	.852	.755
	N	126		172	172	172	172	172	172	170	170	172	171
Baseline intake group Vulnerability	Pearson												
	Correlation	-.187*		-.018	.147	.059	1	-.018	-.585**	-.168*	-.007	-.012	.113
	Sig. (2-tailed)	.036		.813	.055	.442		.820	.000	.029	.932	.875	.141
	N	126		172	172	172	172	172	172	170	170	172	171
Baseline intake group BLIPS	Pearson												
	Correlation	.112		-.035	-.037	-.035	-.018	1	-.246**	.018	-.011	.125	.075
	Sig. (2-tailed)	.213		.646	.634	.651	.820		.001	.813	.883	.103	.328
	N	126		172	172	172	172	172	172	170	170	172	171
Baseline intake group Attenuated psychosis	Pearson												
	Correlation	.001		.066	-.013	-.134	-.585**	-.246**	1	.226**	.126	-.161*	-.200**
	Sig. (2-tailed)	.993		.390	.869	.079	.000	.001		.003	.101	.035	.009
	N	126		172	172	172	172	172	172	170	170	172	171

Baseline BPRS Total	Pearson											
	Correlation	-.057	-.032	-.002	-.266**	-.168*	.018	.226**	1	.568**	-.421**	-.400**
	Sig. (2-tailed)	.530	.682	.974	.000	.029	.813	.003		.000	.000	.000
	N	125	170	170	170	170	170	170	170	170	170	170
Baseline SANS Total	Pearson											
	Correlation	-.063	.050	.166*	-.201**	-.007	-.011	.126	.568**	1	-.463**	-.561**
	Sig. (2-tailed)	.488	.516	.030	.009	.932	.883	.101	.000		.000	.000
	N	125	170	170	170	170	170	170	170	170	170	170
Baseline GAF	Pearson											
	Correlation	.035	-.040	-.219**	.014	-.012	.125	-.161*	-.421**	-.463**	1	.485**
	Sig. (2-tailed)	.699	.598	.004	.852	.875	.103	.035	.000	.000		.000
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline QLS Total	Pearson											
	Correlation	.051	.063	-.093	.024	.113	.075	-.200**	-.400**	-.561**	.485**	1
	Sig. (2-tailed)	.575	.413	.227	.755	.141	.328	.009	.000	.000	.000	
	N	125	171	171	171	171	171	171	170	170	171	171
Baseline disorders of thought content	Pearson											
	Correlation	.107	-.047	.143	-.084	-.261**	.090	.245**	.382**	.191*	-.206**	-.006
	Sig. (2-tailed)	.232	.539	.061	.274	.001	.239	.001	.000	.012	.007	.933
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline perceptual abnormalities	Pearson											
	Correlation	.123	.093	-.205**	.087	-.302**	.090	.359**	.199**	-.083	.001	.099
	Sig. (2-tailed)	.171	.225	.007	.254	.000	.243	.000	.009	.283	.991	.197
	N	126	172	172	172	172	172	172	170	170	172	171
Baseline conceptual disorganisation	Pearson											
	Correlation	.038	.029	.077	-.084	.112	.133	-.013	.294**	.221**	-.102	.017
	Sig. (2-tailed)	.673	.706	.318	.273	.143	.083	.865	.000	.004	.186	.830
	N	125	171	171	171	171	171	171	169	169	171	170
Baseline motor disturbances	Pearson											
	Correlation	-.042	.028	-.008	-.011	-.061	-.123	.121	.311**	.178*	-.113	-.187*

	Sig. (2-tailed)	.645	.717	.922	.890	.431	.112	.118	.000	.021	.142	.015
	N	124	169	169	169	169	169	169	169	169	169	169
Baseline disorders of concentration, attention and memory	Pearson Correlation	-.002	.128	.118	.036	.111	-.048	-.071	.293**	.357**	-.123	-.087
	Sig. (2-tailed)	.984	.096	.126	.641	.148	.537	.357	.000	.000	.110	.261
	N	125	170	170	170	170	170	170	170	170	170	170
Baseline disorders of emotion and affect	Pearson Correlation	-.057	-.002	.172*	-.248**	.061	.014	.112	.399**	.525**	-.236**	-.155*
	Sig. (2-tailed)	.530	.980	.025	.001	.429	.860	.149	.000	.000	.002	.044
	N	124	169	169	169	169	169	169	169	169	169	169
Baseline impaired energy	Pearson Correlation	-.008	.010	.061	-.035	-.078	-.131	.153*	.285**	.351**	-.313**	-.263**
	Sig. (2-tailed)	.927	.899	.430	.649	.317	.090	.048	.000	.000	.000	.001
	N	124	169	169	169	169	169	169	169	169	169	169
Baseline impaired tolerance to normal stress	Pearson Correlation	-.084	.183*	.161*	.064	-.036	-.083	.154*	.389**	.273**	-.397**	-.272**
	Sig. (2-tailed)	.354	.017	.036	.406	.646	.283	.045	.000	.000	.000	.000
	N	125	170	170	170	170	170	170	170	170	170	170

		Baseline							
		Baseline disorders of thought content	Baseline perceptual abnormalities	Baseline conceptual disorganisation	Baseline motor disturbances	Baseline disorders of concentration, attention and memory	Baseline disorders of emotion and affect	Baseline impaired energy	Baseline impaired tolerance to normal stress
Onset of any new mental disorder (calculated from the three main groups)	Pearson Correlation	.107	.123	.038	-.042	-.002	-.057	-.008	-.084
	Sig. (2-tailed)	.232	.171	.673	.645	.984	.530	.927	.354
	N	126	126	125	124	125	124	124	125
Sex	Pearson Correlation	-.047	.093	.029	.028	.128	-.002	.010	.183*
	Sig. (2-tailed)	.539	.225	.706	.717	.096	.980	.899	.017
	N	172	172	171	169	170	169	169	170
Age at baseline assessment	Pearson Correlation	.143	-.205**	.077	-.008	.118	.172*	.061	.161*
	Sig. (2-tailed)	.061	.007	.318	.922	.126	.025	.430	.036
	N	172	172	171	169	170	169	169	170
Pace treatment - Baseline measure	Pearson Correlation	-.084	.087	-.084	-.011	.036	-.248**	-.035	.064
	Sig. (2-tailed)	.274	.254	.273	.890	.641	.001	.649	.406
	N	172	172	171	169	170	169	169	170
Baseline intake group Vulnerability	Pearson Correlation	-.261**	-.302**	.112	-.061	.111	.061	-.078	-.036
	Sig. (2-tailed)	.001	.000	.143	.431	.148	.429	.317	.646
	N	172	172	171	169	170	169	169	170
Baseline intake group BLIPS	Pearson Correlation	.090	.090	.133	-.123	-.048	.014	-.131	-.083
	Sig. (2-tailed)	.239	.243	.083	.112	.537	.860	.090	.283
	N	172	172	171	169	170	169	169	170
Baseline intake group Attenuated psychosis	Pearson Correlation	.245**	.359**	-.013	.121	-.071	.112	.153*	.154*
	Sig. (2-tailed)	.001	.000	.865	.118	.357	.149	.048	.045
	N	172	172	171	169	170	169	169	170
Baseline BPRS Total	Pearson Correlation	.382**	.199**	.294**	.311**	.293**	.399**	.285**	.389**
	Sig. (2-tailed)	.000	.009	.000	.000	.000	.000	.000	.000
	N	170	170	169	169	170	169	169	170
Baseline SANS Total	Pearson Correlation	.191*	-.083	.221**	.178*	.357**	.525**	.351**	.273**
	Sig. (2-tailed)	.012	.283	.004	.021	.000	.000	.000	.000
	N	170	170	169	169	170	169	169	170
Baseline GAF	Pearson Correlation	-.206**	.001	-.102	-.113	-.123	-.236**	-.313**	-.397**
	Sig. (2-tailed)	.007	.991	.186	.142	.110	.002	.000	.000

	N	172	172	171	169	170	169	169	170
Baseline QLS Total	Pearson Correlation	-.006	.099	.017	-.187*	-.087	-.155*	-.263**	-.272**
	Sig. (2-tailed)	.933	.197	.830	.015	.261	.044	.001	.000
	N	171	171	170	169	170	169	169	170
Baseline disorders of thought content	Pearson Correlation	1	.257**	.163*	.056	.241**	.318**	.180*	.056
	Sig. (2-tailed)		.001	.033	.468	.002	.000	.019	.468
	N	172	172	171	169	170	169	169	170
Baseline perceptual abnormalities	Pearson Correlation	.257**	1	-.011	.074	-.001	.013	.049	.204**
	Sig. (2-tailed)	.001		.891	.339	.993	.868	.531	.008
	N	172	172	171	169	170	169	169	170
Baseline conceptual disorganisation	Pearson Correlation	.163*	-.011	1	.215**	.387**	.169*	.068	.096
	Sig. (2-tailed)	.033	.891		.005	.000	.028	.381	.216
	N	171	171	171	169	169	169	169	169
Baseline motor disturbances	Pearson Correlation	.056	.074	.215**	1	.187*	.192*	.129	.158*
	Sig. (2-tailed)	.468	.339	.005		.015	.013	.095	.041
	N	169	169	169	169	169	169	169	169
Baseline disorders of concentration, attention and memory	Pearson Correlation	.241**	-.001	.387**	.187*	1	.259**	.199**	.221**
	Sig. (2-tailed)	.002	.993	.000	.015		.001	.009	.004
	N	170	170	169	169	170	169	169	170
Baseline disorders of emotion and affect	Pearson Correlation	.318**	.013	.169*	.192*	.259**	1	.228**	.099
	Sig. (2-tailed)	.000	.868	.028	.013	.001		.003	.201
	N	169	169	169	169	169	169	169	169
Baseline impaired energy	Pearson Correlation	.180*	.049	.068	.129	.199**	.228**	1	.420**
	Sig. (2-tailed)	.019	.531	.381	.095	.009	.003		.000
	N	169	169	169	169	169	169	169	169
Baseline impaired tolerance to normal stress	Pearson Correlation	.056	.204**	.096	.158*	.221**	.099	.420**	1
	Sig. (2-tailed)	.468	.008	.216	.041	.004	.201	.000	
	N	170	170	169	169	170	169	169	170

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

			Onset of any new mental disorder (calculated from the three main groups)	Sex	Age at baseline assessment	Pace treatment - Baseline measure	Baseline intake group Vulnerability	Baseline intake group BLIPS	Baseline intake group Attenuated psychosis	Baseline BPRS Total	Baseline SANS Total	Baseline GAF
Spearman's rho	Onset of any new mental disorder (calculated from the three main groups)	Correlation Coefficient	1.000	-.135	-.148	.205*	-.187*	.112	.001	-.064	-.070	.022
		Sig. (2-tailed)	.	.132	.099	.021	.036	.213	.993	.480	.438	.806
		N	126	126	126	126	126	126	126	125	125	126
	Sex	Correlation Coefficient	-.135	1.000	-.082	.040	-.018	-.035	.066	-.030	.032	-.052
		Sig. (2-tailed)	.132	.	.286	.606	.813	.646	.390	.695	.681	.501
		N	126	172	172	172	172	172	172	170	170	172
	Age at baseline assessment	Correlation Coefficient	-.148	-.082	1.000	-.020	.111	-.029	.012	.037	.204**	-.226**
		Sig. (2-tailed)	.099	.286	.	.798	.149	.710	.875	.629	.008	.003
		N	126	172	172	172	172	172	172	170	170	172
	Pace treatment - Baseline measure	Correlation Coefficient	.205*	.040	-.020	1.000	.059	-.035	-.134	-.272**	-.256**	-.006
		Sig. (2-tailed)	.021	.606	.798	.	.442	.651	.079	.000	.001	.934
		N	126	172	172	172	172	172	172	170	170	172
	Baseline intake group: Vulnerability	Correlation Coefficient	-.187*	-.018	.111	.059	1.000	-.018	-.585**	-.155*	-.030	.015
		Sig. (2-tailed)	.036	.813	.149	.442	.	.820	.000	.043	.694	.849
		N	126	172	172	172	172	172	172	170	170	172
	Baseline intake group: BLIPS	Correlation Coefficient	.112	-.035	-.029	-.035	-.018	1.000	-.246**	.011	.005	.135
		Sig. (2-tailed)	.213	.646	.710	.651	.820	.	.001	.885	.945	.078
		N	126	172	172	172	172	172	172	170	170	172
	Baseline intake group:	Correlation Coefficient	.001	.066	.012	-.134	-.585**	-.246**	1.000	.226**	.131	-.161*
		Sig. (2-tailed)	.993	.390	.875	.079	.000	.001	.	.003	.089	.035

Attenuated psychosis	N	126	172	172	172	172	172	172	170	170	172
Baseline BPRS Total	Correlation Coefficient	-.064	-.030	.037	-.272**	-.155*	.011	.226**	1.000	.568**	-.414**
	Sig. (2-tailed)	.480	.695	.629	.000	.043	.885	.003	.	.000	.000
	N	125	170	170	170	170	170	170	170	170	170
Baseline SANS Total	Correlation Coefficient	-.070	.032	.204**	-.256**	-.030	.005	.131	.568**	1.000	-.419**
	Sig. (2-tailed)	.438	.681	.008	.001	.694	.945	.089	.000	.	.000
	N	125	170	170	170	170	170	170	170	170	170
Baseline GAF	Correlation Coefficient	.022	-.052	-.226**	-.006	.015	.135	-.161*	-.414**	-.419**	1.000
	Sig. (2-tailed)	.806	.501	.003	.934	.849	.078	.035	.000	.000	.
	N	126	172	172	172	172	172	172	170	170	172
Baseline QLS Total	Correlation Coefficient	.116	.054	-.124	.033	.112	.075	-.210**	-.365**	-.541**	.458**
	Sig. (2-tailed)	.197	.481	.106	.670	.144	.329	.006	.000	.000	.000
	N	125	171	171	171	171	171	171	170	170	171
Baseline disorders of thought content	Correlation Coefficient	.113	-.062	.159*	-.077	-.248**	.050	.238**	.372**	.215**	-.194*
	Sig. (2-tailed)	.209	.420	.037	.314	.001	.514	.002	.000	.005	.011
	N	126	172	172	172	172	172	172	170	170	172
Baseline perceptual abnormalities	Correlation Coefficient	.109	.088	-.209**	.075	-.254**	.090	.292**	.157*	-.117	.028
	Sig. (2-tailed)	.224	.249	.006	.326	.001	.240	.000	.041	.129	.719
	N	126	172	172	172	172	172	172	170	170	172
Baseline conceptual disorganisation	Correlation Coefficient	.041	.026	.103	-.084	.108	.123	-.005	.306**	.235**	-.098
	Sig. (2-tailed)	.650	.737	.181	.277	.161	.108	.951	.000	.002	.201
	N	125	171	171	171	171	171	171	169	169	171

Baseline motor disturbances	Correlation											
	Coefficient	-.055	.013	.016	-.035	-.048	-.127	.097	.285**	.165*	-.073	
	Sig. (2-tailed)	.546	.864	.835	.650	.536	.100	.210	.000	.032	.347	
	N	124	169	169	169	169	169	169	169	169	169	
Baseline disorders of concentration, attention and memory	Correlation											
	Coefficient	.024	.077	.151*	.033	.095	-.041	-.049	.330**	.394**	-.123	
	Sig. (2-tailed)	.792	.319	.050	.665	.218	.596	.528	.000	.000	.110	
	N	125	170	170	170	170	170	170	170	170	170	
Baseline disorders of emotion and affect	Correlation											
	Coefficient	-.049	.000	.192*	-.230**	.063	.014	.123	.415**	.533**	-.235**	
	Sig. (2-tailed)	.587	.996	.012	.003	.416	.858	.110	.000	.000	.002	
	N	124	169	169	169	169	169	169	169	169	169	
Baseline impaired energy	Correlation											
	Coefficient	-.021	.034	.106	-.029	-.059	-.162*	.150	.313**	.350**	-.367**	
	Sig. (2-tailed)	.816	.658	.168	.709	.445	.035	.052	.000	.000	.000	
	N	124	169	169	169	169	169	169	169	169	169	
Baseline impaired tolerance to normal stress	Correlation											
	Coefficient	-.082	.184*	.165*	.089	-.031	-.112	.147	.377**	.253**	-.405**	
	Sig. (2-tailed)	.365	.016	.032	.247	.691	.147	.055	.000	.001	.000	
	N	125	170	170	170	170	170	170	170	170	170	

Nonparametric Correlations

Spearman's Rho correlations of baseline predictors and Incident disorder

			Baseline					Baseline		Baseline	
			QLS Total	disorders of thought content	Baseline perceptual abnormalities	Baseline conceptual disorganisation	Baseline motor disturbances	disorders of concentration, attention and memory	Baseline disorders of emotion and affect	Baseline impaired energy	Baseline impaired tolerance to normal stress
Spearman's rho	Onset of any new mental disorder (calculated from the three main groups)	Correlation Coefficient	.116	.113	.109	.041	-.055	.024	-.049	-.021	-.082
		Sig. (2-tailed)	.197	.209	.224	.650	.546	.792	.587	.816	.365
		N	125	126	126	125	124	125	124	124	125
	Sex	Correlation Coefficient	.054	-.062	.088	.026	.013	.077	.000	.034	.184*
		Sig. (2-tailed)	.481	.420	.249	.737	.864	.319	.996	.658	.016
		N	171	172	172	171	169	170	169	169	170
	Age at baseline assessment	Correlation Coefficient	-.124	.159*	-.209**	.103	.016	.151*	.192*	.106	.165*
		Sig. (2-tailed)	.106	.037	.006	.181	.835	.050	.012	.168	.032
		N	171	172	172	171	169	170	169	169	170
	Pace treatment - Baseline measure	Correlation Coefficient	.033	-.077	.075	-.084	-.035	.033	-.230**	-.029	.089
		Sig. (2-tailed)	.670	.314	.326	.277	.650	.665	.003	.709	.247
		N	171	172	172	171	169	170	169	169	170
	Baseline intake group	Correlation Coefficient	.112	-.248**	-.254**	.108	-.048	.095	.063	-.059	-.031
		Sig. (2-tailed)	.144	.001	.001	.161	.536	.218	.416	.445	.691
	Vulnerability	N	171	172	172	171	169	170	169	169	170
	Baseline intake group BLIPS	Correlation Coefficient	.075	.050	.090	.123	-.127	-.041	.014	-.162*	-.112
		Sig. (2-tailed)	.329	.514	.240	.108	.100	.596	.858	.035	.147
		N	171	172	172	171	169	170	169	169	170
	Baseline intake group Attenuated psychosis	Correlation Coefficient	-.210**	.238**	.292**	-.005	.097	-.049	.123	.150	.147
		Sig. (2-tailed)	.006	.002	.000	.951	.210	.528	.110	.052	.055
		N	171	172	172	171	169	170	169	169	170
	Baseline BPRS	Correlation Coefficient	-.365**	.372**	.157*	.306**	.285**	.330**	.415**	.313**	.377**
	Total	Sig. (2-tailed)	.000	.000	.041	.000	.000	.000	.000	.000	.000
		N	170	170	170	169	169	170	169	169	170
	Baseline SANS	Correlation Coefficient	-.541**	.215**	-.117	.235**	.165*	.394**	.533**	.350**	.253**
	Total	Sig. (2-tailed)	.000	.005	.129	.002	.032	.000	.000	.000	.001
		N	170	170	170	169	169	170	169	169	170

Baseline GAF	Correlation Coefficient	.458**	-.194*	.028	-.098	-.073	-.123	-.235**	-.367**	-.405**
	Sig. (2-tailed)	.000	.011	.719	.201	.347	.110	.002	.000	.000
	N	171	172	172	171	169	170	169	169	170
Baseline QLS	Correlation Coefficient	1.000	.005	.134	.006	-.171*	-.172*	-.169*	-.314**	-.293**
	Sig. (2-tailed)	.	.945	.081	.934	.026	.025	.028	.000	.000
	N	171	171	171	170	169	170	169	169	170
Baseline Disorders of thought content	Correlation Coefficient	.005	1.000	.229**	.143	.050	.230**	.318**	.177*	.070
	Sig. (2-tailed)	.945	.	.003	.061	.520	.003	.000	.021	.368
	N	171	172	172	171	169	170	169	169	170
Baseline Perceptual abnormalities	Correlation Coefficient	.134	.229**	1.000	.005	.023	.016	-.001	.038	.154*
	Sig. (2-tailed)	.081	.003	.	.951	.762	.840	.990	.623	.044
	N	171	172	172	171	169	170	169	169	170
Baseline Conceptual disorganisation	Correlation Coefficient	.006	.143	.005	1.000	.216**	.408**	.144	.067	.095
	Sig. (2-tailed)	.934	.061	.951	.	.005	.000	.062	.385	.220
	N	170	171	171	171	169	169	169	169	169
Baseline Motor disturbances	Correlation Coefficient	-.171*	.050	.023	.216**	1.000	.208**	.184*	.117	.127
	Sig. (2-tailed)	.026	.520	.762	.005	.	.007	.017	.130	.101
	N	169	169	169	169	169	169	169	169	169
Baseline Disorders of concentration, attention and memory	Correlation Coefficient	-.172*	.230**	.016	.408**	.208**	1.000	.275**	.250**	.187*
	Sig. (2-tailed)	.025	.003	.840	.000	.007	.	.000	.001	.015
	N	170	170	170	169	169	170	169	169	170
Baseline Disorders of emotion and affect	Correlation Coefficient	-.169*	.318**	-.001	.144	.184*	.275**	1.000	.218**	.097
	Sig. (2-tailed)	.028	.000	.990	.062	.017	.000	.	.004	.211
	N	169	169	169	169	169	169	169	169	169
Baseline Impaired energy	Correlation Coefficient	-.314**	.177*	.038	.067	.117	.250**	.218**	1.000	.389**
	Sig. (2-tailed)	.000	.021	.623	.385	.130	.001	.004	.	.000
	N	169	169	169	169	169	169	169	169	169

Baseline	Correlation Coefficient	-.293**	.070	.154*	.095	.127	.187*	.097	.389**	1.000
Impaired	Sig. (2-tailed)	.000	.368	.044	.220	.101	.015	.211	.000	.
tolerance to normal stress	N	170	170	170	169	169	170	169	169	170

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Appendix B9

Mood disorder trajectory and functional outcomes at follow-up (GAF)

A similar pattern of findings was found between presence of mood disorder and functioning, as measured by the GAF ²⁸, though here, participants who Never had a disorder had the highest scores (Figure B9). There was a statistically significant difference at the $p < .05$ level in GAF scores for the four trajectory groups ($F(3, 118) = 4.23, p = .01, \eta^2 = .1$) representing a moderate effect size. Post-hoc comparisons using the Tukey HSD test indicated that the mean GAF score for those with a continuous mood disorder ($M = 65.66, SD = 10.19$) was significantly different from the mean GAF score of those with a remitted mood disorder ($M = 72.61, SD = 11.83$). The mean GAF score for those who had an incident mood disorder was not statistically different from the other groups ($M = 67.06, SD = 9.26$). The mean GAF score for those who never had a mood disorder was higher than for all other groups ($M = 73.43, SD = 9.05$), however this difference was not statistically significant, though there were only 12 participants in this group.

²⁸ GAF was measured at both baseline and follow-up. SOFAS was only measured at follow-up

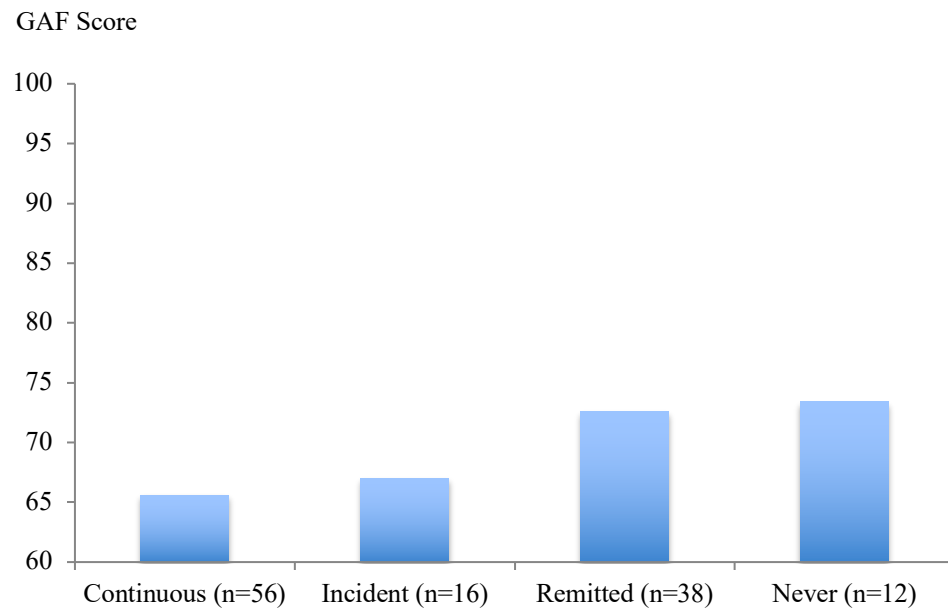


Figure B9: GAF score by trajectory of mood disorder over time

Appendix B10

Anxiety disorder trajectory and functional outcomes at follow-up (GAF)

Similarly, a one-way between-groups analysis of variance was conducted to explore the relationship of trajectory of anxiety disorder on levels of functioning at follow-up, as measured by the GAF. Trajectories were plotted against GAF scores (Figure B10). There difference at the $p < .05$ level in GAF scores for the four trajectory groups was not significant: $F(3, 118) = 2.30$ $p = .08$. The mean GAF scores for those who had a remitted anxiety disorder was higher than all other groups ($M = 72.28$, $SD = 10.20$), though this difference was not significant. Other GAF scores were as follows: Anxiety never ($M = 69.40$, $SD = 11.43$), incident anxiety ($M = 64.72$, $SD = 10.36$), continuous anxiety ($M = 65.59$, $SD = 9.33$).

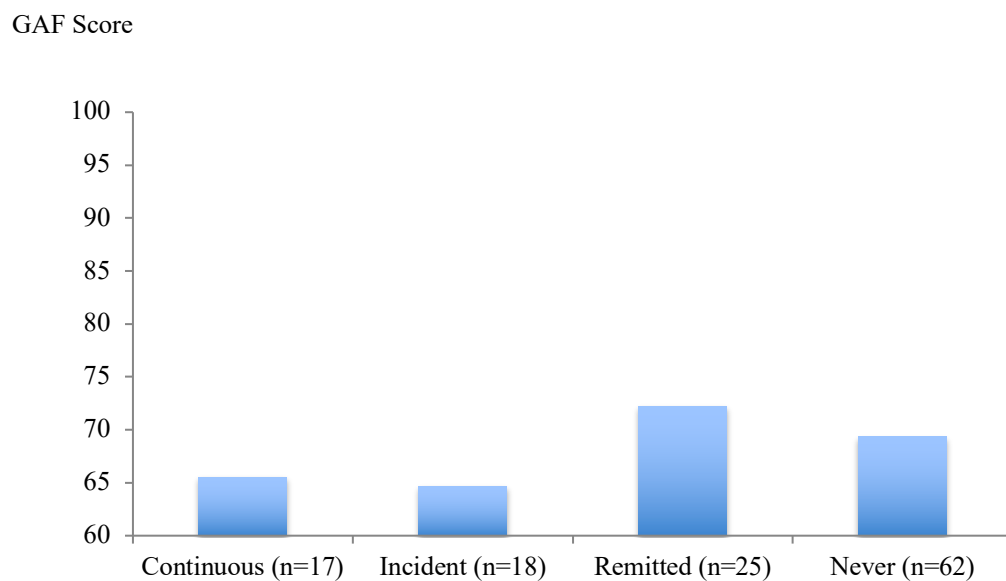


Figure B10: GAF score by trajectory of anxiety disorder over time

Appendix B11

Substance use disorder trajectory and functional outcomes at follow-up (GAF)

One-way between-groups analysis of variance revealed that trajectory of SUD over time had a significant impact on levels of functioning at follow-up, as measured by the GAF (Figure B11). There was a statistically significant difference at the $p < .05$ level in GAF scores for the four trajectory groups ($F(3, 118) = 6.20, p = .001, \eta^2 = .14$) with a large effect size.¹⁴ Post-hoc comparisons using the Tukey HSD test indicated that the mean GAF score for those with an incident SUD ($M = 61.54, SD = 11.64$) was significantly different to the mean GAF score of those who had never had an SUD ($M = 71.53, SD = 9.68$). Those with a continuous SUD had a higher average GAF score ($M = 68.33, SD = 10.94$) than those who had an incident SUD, but this difference was not significant, and the group was small ($n=12$). Those who remitted from an SUD did not vary significantly from other groups ($M = 66.75, SD = 10.57$), however this group was also very small ($n=8$), which might have affected comparisons.

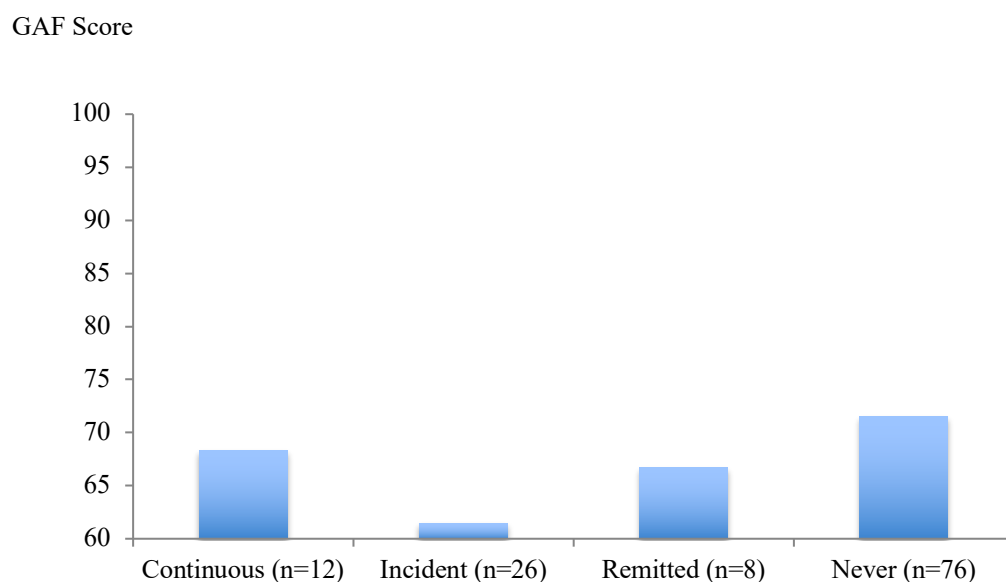


Figure B11: GAF score by trajectory of SUD over time

Appendix B12

Differences in mental illness in baseline treatment groups

A chi-square test for independence revealed a significant association between baseline treatment group and baseline mental disorder ($\chi^2(2, n=170)=11.75, p=.001, \phi = -.26$). Those in the intervention group at baseline had a higher rate of mental disorders.

Table B12

Participants who had a mental disorder at baseline and baseline treatment group

Baseline mental disorder	Baseline treatment group		
	Intervention	Treatment as usual	Total
No	6 (5.8%)	16 (23.9%)	22
Yes	97 (94.2%)	51 (76.1%)	148
Total	103 (100%)	67 (100%)	170

*Note: Intervention group data were missing for two participants

Appendix B13

Table B13:

Intake UHR group and corresponding criteria

Intake group	Criteria	Operationalised in the CAARMS
Attenuated positive psychotic symptoms (APS)	Presence of ≥ 1 of the following symptoms: ideas of reference, odd beliefs or magical thinking, perceptual disturbance, paranoid ideation, odd thinking and speech, odd behaviour, and appearance At least several times a week Present within the past year Present for ≥ 1 week and ≤ 5 years	CAARMS subscales disorders of thought content, perceptual abnormalities, disorganised speech Group A: Severity scale score 3–5 (thought content), 3–4 (perceptual abnormalities), and/or 4–5 (DS) PLUS Frequency scale score 3–6 (thought content, perceptual abnormalities and/or disorganised speech) for ≥ 1 week OR Frequency scale score 2 (thought content, perceptual abnormalities and/or disorganised speech) Group B: Severity scale score 6 (thought content and/or disorganised speech) and/or 5–6 (perceptual abnormalities) PLUS Frequency scale score 1 (thought content, perceptual abnormalities and/or disorganised speech)
Brief limited intermittent psychotic symptoms (BLIPS)	Transient psychotic symptoms: presence of ≥ 1 of the following: ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, and odd thinking or speech Duration of episode: 1 week	CAARMS subscales disorders of thought content, perceptual abnormalities, disorganised speech Intensity scale score 6 (thought content), 6 (disorganised speech), and/or 5–6 (perceptual abnormalities) PLUS Frequency scale score 4–6 (thought content,

Trait and state risk factors	At least several times per week	disorganised speech, and/or perceptual
	Symptoms resolve spontaneously	abnormalities).
	Must have occurred within the past year	
	Schizotypal personality disorder in the	SCID-II (Schizotypal personality disorder)
	identified individual or a	Family questionnaire (family history of
	first-degree relative with a psychotic	psychosis)
	disorder	30% decline in GAF
	Significant decline in mental state or	
	functioning, maintained for	
	at least ≥ 1 month and ≤ 5 years	
	Decline in functioning must have occurred	
	within the past year	

Note: This table was adapted from Hartmann et al., (2016)