Clinical Predictors in Young Help-Seeking People Referred to the Lancashire Early Assessment and Detection Clinic:

A Service Evaluation

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ABSTRACT OF THESIS submitted by Caroline Johnson

For the degree of PhD and entitled Clinical Predictors of Psychosis in Young Help-Seeking People Referred to the Lancashire Early Assessment and Detection Clinic: A Service Evaluation.

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Two main psychopathology-based approaches to detection of the prodrome have emerged; the Ultra High Risk (UHR) and Basic Symptom approaches. Conversion risk varies between studies using these approaches and in one centre conversion rates are reported to be decreasing year on year. There is a need examine the conversion risk across studies to establish a pooled estimate of risk for instruments designed to detect the prodrome of psychosis.

To maximise the detection of those thought to present a risk of psychosis the Lancashire Early Assessment and Detection (LEAD) clinic uses an UHR instrument, the Comprehensive Assessment of at Risk Mental States (CAARMS) and A Basic Symptom instrument, the Schizophrenia Proneness Instrument (SPI-A).

The thesis had two broad aims 1) to conduct a systematic review with meta-analysis of the research field to date and identify areas for further research, 2) to establish the accuracy of the LEAD clinic predictions. The meta-analysis involved a systematic search of MEDLINE, EMBASE, PsychINFO and CINHAL identifying studies of psychopathology-based instruments for the detection of the psychosis prodrome. The service evaluation examined for conversion to psychosis in patients examined for Basic Symptoms (SPI-A), attenuated positive symptoms (CAARMS), schizotypy (SPQ-A) and social functioning (SOFAS).

The meta-analysis found that both the UHR and Basic Symptom approaches yield similar results. The differences in the positive predictive values (PPV) of the two approaches were not significant (Basic Symptoms, 0.34, UHR 0.25). The service evaluation found over a third (n=58) of referrals to the LEAD clinic to be psychotic at baseline and sixty-four patients to have an at risk mental state (ARMS). Conversion risk for CAARMS was 36.67%. and was 28.57% for SPI-A. The COGDIS criterion of SPI-A was found to be the most predictive with a PPV of 0.43, a sensitivity of 0.80 and a specificity of . When patients met a combination of both COGDIS and CAARMS the likelihood ratio increased to 5.25 although the sensitivity was low (0.47).

Overall, the findings of the thesis indicate that both the Basic Symptom and UHR approaches are valid for use in routine clinical settings for the assessment of psychosis risk. The thesis found that a combination of both approaches could provide future opportunities research. The SPQ-A schizotypy assessment was found to correlate with the attenuated symptom criterion of CAARMS and evidence suggests that the SPQ-A score increases closer to transition. The SPQ-A could offer opportunities for developing efficient methods of monitoring progression of prodromal symptoms.

DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

COPYRIGHT STATEMENT

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In the later stages of this PhD, my present manager Dr Tim Riding allowed me the time and flexibility to complete my thesis. I would like to thank him for his understanding and support.

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I would also like to commend all the staff working in the clinics for their hard work and dedication, particularly Dr Alison Summers who developed the standard operating procedures for the clinics. Finally, I would like to thank the service users and their families who attend the LEAD clinics. Without them, this PhD would not have been possible. They were my real inspiration.

DEDICATION

I would like to dedicate this PhD to my family. To my Mum and Dad for always believing in me and making me realise that ‘it’s ok to be average!’, my husband Derek for his unfaltering support and patience, my son Matthew for entertaining his sister while I tried to study, my daughter Caitlyn for trying and failing to keep quiet and finally my brother Paul for proof reading some of my work.

THE AUTHOR

I qualified as a Registered Nurse (Mental Health) in 1994 and have enjoyed a varied career in the NHS. My interest in the Early Detection of Psychosis began in around 2000 when I was working as a Community Psychiatric Nurse in a dedicated psychosis team. At the time, I was undertaking my Masters in Psychosocial Interventions at the University of Manchester and was struck by the number of predominantly young males on my caseload with psychosis for whom I felt I had arrived too late. I couldn't help but feel that had I been able to work with them sooner their outcome would be improved. This led me to focus my Master's thesis on the early detection of psychosis, a field which at the time was in its infancy. I became passionate about early detection and intervention in first-episode psychosis.

When the Early Intervention Service opened in Lancashire in 2005, I was one of the founder members of the service and was lucky enough to find myself working with Professor Max Marshall who shared my interest in Early Detection. Together we established the Lancashire Early Assessment and Detection (LEAD) Clinic as an integral part of the Early Intervention service. I managed the clinics and trained all staff to conduct the assessments used in the clinic.

The establishment of the LEAD clinics was met with some resistance within the EIS as the additional case management requirements of those deemed at-risk by the assessments was seen as an additional burden for case managers. They queried the validity of the assessments used and the rationale for offering a service to people who did not meet psychosis criteria.

With this in mind, I decided that the evaluation of the clinic outcomes would be the focus of my PhD. I sought to determine the how many of the people we assessed subsequently developed a psychosis and ultimately whether the clinic was a valuable addition to the Early Intervention Service.

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Abbreviations

ARMS	At-Risk Mental State
BS	Basic Symptoms
BLIPS	Brief Limited Intermittent Psychotic Symptoms
BSABS	Bonn Scale for the Assessment of Basic Symptoms
CAARMS	Comprehensive Assessment of At Risk Mental States
CER	Cologne Early Recognition
CI	Confidence Interval
COGDIS	Cognitive Disturbances
COPER	Cognitive Perceptive
COPS	Criteria of Prodromal Syndromes
DUI	Duration of Untreated Illness
DUP	Duration of Untreated Psychosis
EI	Early Intervention
EIS	Early Intervention Service
EPOS	European Prediction of Psychosis Study
FETZ	Cologne Early Recognition and Intervention Centre for Mental Crisis
GAF	Global Assessment of Functioning
IRAOS	Interview for the Retrospective Assessment of the Onset of Schizophrenia
LEAD	Lancashire Early Assessment and Detection
LR	Likelihood Ratio
NPV	Negative Predictive Value
OR	Odds Ratio
PPV	Positive Predictive Value
ROC	Receiver Operating Curve
SD	Standard Deviation
SE	Standard Error
SIPS	Structured Interview for Prodromal Symptoms
SOFAS	Social, Occupational and Functional Assessment Scale
SOPS	Scale of Prodromal Symptoms
SPI-A	Schizophrenia Proneness Instrument – Adult Version
SPQ-A	Schizotypal Personality Questionnaire – Version A
SPQ-B	Schizotypal Personality Questionnaire - Brief
UHR	Ultra High Risk
UHR+	Ultra High Risk Positive
UHR -	Ultra High Risk Negative
Y-PARQ	Youth Psychosis at Risk Questionnaire

Introduction

CHAPTER 1: General Introduction

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1.1 Introduction

Current views on the nature of psychosis can be traced back to the work of Emile Kraeplin, who in 1896 identified a condition, which he termed Dementia Praecox (premature dementia). Kraeplin believed this disorder to be progressive, with origins in adolescence and an irreversible and deteriorating course. Eugen Bleuler augmented this analysis in 1911 when he re-labelled the disorder as schizophrenia. Bleuler noted that the condition was not a dementia nor did it manifest itself exclusively in young people. In addition, he noticed that some patients improved and did not have a deteriorating course. Nevertheless, despite these observations, until recently the somewhat pessimistic Kraeplinian concept of schizophrenia has tended to prevail in clinical practice. Perhaps this is because clinical services have tended to focus on the long-term management of patients with a poor outcome. Such a focus on those with more chronic presentations, results in clinicians only ever witnessing poor outcomes thus manifesting what has become known as the “clinician’s illusion” (Cohen and Cohen, 1984).

Increasingly, over the last decade researchers have challenged pessimistic attitudes towards the treatment of psychosis. They have begun to ask whether earlier recognition will lead to the amelioration of the disorder. This idea has its origins in the work of Wyatt (1991) and his review of mirror image studies comparing outcomes of pre-neuroleptic era and neuroleptic era populations. He found that those admitted in the pre-neuroleptic era had poorer outcomes than those in the neuroleptic era, highlighting the possibility that treatment with neuroleptics can alter long-term outcome. This focussed attention on the period between onset of symptoms and commencement of treatment; termed Duration of Untreated Psychosis (DUP).

The length of the DUP period has been found to range from 4 to 624 weeks with a mean duration of 38 weeks, median 12 weeks (Drake et al., 2000) and there is evidence of an association between the length of this period and

outcome (Marshall et al., 2005). The recognition of the importance of reducing the length of DUP has shifted emphasis from traditional maintenance and stabilisation interventions to early intervention designed to reduce the DUP.

As researchers have traced back DUP, to determine time of illness onset they have realised that the period of untreated psychosis is itself preceded by precursor signs. This extended period of illness is termed the Duration of Untreated Illness (DUI). The ABC schizophrenia study (Hafner and an der Heiden, 1999, Hafner et al., 1998), found that 73% of first episodes started with non-specific prodromal signs or negative symptoms. These symptoms were elicited retrospectively through the 'Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS) (Hafner et al., 1992). In 68% of cases DUI was found to last for over one year (Hafner et al., 2004), the mean length of this period was 5 years, and social disability appeared 2-4 years before first admission (Hafner et al., 1998). Ten symptoms were found to be the most frequent in this phase (restlessness, depressed mood, anxiety, trouble with thinking and concentration, worrying, loss of self-confidence, loss of energy/slowness, poor work performance, social withdrawal with suspiciousness, and social withdrawal with communication difficulties. Interestingly none of these were positive psychotic symptoms.

The discovery of this pre-psychotic phase offered researchers new and exciting possibilities of firstly predicting who is at risk of developing the disorder and secondly preventing onset. Consequently, researchers have used a number of different approaches to understand the pathogenesis of psychosis. One approach is the genetic high-risk approach, which involves the study of the offspring and other family members of people with psychosis. Neuroimaging studies have found reductions in grey matter volume in some cortical and subcortical regions of the brain, particularly the hippocampus, which can at least in part be accounted for by an inherited genotype for psychosis (Cannon et al., 2003).

It is estimated that individuals with a first-degree relative history of psychosis present a 10-15 fold increased risk of psychosis compared with the general population (Kendler and Gardner, 1997). However, as Asarnow (1988) points out 85-90% of people with psychosis do not have a relative with the disorder, making it impossible to generalise the findings of genetic high-risk studies to the total population of people with psychosis.

The recognition that the onset of psychosis is preceded by precursor symptoms and that family history of the disorder presents an increased risk prompted researchers to consider a combination of the two approaches (Yung et al., 1998b). Targeting populations known to present an increased risk of a disease with minimal but detectable symptoms or biological markers for predisposition to the disorder is termed indicated prevention. Mrazek and Haggerty (1994) herald indicated prevention as the 'best hope for the prevention of schizophrenia'.

This preventative approach has much in common with advances in the early diagnosis of disorders such as cervical cancer. Certain precursor signs (cervical dysplasia) precede onset in this disorder and tend to be more common in certain subsections of the population (sexually active women). A screening and treatment programme targeted at this subsection of the population has successfully reduced the number of deaths per year from cervical cancer by 5000 (Peto et al., 2004).

However, if indicated prevention of psychosis is to become a reality it must firstly be possible to identify the existence of precursor symptoms and secondly these symptoms must be sufficiently specific and sensitive to be useful in the population to be screened. This has led to the development of two main approaches to the detection of precursor symptoms – Basic Symptoms (Gross, 1989, Huber and Gross, 1989, Klosterkotter et al., 2001a) and the Ultra-high Risk' approach (McGorry, 1998, Yung et al., 1998b, McGorry et al., 2003, McGlashan et al., 2001, Miller et al., 2003a). To date the Ultra-High Risk (UHR) has been the most widely applied approach and

comprises state and trait factors thought to indicate a high risk of developing a psychosis. Trait factors are a first-degree family history of psychosis and/or schizotypal personality traits accompanied by a drop in functioning. State factors comprise attenuated psychotic symptoms and Brief Limited intermittent Psychotic Symptoms (BLIPS). Attenuated symptoms are sub-threshold psychotic symptoms which differ from normal phenomena but are not overtly psychotic and BLIPS are frank psychotic symptoms that occur for one week and spontaneously remit without treatment (Phillips et al., 2005). Basic symptoms are self-experienced subtle disturbances of thought; speech and perception and are phenomenologically different from what the person considers their normal self. They are not necessarily observable by others. Chapters 2 and 3 describe both approaches in more detail.

As both the Basic Symptom and UHR approaches rely on people approaching services to seek help, little is known about the prevalence of prodromal symptoms in the general population; current estimates vary from between 4% and 8% (Fusar-Poli et al., 2012). A recent meta-analysis of both approaches (Fusar-Poli et al., 2013) found that a mean of 29.2% (95% CI: 27.3%, 31.3%) patients develop psychosis when deemed at risk by either UHR or basic symptom criteria. The risk for those meeting UHR criteria was 27.7% compared with 48.5% for those meeting Basic Symptom criteria. This raises an important issue for researchers particularly those interested in developing treatments for the prevention of psychosis; the issue being that most people thought to present a high risk for psychosis do not develop one.

1.2 Treatment of the Pre-Psychotic Phase

There have been a small number of treatment trials with the aim of preventing conversion to psychosis. Treatments include antipsychotic medication (McGlashan et al., 2006, McGorry et al., 2002, Phillips et al., 2007), cognitive behavioural therapy (CBT) (Bechdolf et al., 2007, Morrison et al., 2002, Morrison et al., 2007), omega-3 polyunsaturated fatty acids (Amminger et al., 2010) and intensive community care (Nordentoft et al.,

2006). A meta-analysis (Preti and Cella, 2010) found an association between lower risk of conversion and receipt of any one of these interventions when compared with no treatment of treatment as usual (Relative Risk = 0.36; 95%CI: 0.22, 0.59). However, transition rates across detection studies have been reducing (Yung et al., 2007), increasing the number of false-positive predictions. In view of this, McGorry et al. (2009) assert the importance of offering safer first line interventions to people thought to present a risk of psychosis. This approach to offering safer interventions in the earlier course of the illness is known as a clinical staging model and is proposed by (McGorry et al., 2009) as the 'way forward' for the treatment of the psychosis prodrome. Preti and Cella (2010) suggest that CBT may be a safer and more cost effective treatment of the earlier course of the illness as interventions are time-limited and not subject to the side effects that anti-psychotics have. However, a three-year follow-up analysis of CBT administered to UHR patients found that CBT did not significantly reduce the likelihood of conversion to psychosis (Morrison et al., 2007).

Cornblatt et al. (2007) carried out a naturalistic study of symptom-based interventions for patients participating in the Recognition and Prevention (RAP) high-risk programme in New York. None of the patients who were prescribed antidepressants (n = 20) converted to psychosis over the course of the follow-up period (5 years) compared with 12 in the second-generation antipsychotic treatment group (n = 28). While the naturalistic design of the study prevents comparisons of the two treatment groups, the absence of conversions in the antidepressant group raises important questions about the use of antidepressants in the prodrome. Cornblatt et al (2007) suggest that while it is possible that many patients who responded to antidepressants were false positives, antidepressants could be used as an initial screen in many cases. Positive attenuated symptoms that show a poor response to initial treatment with antidepressants could receive treatment with antipsychotics. This would be in line with the staging model suggested by McGorry (2009).

1.3 Models of Psychosis Development

Cornblatt et al. (2003) propose that the development of psychosis involves two distinct dimensions, biological vulnerability, and the later development of positive symptoms. Biological vulnerability is purported be a necessary core element in the development of psychosis and is thought to arise from a strong genetic liability characterised by deficits and behavioural disturbances. In the absence of the disorder, they hypothesise that the biological vulnerability traits manifest as non-specific spectrum disorders such as schizotypal, avoidant and schizoid personality disorders. Four domains are proposed to reflect the underlying vulnerability for schizophrenia, 1) cognitive deficits 2) affective disturbances 3) social isolation and 4) school failure. The acronym for these four domains is the CASIS model. Cognitive deficits are thought to be a reflection of underlining brain pathology and are usually displayed developmentally. Neurocognitive deficits such as poor working memory would be a typical example of a cognitive deficit. The inclusion of affective deficits and social isolation is based upon the work of Hafner and an der Heiden (1999) in the ABC Schizophrenia study who found that depression was one of the ten most common symptoms that precede psychosis onset. Social isolation was found to closely follow the onset of depression. School function was included as a domain as studies of at-risk children and adolescents have found school difficulties to characterise the pre-psychotic phase (Cornblatt et al., 2003).

The next step in the developmental course of psychosis proposed by CASIS model is the addition of an environmental or biological trigger leading to the development of positive attenuated symptoms. Cornblatt et al (2003) suggest that typically these positive symptoms will manifest in mid to late adolescence.

The German Research Network (Schultze-Lutter et al., 2010b, Hafner et al., 2004) proposes a two-stage model for the development of psychosis; the Early Initial State (EIPS) and the Late Initial Prodrome State (LIPS). The EIPS is characterised by any one of ten Basic Symptoms (COPER) and the

absence of attenuated symptoms and Brief Limited Intermittent psychotic Symptoms (BLIPS) or alternatively a combination of genetic and obstetric risk factors for psychosis and functional decline. The LIPS is characterised by attenuated psychotic symptoms or BLIPS. The sequence of psychosis onset is assumed to begin with 'unspecific mental problems' in conjunction with biological risk factors and functional decline, followed by basic symptoms, attenuated psychotic symptoms, BLIPS and eventually psychotic symptoms (Scultze-Lutter et al 2010b). Basic symptoms are thought to manifest in the early prodromal phase and persist through the later attenuated prodromal phase to psychosis.

Schultze-Lutter et al (2010) tested the model retrospectively in a cohort of 126 first-episode psychosis patients. A third of patients reported an earlier onset of Basic Symptoms than attenuated psychotic symptoms. The general sequence of Basic Symptoms or Attenuated Symptoms followed by BLIPS was detected; however, the hypothesised sequence of Basic Symptoms followed by Attenuated symptoms and then BLIPS was not found to a statistically significant level.

In the European Prediction of Psychosis Study (EPOS) Ruhrmann et al (2010) found that the presence of both Basic Symptoms and Attenuated Psychotic symptoms seemed to indicate an increased risk of psychosis. Similarly, Simon et al (2006a) found that when basic symptoms were included in a set of at-risk criteria only a few differences on clinical and cognitive measures remained significant between at risk patients and first episode patients. They concluded that this seemed to suggest that adding Basic Symptoms into the assessment algorithm achieves a more homogenous sample of clinically and cognitively impaired individuals.

1.4 The Context of the Thesis

To date the majority of the UHR and Basic Symptom studies have been conducted in highly specialised clinics outside the United Kingdom (UK). However, since the introduction of 50 Early Intervention (EI) Teams nationally (Department of Health, 2001), UK interest in the early detection of psychosis has increased. The primary role of EI teams is to reduce delays in the treatment of first episode psychosis. Evaluation of their effectiveness has shown that there is some evidence of an association with reduced readmissions and lower relapse rates (Craig et al., 2004).

There is an expectation that in cases where there is a suspicion of psychosis but no firm diagnosis, EI services should adopt a 'watching brief' (Department of Health, 2001). In order to ensure that the right people are subject to a 'watching brief', the Lancashire Early Intervention Service (EIS) developed a dedicated prodrome clinic. The Lancashire Early Assessment and Detection (LEAD) use both the Basic Symptom and Ultra High Risk approaches to detection. All service users referred to the EIS who are not currently psychotic and would otherwise meet the criteria for the service are referred to this clinic. Following the LEAD clinic assessment patients thought to present a risk of psychosis are offered care coordination by the EIS for a period of 12-months. If they convert to psychosis during this 12-month period, they are offered a further three years of care coordination.

EI services are primarily funded for people in their first episode of psychosis and those requiring a watching brief are not counted on caseload for funding purposes. Consequently, the Lancashire EIS are offering a 12-month service to a group of service users for whom they are not funded. It is therefore essential that the efficiency and effectiveness of the LEAD clinic are evaluated. In doing so, the efficiency of the assessment process can be improved by identifying redundant or inaccurate tests. The length of time people require a watching brief can also be considered based upon analysis of survival time.

The thesis has two broad aims. The first aim is to conduct a comprehensive synthesis and meta-analysis of studies using psychopathology-based early detection instruments. In doing so we will summarise the research field to date and determine the validity of pre-curser symptoms in the prediction of psychosis onset. Where possible we will conduct a quantitative analysis of the sensitivity, specificity, positive and negative predictive values and likelihood ratios for the candidate tests. The second aim of the thesis is to establish the accuracy of the current predictions made within the LEAD clinic. This will enable us to improve the overall efficiency of the clinic. It will also provide an opportunity to determine the predictive validity of the Basic Symptom and Ultra-High risk approaches within a routine clinical setting.

CHAPTER 2: The Basic Symptoms Approach

Chapter 2: The Basic Symptom Approach

2.1 Introduction

This chapter aims to provide an overview of the historical background of the Basic Symptom approach and to present a summary of the research literature to date.

2.2 Development of the Basic Symptom Approach

The basic symptom approach has its origins in the work of Emile Kraeplin and Eugene Bleuler, who both regarded first rank psychotic symptoms as the 'tip of the iceberg' (Klosterkotter et al., 2008) They believed that those presenting with psychotic symptoms only accounted for a small proportion of a widely distributed population of milder forms of the disease. Bleuler identified Basic Core Symptoms known as 'Grund-Symptome', which encompassed abnormalities in association, affect, ambivalence and autism. He contrasted these core symptoms with 'Akzessorische Symptome' (accessory symptoms) such as delusions, hallucinations, and catatonic features. He concluded that loosening of associations was the only one of the core symptoms that could theoretically be linked to the 'Primastörung' (primary disturbance of the disorder) of psychosis (Koehler and Sauer, 1984). It was not until the 1950s, however, that this work began to receive further attention. This was largely due to greater interest in the first-rank symptoms work of Kurt Schneider (1959).

It was as a pupil of Schneider; that Gerd Huber made two observations; one concerned the 'Pure Defect Syndrome' of schizophrenia and the other the 'cenesthetic' type of schizophrenia (Gross and Huber, 2010). The pure defect syndrome (shown in table 1 below) was determined by dynamic and cognitive disturbances reported by patients such as diminished resistance to certain stressors, decreased drive, energy, increased exhaustion etc. Huber

noted that patients describe these basic symptoms as deficiencies and develop coping strategies to compensate for them.

Cenesthetic schizophrenia was characterised by long-lasting prodromal periods preceding the onset of first-rank symptoms. Huber (2010) reports observing many patients in the 1950s with diagnostically unclear presentations who complained 'in a peculiar manner of manifold bodily sensations'. Follow-up of these patients over a number of years revealed that schizophrenic psychosis followed such peculiar symptoms. He found that on average the prodrome lasted for 7 years in this group.

Table 1: Huber's Pure Deficit Symptoms

1	Cognitive disturbances (concentration, thought and memory disorders)
2	Somatic and mental fatigability and exhaustion
3	Disturbance in the general sense of well-being and feeling of deficiency in performance
4	Decrease in vigour, energy, endurance and patience
5	Coenaesthesia (disagreeable/unusual bodily sensations
6	Increased excitability and impressionability
7	Inability to tolerate everyday stress
8	Oversensitivity to noise and the weather
9	Sleep disturbances (aside to 19)
10	Loss of self-confidence, feeling of insufficiency
11	Tendency to coenaesthesic –dysthymic paroxysms and mood states
12	Disagreeable experiencing of autonomic functions
13	Decrease in drive and energy
14	Loss of naturalness, greater tendency to obsessional reflection
15	Tendency to sub-depressive and or hypomanic mood changes
16	Inability to appear in public or socially interact
17	Inability to be as happy as before
18	Feeling of having no feeling
19	Increased need for sleep
20	Difficulty in adjusting to new situations
21	Sensory disturbances
22	Intolerance to coffee/tea/smoking
23	Indecisiveness
24	General loss of naturalness and openness

Huber's (1980) basic symptoms are not defined by behavioural observation. Instead they are based upon the patient's own descriptions. Huber asserts that observation of patients' behaviours alone can be quite deceiving as they may appear quite 'normal' yet upon questioning regarding any complaints that they may have, basic symptoms frequently come to light. Indeed most people are very aware of the symptoms as a change from their normal self and are often troubled greatly by them in their everyday life. Behavioural changes observable by others result because of coping strategies such as social withdrawal or avoidance. They differ greatly from first rank psychotic symptoms in that they are recognised by the person as real disturbances in their own mental processes (Schultze-Lutter, 2009a).

2.3 Instruments for Detecting Basic Symptoms

Gross & Huber et al (1987) developed the Bonn Scale for the Assessment of Basic Symptoms (BSABS) from retrospective analysis of patients with schizophrenia. The scale comprises 98 items divided into the following categories: dynamic deficiencies, disturbances of thought, disturbances of perception, disturbances of action, cenesthesias and disturbances of the central autonomic nervous system (including sleep disturbances). Dimensional analysis led to a shorter 66-item BSABS developed by Klosterkotter et al (2001a, 1996). The 66-items consist of five clusters:

1. Thought, language, perception and motor disturbances (35-items)
2. Impaired body sensations (13-items)
3. Impaired tolerance to normal stress (5-items)
4. Disorders of emotion and affect, including impaired thought, energy, concentration and memory (7-items)
5. Increased emotional reactivity, impaired ability to maintain or initiate social contacts, disturbances in non-verbal expression (6-items)

Klosterkotter et al (2001a) used the 66-item BSABS in the Cologne Early Recognition Study (CER) to prospectively examine 695 patients referred to 5

German psychiatric university departments between 1987 and 1991. Of these 695 subjects, 385 met the inclusion criteria. However, as the follow-up did not begin until 1995 only 160 agreed to participate. Of these 110 were deemed at risk and 50 were not. The mean follow-up period was 9.6 years (SD 7.6, median 7.8). Of the 110 people deemed at-risk at baseline, 77 (70%) had developed a psychosis by the end of the follow-up period. Two (4%) people deemed not at-risk at baseline developed a psychosis. The sensitivity of the BSABS was 0.97 (95% CI: 0.90, 1.0), specificity 0.59 (95% CI: 0.48, 0.70), positive predictive value (PPV) 0.7 (95% CI: 0.60, 0.78), negative predictive value (NPV) 0.96 (95% CI: 0.85, 0.99), positive likelihood ratio (+LR) 2.39, negative likelihood ratio (-LR) 0.04.

Receiver Operating Curve (ROC) analysis of the CER data showed that cluster one of the BSABS (thought, language, perception and motor disturbances) showed significantly greater predictive discrimination. With a sensitivity of 0.84 and specificity of 0.77, this cluster discriminated between patients developing a psychosis and those who did not. The predictive discrimination of the other clusters was no better than chance.

In order to determine the most predictive items of the BSABS Klosterkötter et al (2001) used sensitivity and PPV. They focussed on these as the minimum acceptable value for both as defined in two previous diagnostic accuracy studies (Andreasen and Flaum, 1991, Jackson et al., 1995). The minimum value for sensitivity was ≥0.25 and ≥ 70 for PPV. Ten BSABS items reported at baseline by at least 25% of the patients who later developed psychosis, fulfilled the sensitivity PPV criteria (Klosterkotter et al., 2008). All other symptoms showed a sensitivity of <0.25 or a PPV of <0.70 so were not included.

The 10 most predictive items were as follows:

1. Thought Interference
2. Thought perseveration

3. Thought pressure
4. Thought blockage
5. Disturbance of receptive language
6. Decreased ability to distinguish between ideas of perception, fantasy and true memory
7. Unstable ideas of reference
8. Derealisation
9. Visual Perceptual disturbances
10. Acoustic perception disturbances

Logistic regression analysis of these 10 symptoms led to correct predictions in 81.2% of the development and in 76.2% of the validation sample. These symptoms were later termed Cognitive-perceptual or COPER symptoms (Klosterkotter et al., 2008). Twenty percent of patients with any one of the COPER symptoms developed psychosis within the first year of follow-up, 17% in the second, 13% in the third and 15% in the remaining follow-up period.

Further analysis of the CER data by (Schultze-Lutter et al., 2007b) resulted in a further cluster of 9 basic symptoms that were the most predictive of seven examined symptoms clusters. This cluster termed Cognitive-Disturbances or COGDIS requires two or more of the nine symptoms to be present. People meeting COGDIS also meet COPER criteria but not necessarily the other way around (see table 2 for both COPER and COGDIS criteria). The COGDIS one-year transition rate was 23.9%. In the second year 22.4% made the transition and in the third year 14.9% and 17.9% in over 3 years.

The most predictive BSABS items from the CER study were used by Schultze-Lutter et al (2007a) in the development of the Schizophrenia Proneness Instrument – Adult Version (SPI-A). The SPI-A was designed to focus upon the most predictive basic symptoms occurring early in the course of the illness.

Schultze-Lutter et al (2007b) tested the predictive ability of both the COPER and COGDIS criteria in a prospective study of 146 help-seeking people from the Cologne Early Recognition and Intervention Centre for Mental Crisis (FETZ). Subjects were assessed using the SPI-A and COPER and COGDIS criteria were applied to inform the at-risk status. The mean follow-up time was 20.6 months (SD 16.1, range 1-70 months, median 18-months). One hundred and twenty four people met COGDIS criteria and 22 met COPER. Fifty-one (34.9%) subjects developed a psychosis by the end of the follow-up period, 8 (36.4%) of COPER group and 43 (34.7%) of the COGDIS group.

Table 2: COPER & COGDIS Criteria

Cognitive Perceptive Disturbances – COPER Presence of at least any one of the following ten basic symptoms with a SPI-A score of ≥ 3 within the last 3 months and first occurrence ≥ 12-months ago
• Thought Interference • Thought Perseveration • Thought Pressure • Thought Blockages • Disturbance of receptive speech • Decreased ability to discriminate between ideas/perception, fantasy/true memories • Unstable ideas of reference • Derealisation • Visual perception disturbances (excl. hypersensitivity to light or blurred vision) • Acoustic perception disturbances (excl. hypersensitivity to sounds)
High Risk Criterion Cognitive disturbances – COGDIS Presence of at least two of the nine following basic symptoms with a SPI-A score of ≥3 within the last 3 months
• Inability to divide attention • Thought Interference • Thought pressure • Thought blockages • Disturbance of receptive speech • Disturbance of Expressive Speech • Unstable ideas of reference • Disturbances of abstract thinking • Captivation of attention by details of the visual field

2.4 Distinguishing Basic Symptoms of Psychosis from Depression

Schultze-Lutter et al (2007c) analysed the ability of the SPI-A to distinguish between the early stages of psychosis and depression. This is particularly important, as clinically relevant depression is frequent in both first-episode psychosis and the prodrome. Therefore, any instrument designed to detect the prodrome must be able to distinguish potentially prodromal individuals from those suffering primarily from a depressive disorder.

Four hundred and fourteen participants were recruited from help-seeking individuals presenting to the Cologne Early Recognition and Intervention Centre for Mental Crisis (FETZ) and in-patients of the Department of Psychiatry and Psychotherapy of the University of Cologne. Of the 414 participants, 146 were thought to be at risk of psychosis, 153 were diagnosed with first episode psychosis, and 115 were suffering from depression. All participants were assessed using the SPI-A, in addition the structured clinical Interview for DSM-IV (SCID-1, German version) (Wittchen et al., 1997) was administered to rule out past or present psychosis, confirm the diagnosis and to assess co-morbidity with affective disorders.

Depression was reported in 38% of at-risk group and 21% of the first-episode psychosis group. Comparisons of the various subgroups showed no difference in either the psychosis or at-risk group between those with or without current depressive disorder on any of the SPI-A subscales. The severity of the SPI-A subscales were greater for the psychosis and at-risk group than for the depression group. Multivariate analysis demonstrated correct classifications except in the at-risk with depression group. Schultze-Lutter, Ruhrmann et al (2007c) suggest that the introduction of a second step algorithm especially designed to distinguish depressive subjects with regard to the prodrome may increase the number of correct classifications in this group. While basic symptoms are an effective tool in distinguishing the prodrome from affective disorders, a second step assessment may be required to account for those with co-morbid depressive disorder and a prodrome.

2.5 Studies Using Both the Basic Symptom and UHR Criteria

The European Prediction of Psychosis Study (EPOS) (Klosterkotter et al., 2005, Ruhrmann et al., 2010) is a large multi-centre study focussing on the detection of patients at-risk of developing psychosis. Six early detection outpatient clinics across Europe (Germany, Finland, the Netherlands and England) participated in the study. Patients were assessed using both the BSABS prediction checklist (COGDIS criterion) and the Structured Interview for Prodromal Syndromes (SIPS). The total sample comprised 245 subjects meeting either the COGDIS criterion or SIPS UHR+ criteria. Follow-up evaluations were conducted after 9 and 18 months and the outcome was known for 183 subjects. After 18 months 37 (20.22%) subjects had converted to psychosis. The mean time to transition was 496.8 days (SE, 8.5 days). Subjects meeting UHR criteria had a 20.6% conversion rate compared with 19.1% for those meeting COGDIS criteria. When patients fulfilled both UHR and COGDIS criteria the conversion rate increased slightly to 23.8%. A combination of both criteria gave a sensitivity of 0.68 and specificity of 0.46 compared with the COGDIS criterion alone (sensitivity 0.03, specificity 0.88) and UHR criteria alone (sensitivity 0.30, specificity 0.67).

Ziermans et al (2011) used the EPOS criteria for inclusion in his study of 57 patients who completed a 2-year follow-up period. Nine (15.79%) people had developed psychosis by the end of follow-up period. The paper does not offer data distinguishing between the transition rates of COGDIS and SIPS, however in their discussion of the study Ziermans et al (2011) state that the COGDIS criterion did not have an additional discriminative value in the prediction of conversion or remission from UHR status.

2.6 Discussion

The Basic Symptom approach pioneered in Germany by Gerd Huber (1980) has led to the development of two instruments, the BSABS and the SPI-A. The SPI-A is essentially the third generation of the BSABS as it is derived from the most predictive items of the BSABS. Studies of the Basic Symptom approach are still relatively few in number but interest in their utility is steadily increasing. Researchers have become increasingly interested in using Basic Symptom approaches in conjunction with the UHR risk approach to detect both the Early Initial and Late Initial Prodrome states proposed by the German Research Network (Hafner et al, 2004, Schultze-Lutter et al 2010).

There was evidence from the EPOS study of a combination of both approaches improving the sensitivity of detection. However, Ziermans et al (2010) found that using the COGDIS criterion in combination with SIPS did not improve detection. There are no studies to our knowledge of CAARMS used in combination with the SPI-A criterions. Equally, there is little evidence of how well SPI-A performs within a representative UK Mental Health setting. It will therefore be interesting to see how well the SPI-A criterions both individually and in combination with CAARMS will perform in the LEAD clinic. This analysis will be presented in chapters 7 and 8.

CHAPTER 3: Ultra-High Risk Approaches to Detection

Chapter 3: Ultra-High Risk Approaches to Detection

3.1 Introduction

The purpose of this chapter is to provide an overview of the Ultra-High Risk (UHR) approach and its component parts such as schizotypy, family history of psychosis and social functioning. The chapter will also provide an overview of the UHR research literature to date.

3.2 The UHR Approach

The Ultra-High Risk approach pioneered in Melbourne, Australia by Yung et al (1998b, 2003a, 2004a, 2006c), combines state, and trait risk factors to maximise the detection of people at risk of developing a psychosis. State factors fall into two categories, attenuated (sub-threshold) psychotic symptoms, and Brief Limited Intermittent Psychotic Symptoms (BLIPS). Trait factors include a first-degree relative with psychosis and schizotypal personality traits. These categories are accompanied by persistent low functioning.

Two instruments have been developed using the UHR approach: the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al, 1998a, 1998b, 2007) and the Structured Interview for Psychotic Syndromes (SIPS) (Miller et al., 2003). There are slight differences between the two instruments mainly found in the frequency and duration criteria. For example, CAARMS would categorise some people as having attenuated psychotic symptoms, whereas SIPS would categorise them as having BLIPS, and some people in the BLIPS subgroup of CAARMS would be deemed psychotic by the SIPS.

The CAARMS is a composite instrument developed from the psychotic subscales of the Brief Psychiatric Rating scale (BPRS); (Overall and Gorham, 1962) and the delusions subscale of the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). As

neither the CASH nor BPRS specified frequency, duration and recency of the symptoms, the CAARMS was developed to include these domains (Yung et al., 2006c). The CAARMS also includes some Basic Symptoms of thought, language and perceptual disturbances (Yung et al., 2005).

Attenuated Symptoms are elicited through a semi-structured interview designed to assess four symptom subgroups – unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganised speech. In order to meet the criteria for each subscale the person must meet criteria for symptom severity, frequency and duration. Schizotypal personality is assessed using DSM-IV (American Psychiatric Association, 1994) criteria and family history is assessed using the Family Interview for Genetic Studies (Maxwell, 1992). The symptoms and traits must also have been present within the past year and the patient must have experienced a significant drop in functioning. Functioning is assessed using the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 1994).

Ultra High Risk is determined by CAARMS when patients meet criteria in one of three groups:

- ***Group 1: Vulnerability***: Individuals who have a schizotypal personality or have a first-degree relative with a psychotic disorder. These must also be accompanied by a 30- point drop in their social functioning within the last year, or a score of 50 or less sustained for 12-months.
- ***Group 2***: ***Attenuated psychotic symptoms:*** Individuals who have experienced sub-threshold, attenuated positive symptoms in the past year. Accompanied by a 30-point drop in social functioning over the past year, or a score of 50 or less sustained for 12-months.
- ***Group 3: Brief limited intermittent psychotic symptoms:*** Individuals who have experienced frank psychotic symptoms that have lasted for no more than one week in the past year and remitted

spontaneously. Accompanied by a 30-point drop in functioning sustained for at least one month in the past year, or a score of 50 or less sustained for 12-months.

Modelled upon the Australian Ultra-High Risk approach Miller et al (2002, 1999) developed a diagnostic semi-structured interview, the Structured Interview for Prodromal Syndromes (SIPS) and a severity scale, the Scale of Prodromal Symptoms (SOPS). These scales are designed to 'define, diagnose and measure change systematically in individuals who may be in a pre-psychotic state' (Miller et al., 1999). The scales were based upon the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), with modifications of the positive symptom scales to enable a detailed scoring of the lower ranges of severity, which would be considered pre-psychotic.

The SIPS/SOPS has three goals:

a. To measure the presence/absence of prodromal states.
b. The cross-sectional and longitudinal measurement of the severity of prodromal symptoms.
c. To operationally define the threshold of psychosis.

The SOPS contains five positive symptom items, 6 negative symptom items and four disorganisation symptom items. The SIPS includes 29 questions relating to each positive symptom in the SOPS. The SIPS also includes a rating of functioning as assessed by the GAF (Endicott et al., 1976), a DSM IV schizotypal personality checklist (American-Psychiatric-Association, 1994a), and an assessment of family history of psychosis. Diagnosis of the prodrome is made using the Criteria for Prodromal Symptoms (COPS), which is modelled upon the Australian approach. The SOPS is used to determine the severity of the prodrome once it has been diagnosed.

3.3 Trait factors - Schizotypal Personality Disorder

Meehl (1962) suggests that schizotypy is a 'personality organisation' resulting from influence of environmental factors on schizotaxic individuals'. Schizotaxia is described by Meehl (1962) as a phenotypic consequence of a genetic mutation referred to as a 'neural integrative defect'. He suggests that if the schizotaxic person was fortunate to have a favourable 'interpersonal regime' and have inherited a general resistance to stress and anxiety they may remain a 'normal schizotype' never developing the symptoms of a mental disorder. While schizophrenia affects 1% of the population schizotypal personality disorder (SPD) is estimated at 3% (Cadenhead and Braff, 2002), indicating considerable heterogeneity of the risk profiles of the population. Fewer people with schizotypy develop psychosis than do not (Diwadkar et al., 2006). Therefore, while it would seem that schizotypy may be an important mediating factor in the development of psychosis (Cadenhead and Braff, 2002), it remains unclear how those with schizotypy as a clinical endpoint can be differentiated from those with similar symptoms that subsequently develop psychosis (Bedwell and Donnelly, 2005b).

Historically there have been two schools of thought in schizotypy research, the familial, and the clinical. The familial concept emerged from observations of the families of those with schizophrenia and the clinical from descriptions of patients who although not classically schizophrenic demonstrate attenuated symptoms of the disorder. Both Bleuler and Kraeplin (1950, 1911) noted that the relatives of people with schizophrenia often displayed interpersonal 'oddities' and subtle thought disorder. In a subset of 232 subjects drawn from the New York High Risk Project, Gooding et al (2012) found evidence to support Bleuler and Kraeplin's observations. They found that the offspring of people with schizophrenia had significantly more thought disorder ($p<0.001$) than the offspring of parents with affective disorders or no mental health disorder. Negative symptoms, odd speech and social dysfunction have also been found to discriminate the relatives of people with schizophrenia from normal controls (Kendler et al., 1995). Calkins et al

(2004) suggest that these disturbances may be part of a constellation of genetic vulnerability markers for the disorder.

The DSM-III schizotypal personality disorder criteria, developed by Spitzer and colleagues (Spitzer et al., 1979) was based upon criteria for borderline schizophrenia used by Kety et al (1976) in the Danish Adoption Study of schizophrenia. Kendler (1985) notes that the criteria used in the Danish study was more heavily influenced by the clinical model of schizotypy. However, he suggests that the DSM-III criteria is more likely a mix of both the clinical and familial traditions as at least one of the original investigators on the Danish Adoption study shared Bleuler's familial observations.

Historically, SPD has been seen in terms of two dimensions, Positive and Negative. The Positive dimension is characterised by unusual perceptual experiences and magical ideation, whereas the Negative dimension includes physical and social anhedonia with 'a high negative loading in extroversion' (Venables and Rector, 2000). Bergman et al (2000) suggest that if schizotypy is indeed to be seen as being on a continuum with schizophrenia a three factor model as typically proposed for schizophrenia (positive negative and disorganised symptoms) would be appropriate. Confirmatory factor analysis was used by Bergman (2000) to test DSM-III-R schizotypal symptoms in 72 first degree relatives of schizophrenic patients. The results indicated that a 3-factor model of cognitive/perceptual, interpersonal and disorganisation, was the best fit.

The 3-factor model was used in the self-report Schizotypal Personality Questionnaire (SPQ) developed by Raine (1991). The instrument consists of 74-items designed to assess the nine DSM-III-R (American Psychiatric Association, 1987) features of schizotypy (see table 3 below); across the three broad schizotypal factors: Cognitive-perceptual, Interpersonal and Disorganisation. In order to test how well the test can be replicated Raine (1991) recruited two groups of healthy university undergraduates in the United States (US) (n=302, n=195). The first cohort was divided into two samples (1a and 1b). Sample 1a was used in the initial construction of the

questionnaire with sample 1b used as a replication sample. The second cohort was used to test how well the results of the first cohort could be replicated.

The high schizotype cut-off point on the SPQ-A was 41, slightly higher than the cut-off of 39 found in a later English study of the SPQ-A (Hall and Habbits, 1996). The low cut-off of 10 was the same in both studies. In order to test the criterion validity of the SPQ-A Raine (1991) asked subjects who met either the low or high cut-off criteria to volunteer for an interview using the SCID-II questionnaire for assessing DSM-III-R criteria for schizotypal personality disorder (American Psychiatric Association, 1987). Eleven high scoring and 14 low scoring subjects agreed to be interviewed using the SCID-II. Of the 11 people who scored in the top 10% cut off range, six received SCID-II diagnoses of SPD. None of the 14 people in the bottom 10% received an SPD diagnosis. Discriminant and criterion validity were 0.63 and 0.68 respectively. The scale also showed considerable reliability and validity with internal validity being 0.91, test-retest reliability being 0.82 and convergent validity 0.59 to 0.81.

Table 3: DSM-III-R Criteria for Schizotypal Personality Disorder

A:	A pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behaviour, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
1	Ideas of reference (excluding delusions of reference).
2	Odd beliefs or magical thinking that influences behaviour and is inconsistent with sub-cultural norms (e.g., superstition, belief in clairvoyance, telepathy, or “sixth sense”; in children and adolescents, bizarre fantasies or preoccupations).
3	Unusual perceptual experiences, including bodily illusions.
4	Odd thinking and speech (e.g., vague, circumstantial, metaphorical, over-elaborate, or stereotyped).
5	Suspiciousness or paranoid ideation
6	Inappropriate or constricted affect.
7	Behaviour or appearance that is odd, eccentric or peculiar

8	Lack of close friends or confidants other than first-degree relatives.
9	Excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self.
B	Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, another psychotic disorder, or a pervasive developmental disorder.

Bedwell & Donnelly (2005a) sought to determine the degree of overlap between schizotypal personality disorder and heightened risk for psychosis. They assessed 998 young adults aged between 18 and 34 using the SPQ-B; an abbreviated version of the SPQ-A (Raine and Benishay, 1995) and the Youth Psychosis at Risk Questionnaire (Y-PARQ) (Ord et al., 2004). The SPQ-B was found to have a statistically significant positive correlation with the Y-PARQ $r_s = .66$, $p < .001$, $R^2 = .43$). The schizotypal factor cognitive-perceptual showed the strongest correlation with the Y-PARQ $r_s(998) = .65$, $p < .001$. The disorganised subscale correlation was $r_s(998) = .59$, $p < .001$ and the interpersonal was $r_s(998) = .34$, $p < .001$. Seventy-five percent of those deemed at risk by one measure were not by the other, leading the authors to conclude that while the measures overlap they detect distinct constructs.

The European Prediction of Psychosis Study (EPOS) (Salokangas et al., 2013), a prospective multi-centre follow-up study of 245 high-risk patients, investigated how well schizotypal features identified by the SPQ predicted transition to psychosis in clinically high risk (CHR) patients. Subjects were assessed at baseline using the BSABS, SIPS and SPQ-A. Subjects were followed-up at nine and 18-month time points. By the end of the follow-up period 37 people had developed psychosis, although only 36 were included in the analysis as one had not completed the SPQ-A at baseline. Cox regression analysis found that two SPQ-A subscales (ideas of reference and no close friends) were significantly associated with transition to psychosis. If either was present, the risk of transition was 15.4% (p=0.076, HR 2.652, 95%

CI: 0.902, 7.797). If both were present the risk increased to 31% (p=0.002, HR 5.890, 95% CI: 1.902, 18.069) and remained significant when the effect of SPD was accounted for. Therefore, even in those people without SPD, ideas of reference and no close friends indicated an increased risk for psychosis.

3.3.1 Schizotypy and Cannabis Use

Cannabis use has been associated with an increased risk for developing psychosis (Zammit et al., 2002, Arseneault et al., 2002). Prospective birth cohort studies suggest that this association may be causal (Henquet et al., 2005, Moore et al.). Meta-analysis of prospective studies investigating this association found an odds ratio of 2.1 (95% CI: 1.7–2.5; test for heterogeneity: Q =5.0, p = .54) (Henquet et al., 2005). The prevalence of cannabis use in the UK is high with the Home Office (2012) estimating a 15% lifetime use for young people aged between 16 and 24. Therefore while an odds ratio of 2.1 is not a large effect size, Henquet et al (2005) argue that the high prevalence of cannabis use in young people, makes the finding extremely relevant and a very real a public health issue.

Schiffman et al. (2005) administered the SPQ-B to 189 non-clinical undergraduate students in Hawaii, to investigate the presence of schizotypal personality traits in cannabis users and non-users. In addition, they sought to determine the order with which schizotypal traits and cannabis use occur. Students who had recently used cannabis had significantly higher scores on the cognitive-perceptual (t_{187}=2.30, P=0.02) and disorganised (t_{187}=2.29, P=0.02) domains of the SPQ and lower scores on the interpersonal domain (t_{187}=−1.81, P=0.07). Schizotypal traits were found to precede first cannabis use in 62% of cases. The probability of having schizotypal traits prior to cannabis use was significantly greater than chance (p=0.02). This led Schiffman et al. (2005) to conclude that cannabis use does not have a causal relationship with schizotypy.

While, cannabis may not have a causal relationship with schizotypy the question arises whether schizotypy is a mediating factor between cannabis and psychosis. In order to investigate this link Barkus et al. (2006) explored whether people who score highly on a measure of schizotypy are more prone to psychosis-like experiences when they use cannabis. They assessed 137 healthy volunteers from Manchester University, England using the Cannabis Experiences Questionnaire (CEQ) and the SPQ-B. The CEQ was developed specifically for the purpose of the study. They found that 72.5% of the sample had used cannabis at least once and high-scoring schizotypes were more likely to report psychotic-like experiences and unpleasant after effects. Psychosis-like experiences were delusional thinking, auditory hallucinations, and paranoia and after effects were symptoms such as loss of drive and feeling generally slowed down. These findings suggest that schizotypy may indeed be a mediating factor between cannabis and psychosis.

3.4 Family History of Psychosis

Inherited risk for psychosis has been prospectively examined by high-risk studies such as the New York, Edinburgh, and Copenhagen High Risk Projects (Erlenmeyer-Kimling et al., 1995, Johnstone et al., 2005, Parnas et al., 1993) and found to be associated with a 10 to 15-fold increase in risk for psychosis. An association has also been found between family history and earlier age of onset (Esterberg and Compton, 2012). Van Os et al. (2008) assert however that there is an increasing body of evidence demonstrating that gene effects alone have little or no impact on psychosis onset. Rather, onset is influenced by the interplay between genetic and environmental factors.

3.5 Social Functioning

Severe deficits during the prodromal phase in social-role functioning have been found to occur 2 to 4 years before first admission (Hafner and an der Heiden, 1999). Yung et al (2004a, 2003a, 2006c) found significantly lower Global Assessment of Functioning (GAF) scores (American-Psychiatric-Association, 1994b) at baseline for those who develop psychosis and those who do not, found that and GAF scores less than 51 present increased the odds of developing psychosis within 6 months (odds Ratio 3.7, 95% CI: 1.1, 12.3).

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Hafner and an Der Heiden (1999) suggest that early functional impairment results from negative symptoms, such as trouble with thinking and concentration, lack of energy or poor work performance. Baseline data from a prospective study of 82 subjects recruited into the Zucker Hillside Hospital Recognition and Prevention Program (RAP) (Lencz et al., 2004), showed that social isolation was the most common presenting problem. Additionally, negative symptom indicators were found in equal measures in all three-study groups (CHR- attenuated negative symptoms, CHR+ attenuated positive symptoms, Schizophrenia like psychosis). Thus, the authors hypothesize that 'a cluster of cognitive, affective, social and school impairments may serve as a necessary but not sufficient foundation for the development of schizophrenia' (Cornblatt et al., 2002).

In a study of 121 prodromal subjects and 44 normal controls (NC) Cornblatt and Andrea (2007) found that role functioning fluctuates substantially whereas social functioning appears the most stable of the two. NC's showed significantly higher levels of functioning compared with prodromal subjects.

Initially, social functioning was assessed by the GAF in order to inform the CAARMS intake criteria. However, the latest edition of the CAARMS (Yung et al., 2006a) uses a revised version of the GAF, known as the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992). The GAF combines several dimensions of psychopathology on a

single 100-point scale. The behavioural measures for psychological functioning are combined with the measures of social, occupational or school functioning by 'or' statements, which only makes rating the GAF easy when symptoms and social functioning are equally impaired (Goldman, 2005). Therefore, someone may score very low on GAF because of the intensity of their symptoms, when conversely their functioning would suggest a much higher rating. The SOFAS however, extracts from the GAF the measures of social, occupational and school functioning and rates them separately. This enables an assessment of functioning independent of psychotic symptoms.

The concurrent validity of a revised version of the GAF (Goldman et al., 1992) which is almost identical to the SOFAS was examined by Roy-Byrne and colleagues (1996). The study utilised the revised GAF alongside a standard battery of admission assessments with 337 patients admitted to two in-patient units over an 8-month period. However, they did not compare findings with the original GAF so it is difficult to make comparisons. Nevertheless, the study findings were surprising in that although symptomatic descriptors were eliminated from the revised scale's anchor points, the results were more strongly related to psychiatric symptoms than to functional abilities. This led the authors to conclude that when the revised GAF is used in settings where clinical scales are typically used, the revised GAF may add little to the formal assessment of psychiatric symptoms.

3.6. The Australian Approach

The first study of the UHR approach was conducted at the Personal Assessment and Crisis Evaluation (PACE) clinic in Melbourne (Yung et al., 2003a) and sought to determine how well the UHR criteria described in section 3.2 (vulnerability traits, attenuated symptoms and BLIPS) predict conversion to psychosis. The study involved the follow-up evaluation of 49 individuals assessed in the clinic between 1995 and 1996. The study did not use the CAARMS semi-structure interview to elicit attenuated symptoms;

rather it used the instruments from which the CAARMS interview was derived (section 3.2).

Assessments were conducted at intake and at monthly intervals over a 12-month period, to monitor the development of psychotic symptoms. Twenty subjects (40.8%) developed a psychosis within the 12-month follow-up period. Survival analysis indicated that the highest risk of developing a psychosis occurred within 4.5 months of entering the study. The vast majority 70% (n=14) of subjects developed a psychosis within this period. Subjects who did not meet UHR criteria (UHR-) were not subject to followed-up evaluation therefore the sensitivity and specificity of the CAARMS was not established by this study.

Yung et al (2003) further examined their data using Cox regression analysis to determine the most significant predictors of psychosis. They found having four or more of the following to be the most predictive of psychosis at follow-up:

- Duration of symptoms greater than 900 days
- GAF score less than 51
- BPRS total score greater than 15
- BPRS psychotic subscale score greater than 15
- The Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) attention score greater than 1.
- Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) score greater than 18

However, in a study of 74 UHR+ patients Mason et al (2004) did not replicate these findings. They found that who found none of these variables were significantly associated with transition in their sample. In addition, they investigated whether other risk factors for psychosis could enhance the UHR criteria (age, family history, perinatal complications, pre-morbid social functioning, pre-morbid personality, recent life events, and current symptomatology). Hierarchical analysis of age, family history and number of

obstetric complications did not predict transition either (x^2=4.47, df= 3, p > 0.05). The most predictive model was found to be comprised of the following: premorbid factors of years of education, premorbid intellectual ability, schizotypal personality and premorbid adjustment (x^2=23.8, df = 4, p<0.01). However, schizotypal personality was the only significant predictor of psychosis. (Wald=13.7, df =1, p<0.001).

Of the 74 participants that met UHR+ criteria 37 (50%) made the transition to psychosis. Those who made the transition were most likely to come from the BLIPS group (14/23), followed by the attenuated psychosis group (22/43) and only a few in the state and trait group (2/13). There was some overlap between groups with some individuals meeting criteria for more than one group.

Recognising the importance of establishing how many people not judged as UHR develop a psychosis Yung et al. (2006c, 2008) conducted a further study of 149 help-seeking individuals and 143 PACE clinic patients (n=292), consecutively referred to the Orygen Youth Health (OYH) triage service. The CAARMS interview was used to elicit attenuated symptoms. One hundred and nineteen patients were UHR+ and 173 were not (UHR-). Both UHR+ and UHR- patients received follow-up evaluations.

Yung et al (2006) anticipated that the transition rate in this study would be lower than the previous one as a large proportion of the sample (63%, n=173) were UHR-. She also hypothesised that UHR+ individuals with low functioning would present an increased risk of psychosis compared with higher functioning individuals.

At 6-month follow-up CAARMS, data was available for 195 participants and the notes-based review was conducted for the remaining ninety-five. At 6-months follow-up 12 (10.08%) of the UHR+ patients and only one (0.58%)of the UHR- patients had converted to psychosis. At 2-year follow-up twenty-one patients (7.2%) had converted to psychosis, 19 (16%) of the UHR+

group and two (1.16%) of the UHR- group. The sensitivity of the CAARMS was

Yung, et al (2008) note that whilst higher than expected in the general population, the transition rate of 16% in the UHR+ group is significantly lower their initial study which reported rates of over 40% (Yung et al., 2003a). They offer some suggestions for why this may be the case. Firstly, they propose that the decline in transition could be related to the earlier detection of individuals, due to referring agencies becoming more vigilant for psychosis resulting in referrals earlier in the course of the disorder. Additionally, all subjects received case management, some CBT, others antidepressants which Yung et al (2008) suggest may have delayed or even averted transition.

In view of declining conversion rates between studies, Yung (2007) examined conversion rates between 1995 and 2000 and established that the decline was occurring year on year. Kaplan-Meier estimates for the 12-month conversion rates were 0.50, 0.33, 0.32, 0.29, 0.21, and 0.12. They noted that over each successive year the duration of symptoms prior to referral was reducing. In the 1995 cohort, the mean number of days for which the patient experienced symptoms, before seeking help was 559.6. This had decreased considerably to 46.5 days by the year 2000 cohort. Yung et al (2007) hypothesise that in later cohorts patients are being referred sooner in the course of their symptoms therefore the transition rate may not remain as low if patients are followed up for longer. They further suggest, that earlier referral and resultant early detection may also prevent conversion in some cases.

3.7 The North American Approach

In a preliminary validation study of 29 patients assessed using the SIPS (Miller et al., 2002) 13 met the criteria for prodromal syndrome at baseline,

while 16 did not. After 6-months follow-up 46% (n=6) had converted to psychosis. This increased to 54% (n=7) after 12 months (Miller et al., 2003b). None of those individuals deemed non-prodromal at baseline converted within 12 months. The validity study sample was further updated and a total sample of 34 participants was achieved. These were drawn from 123 consecutive treatment-seeking patients referred to the PRIME Clinic for suspected prodromal syndrome (Miller et al., 2003b). Of these, 14 met the criteria for prodromal syndrome and 20 did not. Of the 14 who met the prodromal syndrome criteria 13 met attenuated positive symptom criteria and one met BLIPS criteria. Follow-up evaluations conducted at 6, 12, 18, and 24 months revealed conversion rates of 42.86%, 50%, 57.14%, and 57.14% respectively. All conversions occurred within 18 months of follow-up. The sensitivity of the SIPS/SOPS was 1 (95% CI: 0.60, 1), specificity was 0.80 (95% CI: 0.59, 0.92). This was better than for the CAARMS however, the sample size was very small.

Addington et al (2007) observed that due to the low annual incidence of new cases (1 case per 10 000 persons per year), achieving adequately powered sample sizes is a significant challenge. As a result, a consortium of prodromal psychosis research has been established in North America known as the North American Prodrome Longitudinal Study (NAPLS) (Cannon et al., 2008). The consortium consists of eight research centres (Emory University; Harvard Medical School; University of California, San Diego; University of North Carolina, Chapel Hill; University of Toronto; Yale University and Zucker Hillside Hospital). The preliminary aims of the NAPLS study are:

- To determine the rate of conversion to psychosis
- To ascertain the rate of survival function across 2.5 years follow-up
- To develop a multivariate risk prediction algorithm to guide selection of cases in future studies

NAPLS administered the SIPS assessment at baseline at 6-monthly intervals throughout the study. Additional reassessments occurred for individuals demonstrating signs of clinical deterioration between follow-up examinations. The primary outcome was time to conversion to psychosis from baseline as established by SIPS psychosis criteria. Those who did not meet SIPS criteria at baseline for prodromal syndrome were not subject to a follow-up evaluation.

The study recruited 370 subjects meeting SIPS UHR criteria at baseline, of which 291 completed at least one clinical evaluation and 79 were lost to follow-up. Eighty-two (28.18%) of the 291 patients made the transition to psychosis. Kaplan-Meier analysis found the cumulative prevalence rate ± standard error (SE) for conversion to psychosis at 6, 12, 18, 18, 24 and 30 months to be 12.7%±1.9, 21.7%± 2.5, 26.8%±2.8, 32.6±3.3 and 35.3%±3.7 respectively

3.8 Discussion

As can be seen from this chapter, two instruments have been developed using the UHR approach – SIPS (Miller et al, 2003) and CAARMS (Yung et al 1998). The UHR approach aims to detect individuals in the later stage of the prodromal period, very close to the point of conversion. However, declining transition rates between studies indicate that earlier detection is resulting in a greater number of people being identified as at risk who will never progress further to psychosis (Ziermans et al, 2011). A number of reasons have been suggested for this ranging from earlier referral to the model of care delivery in EI services. Keshavan et al. (2011) suggest that the development of psychosis can be dichotomous or continuous, resulting in some individuals having symptoms reliably present over the developmental course of the disorder while others may experience symptoms ‘waxing and waning’. This could explain why some patients presenting with attenuated symptoms experience remission of symptoms by follow-up. With the development of Early Intervention services across the UK and emphasis

upon the reduction of the duration of untreated psychosis, it could be suggested that General Practitioners (GPs) are referring patients earlier in the course of their illness; therefore, our study may also experience lower conversion rates.

The Basic symptom approach aims to detect people at risk of psychosis in the Early and Late stages of the prodrome. This offers the opportunity for earlier detection of symptoms possibly before the onset of functional decline. However, the potential disadvantage of this approach is the length of follow-up required to observe conversion. The study by Klosterkotter et al (2001) achieved 70% conversion rates over a mean follow-up period of 9.6 years. Such a long follow-up period would clearly not be feasible in a routine healthcare setting. There is however, emerging evidence to suggest that there is an advantage of using both the UHR and Basic Symptoms approaches together. The inclusion of self-experienced Basic symptoms has improved the sensitivity of prediction models (Ruhrmann et al, 2010).

From a purely practical point of view, the CAARMS is much easier to implement into clinical practice, as concordance is easier to achieve. The practitioners with the EIS are all familiar with psychosis assessment using the PANSS (Kay et al., 1987), and the CAARMS interview is similar. However, the SPI-A is unlike any assessment the EIS practitioners have ever used and requires intensive training to gain concordance. The danger with SPI-A is that practitioners tend to be over inclusive and rate symptoms as basic symptoms when they are not. The use of the SPI-A would need to be confined to a specialist clinic to establish and maintain concordance, whereas CAARMS could be used more broadly.

CHAPTER 4: Aims and Objectives

Chapter 4: Aims and Objectives

4.1 Introduction

This chapter seeks to outline the aims and objectives of the thesis. There are two parts to the thesis, a systematic review with meta-analysis and a service evaluation of an Early Detection Clinic.

4.2 Aims

There are two broad aims of the thesis:

1. To identify all available psychopathology based instruments for the detection of at risk mental states and evaluate the sensitivity and specificity of the instruments through meta-analysis.

2. To establish the accuracy of the current predictions made within the Lancashire Early Assessment and Detection (LEAD) Clinic using the Basic Symptom and UHR approach.

4.3 Objectives of the Systematic Review with Meta-Analysis

The overall objective of the review is to conduct a comprehensive synthesis of the high-risk research literature to date; to identify all available psychopathology-based instruments for the detection of the psychosis prodrome. Where possible a quantitative analysis of the data will be undertaken, in order to determine the sensitivity, specificity, positive and negative predictive values and likelihood ratios of the available instruments. In doing so the review will:

1. Summarise the research field to date and identify areas for further research.

2. Determine the validity of pre-cursor symptoms in the prediction of psychosis onset.

4.4 Systematic Review Hypothesis

It is hypothesised that the review will identify two main approaches (Basic Symptoms and UHR) that were able to identify a cohort of patients that would subsequently develop psychosis but that they would differ in their predictive power, resulting in significant heterogeneity in PPV and hence sensitivity and NPV.

4.5 Objectives of the Service Evaluation

The service evaluation has five objectives:

- To determine how many people assessed in the clinic between January 2008 and December 2011 subsequently developed psychosis.
- To establish the accuracy of our current predictions concerning which non−psychotic patients will develop psychosis.
- To improve the efficiency of the assessment process by identifying redundant or inaccurate techniques
- To determine whether combining UHR and BS instruments has an additive effect and improves predictive ability.
- to determine time to transition and inform the duration of care co-ordination follow-up offered by the Lancashire EIS

4.6 Service Evaluation Hypotheses

It is hypothesised that combining the SPI-A assessment with the CAARMS will result in greater sensitivity and specificity than when the CAARMS or SPI-A are evaluated individually. It is also hypothesised that the use of the SPQ-A as a measure of schizotypy will increase the overall sensitivity and specificity of the CAARMS.

Methods

CHAPTER 5: Methods

Chapter 5: Methods

5.1 Introduction

This chapter describes the methods used to achieve the overall aims and objectives of the thesis. Section 5.1 provides an overview of the methods employed in undertaking a systematic review with meta-analysis of the accuracy of psychopathology-based risk assessments in identifying people at-risk of developing a psychosis. Section 5.2 describes the methodology of a service evaluation undertaken to determine the predictive accuracy of the diagnostic instruments used within the LEAD clinic.

5.2 Systematic Review with Meta-Analysis

The systematic review was conducted using the guidelines developed by Deville et al. (2002) from their experience and expertise of working with the Cochrane Collaboration

5.2.1 Eligibility Criteria

The detection of individuals thought to present a risk of psychosis is a developing field of research and applying the most exacting criteria for inclusion would lead to the exclusion of key studies. Inclusion criteria were therefore set suitably low to enable identification of all studies relevant to the review.

Studies were eligible if they met the following criteria:

1. The participants were considered at risk of psychosis following a clinical review.

2. The participants were assessed using a psychopathology-based instrument which evaluated how far they were at risk of developing psychosis.
3. Following the assessment, participants were followed up for at least 6-months.
4. At the end of follow-up participants were reassessed to determine if they had developed psychosis.

Studies were excluded if they were treatment trials.

5.2.2 Search Strategy

The search strategy aimed to identify all studies that employed psychopathology based interviews for the prediction of psychosis onset. Unlike randomised controlled trials, studies of this nature are not well indexed. Therefore, the search criteria were set sufficiently broad to capture all of the available studies in this field.

Electronic searches of Medline (1946-Nov 2011), Embase (1973-Nov 2011), CINHAL (1937-Nov 2011), and Psychinfo (1806– Nov 2011) were undertaken using the search strategy detailed in Table 4. The search strategy was sensitive rather than specific in order to ensure that all relevant studies were captured. The reference lists of identified studies were also screened to ensure no studies were missed.

Table 4: Search Strategy

1	exp Schizophrenia, Paranoid/ or exp Schizophrenia, Catatonic/ or exp Schizophrenia, Disorganized/ or exp Schizophrenia/ or exp Schizophrenia, Childhood/
2	exp Paranoid Disorders/
3	((chronic$ or severe$) adj5 MENTAL$ adj5 (ILL$ or DISORDER$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4	(schizo$ or psychotic$ or psychosis or psychoses or hebephreni$ or oligophreni$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5	1 or 2 or 3 or 4
6	((risk$ adj3 schiz$) or (screen$ adj4 schiz$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7	((duration or length) adj3 untreat$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8	((first or initial or primary) adj3 untreat).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
9	(early adj3 (intervent$ or treat$ or recogni$ or detect$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
10	(delay$ adj3 treat$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11	6 or 7 or 8 or 9 or 10
12	5 and 11
13	(animal not human).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
14	12 not 13

.

5.2.3 Study Selection

Studies were selected for inclusion if they met the eligibility criteria defined in section 5.2.1. The literature search and application of the inclusion/exclusion criteria were undertaken by the corresponding author (CJ).

5.2.4 Data Collection Process

Once the studies eligible for inclusion were identified, the data extraction was performed in duplicate by two reviewers (CJ and BW). Any disagreements were resolved by the third reviewer (MM). Data was extracted into an Excel database.

The following information was recorded for each eligible study:

- Description of clinical setting
- Participant characteristics
- Instrument used to assess risk at baseline
- Instrument used to assess psychosis at follow-up

From each eligible study the following data were extracted:

- Number tested positive
- Number tested negative
- Number found to be psychotic at follow-up
- Number not found to be psychotic at follow-up
- Number not reassessed.

In order to ensure that overlapping cohorts were not included in the review, the recruitment dates were carefully screened and where appropriate the authors contacted to provide clarity.

5.2.5 Risk of Bias (Quality assessment)

The quality of each included study was assessed by CJ and IC using a 14-item Quality Assessment Tool for Diagnostic Assessment Studies (QUADAS) (Whiting et al., 2011). The QUADAS tool was developed specifically to enable an objective assessment of the quality and potential biases within the included studies as part of a systematic review. Understanding the quality of primary studies enables the effects of different biases and variations between studies to be investigated within the review (Whiting et al., 2003).

5.2.6 Summary Measures

The target study design for this review was one which at baseline discriminated the 'at risk' cohort from the 'not at risk' and re-assessed the respective cohorts after a follow-up period to assess how many had undergone a transition to psychosis. Ideally, a suitable reference standard would be applied to both cohorts at follow-up and this would allow summary positive and negative predictive values (PPV and NPV), sensitivity, and specificity to be calculated.

5.2.7 Synthesis of Results

It was intended that the data extracted from the studies would be modelled using a bivariate random effects model which are the main tests recommended for synthesising diagnostic test accuracy data (Chu et al., 2006).

However, studies which only followed up the 'at risk group' or re-applied the index test (instead of a reference standard) at follow-up were also included and analysed using univarate random effects methods (DerSimonian and Laird, 1986) after a logit transformation of the data. Where studies reported on patients at different follow-up times data from the longest follow-up period were used in meta-analyses unless otherwise stated.

Heterogeneity was assessed using the Cochrane Q statistic and the I^2 statistic (Higgins et al., 2003). As part of the investigation of heterogeneity, meta-regression was also planned using a logistic regression mixed effects model. The log likelihood ratio test statistic (*LRT*), which has an asymptotic χ^2 distribution with *df* degrees of freedom was used to compare models. Statistical significance was set at $p<0{\cdot}05$.

5.3 Methodology of the Service Evaluation

5.3.1 Study Setting

The service evaluation was conducted within the Lancashire EIS. The EIS is a specialist service for young people aged 14-35 with a first episode psychosis. In line with National guidance (Department of Health, 2001), they also offer a 'watching brief' to young people thought to present a risk of psychosis. Since the EIS receives many referrals of people who are not psychotic but display some mild but detectible signs of a possible developing psychosis, a key issue for the service is to distinguish those at-risk from those who are not. A number of diagnostic tests are available to make this distinction. However, they could not be routinely used at the point of initial assessment by case managers, as they require specialist expertise. Consequently, the Lancashire Early and Detection (LEAD) Clinic was set up to provide this specialist assessment service.

There are currently three LEAD clinics across Lancashire (East, North and Central Lancashire), each offering assessment of at-risk mental states by specially trained clinicians. The demographic profile of Lancashire is diverse with mix of affluent rural and semi-rural areas alongside extremely deprived urban areas. The population is 1.5 million, of which 9% are from ethnic minorities, and 17.4% are from areas in the top 10% of the deprivation index. Preston and Lancaster have the highest proportion of young people aged 15-24 (17.6% each), reflecting the locations of two large universities (Lancashire County Council, 2010).

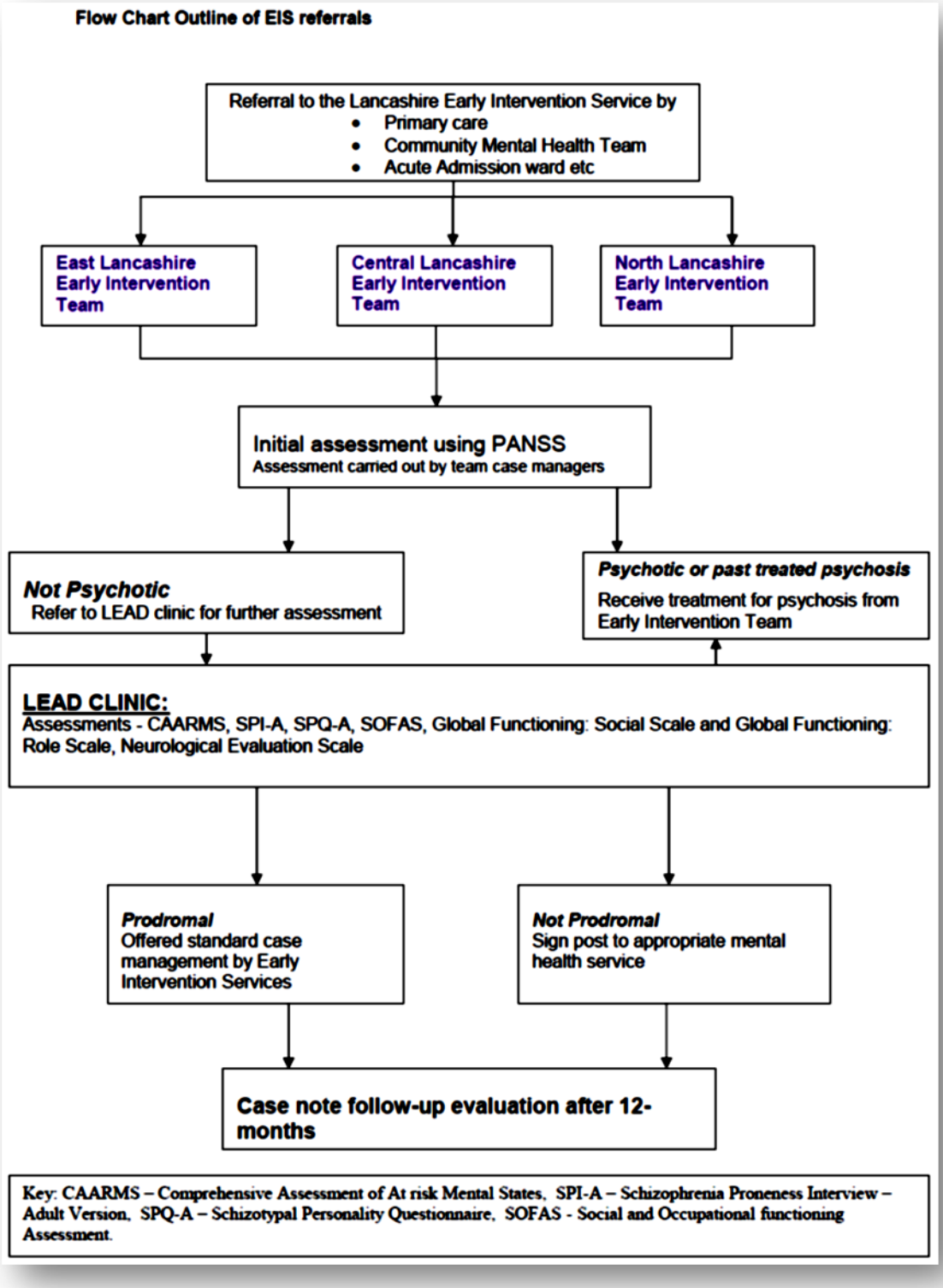
5.3.2 Referral Process

The EIS receives referrals for people who are in the first episode of psychosis or who are considered at risk of developing a psychosis. Standard clinical practice within the EIS is that new referrals are assessed by a clinical

case manager using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and their clinical record is reviewed. If this assessment shows evidence of a first episode of psychosis, the patient is accepted into the EIS for a period of 3-years case management and treatment. If the assessment finds no evidence of psychosis, then the patient is referred to the LEAD clinic for further assessment (see figure 1 below for the EIS referral flowchart).

The LEAD clinic is designed to provide an in-depth assessment by trained clinicians who apply specialised diagnostic techniques to identify people with prodromal symptoms (i.e. those who are at risk of developing psychosis). These "prodromal" patients are then monitored and supported by the EIS for a period of 12-months, while those considered not prodromal are referred other more suitable services. During this 12-month period, they have access to the full range of interventions and support provided by the EIS such as Cognitive Behavioural Therapy (CBT), Case Management, Support, Time and Recovery (ST&R) Workers and medication reviews by a Psychiatrist where appropriate. The 12-month period of follow-up was agreed based the Yung et al (2003) research that demonstrated that 40.8% of transitions to psychosis occurred within the first 12-months. Discussions with the Melbourne group at the time of establishing the clinic indicated that they also provided a follow-up period of 12-months in their PACE Clinic. However, they subsequently informed us that they have reduced duration of follow-up to 6-months as their research has shown that the majority of transitions occur within the first 6-months of follow-up (Yung et al, 2008).

Figure 1: EIS Referral Flowchart



5.3.3 Study Design

Following an assessment at the LEAD, clinic people thought to present a risk for psychosis are offered case management by the EIS for 12-months. The EIS is not funded to case manage people at-risk of psychosis and as the clinics identify a number of people in this category, they place an additional strain on the case manager resource. It was therefore important to establish how many young people deemed at-risk of psychosis by the assessment process did indeed develop a psychosis. This would enable us to establish the accuracy of our predictions, improve the efficiency of the assessment process by identifying redundant or inaccurate tests, and determine the length of follow-up required.

In order to achieve the required outcomes it was agreed that the most appropriate design was that of a service evaluation of consecutive referrals to the LEAD clinic between January 2008 and December 2011. The follow-up period ended in December 2012. A casenote review was undertaken at the end of the follow-up period to determine conversion to psychosis. We selected this approach in preference to a study that involved a follow-up interview at 12-months for a number of reasons. Firstly, the LEAD clinic did not have capacity to offer follow-up assessments, the waiting lists for initial assessments were already approaching several weeks, and we did not have any additional funding for this study. Secondly, we wanted to know the outcome for all our patients and introducing follow-up analysis with informed consent would have resulted in the introduction of biases through attrition. Finally, we agreed that of all the data we were going to use within the study was routinely collected by the service, therefore a service evaluation methodology was the most appropriate choice.

5.3.4 Inclusion/Exclusion Criteria

The study includes all patients referred to the LEAD clinic aged 14-35 who were not currently psychotic and do not have a history of psychosis. Patients

found to be psychotic or receiving a therapeutic dose of antipsychotics at baseline will be excluded from the follow-up evaluation.

5.3.5 Measures

A summary of routine measures used in the clinic are shown in table 5 and a more detailed description of each is given below.

Table 5:Assessments Completed in the LEAD Clinic

Title	Type of Assessment	Mode of assessment	Training required	Time
CAARMS	UHR	Semi-structured Interview Clinician Rated	DVD	45 minutes
SOFAS	Social and Occupational Functioning	Unstructured clinician delivered interview and rating scale	none	15 minutes
SPQ-A	Schizotypy	Self-rated questionnaire	none	10-15 minutes
SPI-A	Basic Symptoms	Semi-structured Interview Clinician Rated	One Weeks theory and practical training	1 hour

The Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2006a)

The CAARMS is a semi-structured interview designed to detect people in the later stage of the prodrome. In order be deemed at-risk of psychosis by CAARMS, patients must fulfil one of three criteria:

a) **Vulnerability traits**: Schizotypal personality disorder and/or a first-degree relative with a history of psychosis accompanied by a 30% drop in functioning either sustained for at least a month or a score of 50 or below on the SOFAS sustained for 12-months or more.

b) **Attenuated Psychotic Symptoms**: The patient will meet criteria for sub-threshold psychotic symptoms in relation to the frequency, duration and severity of their experiences. The Symptoms will neither be severe enough nor frequent enough to meet criteria for a psychosis. For example, the patient may hear their name being called 3-6 times a week but not hear additional and persistent auditory hallucinations. The symptoms must have been present within the last year and be accompanied by a 30% drop in functioning sustained for at least a month or a score of 50 or below on the SOFAS sustained for 12-months or more.

c) **BLIPS:** The patient experiences symptoms that meet psychosis criteria but they only last for 7 days and spontaneously remit without treatment. The symptoms must have been present within the last year and accompanied by a 30% drop in functioning sustained for at least a month or a score of 50 or below on the SOFAS sustained for 12-months or more.

The CAARMS also has criteria for determining whether a patient is currently psychotic. In order to meet psychosis criteria the symptoms must be severe and frequent and have persisted for more than 7 days.

Social and Occupational Functioning Assessment (SOFAS) (Goldman et al., 1992).

The SOFAS is rated on a 0-100 scale on the basis of a clinical interview. Anchor points are provided to assist in determining the score. The clinician determines a rating of both the premorbid and lowest level of functioning within the last year. The period of time for which the lowest level of

functioning has been maintained is also determined. The percentage drop in functioning from the pre-morbid level is calculated.

Schizotypal Personality Questionnaire (SPQ-A) (Raine, 1991)

The SPQ-A is a 72-item self-report questionnaire used to detect schizotypal personality traits. Patients tick yes or no in response to each question. The sum of the 'yes' answers gives the overall score. A score of 39 or more is used as the cut-off for schizotypal personality traits (Hall and Habbits, 1996).

Schizophrenia Proneness instrument (SPI-A) (Schultze-Lutter et al., 2007).

The SPI-A is a semi-structured interview designed to elicit Basic Symptoms. Symptoms are scored on a 0-9 point scale with scores between 3 and 6 indicating the presence of a basic symptom. A score of 7 indicates that the symptom has always been present at the same severity. If a trait symptom has increased recently in severity then this would be scored within the 0-6 range. Scores of 8 and 9 indicate that the symptom is present but there is not sufficient information to give a rating of between 0 and 6. SPI-A uses two-overlapping criteria to determine at-risk status: – Cognitive-Perceptive (COPER) and Cognitive-Disturbances (COGDIS). In order to enable the clinic to use both CAARMS and SPI-A within the two-and-a-half hour clinic time available, only the items required to determine COPER and COGDIS status were used from the SPI-A.

Professor Max Marshall (MM) and I (CJ) received training from the author of the SPI-A, Frauke Schultze-Lutter. Both CJ and MM later trained Dr Kishen Neelam (KN) who was one of the founders of the clinic. CAARMS training was undertaken using a training DVD produced by the authors of the CAARMS. CJ also attended a master-class with Alison Yung; the principle author of the CAARMS.

All other assessors working in the clinic received training from CJ and were observed in clinics by CJ, MM or KN until they reached concordance. All assessments were completed by two trained clinicians to ensure quality.

5.3.6 Approval to Conduct the Evaluation

The service evaluation was approved by the Lancashire Care NHS Foundation Trust Research Governance Committee. We consulted the National Research Ethics Committee (NRES) guidance to determine whether we needed ethical approval to conduct the evaluation. The guidance was clear that as the study was an evaluation of a routine service and used routinely collected data, ethical approval was not required ((National-Research-Ethics-Authority, 2006). The NRES guidance table for distinguishing between research and service evaluations is shown in appendix 2.

5.3.7 Evaluation at Baseline

Baseline assessments were carried out on a weekly basis and last approximately 2½ hours. The assessments form part of the routine clinical evaluation of all referrals to the Lancashire EIS. Upon arrival at the clinic patients who have suitable levels of literacy are asked to complete the SPQ-A in the waiting room. The assessment begins with a clinical interview to determine the history of the presenting complaint, family history of psychosis, substance use history, and social functioning (pre-morbid and current). The SPI-A and CAARMS interviews are then completed. Once the assessments are complete, the patient is asked to return to the waiting room. The clinicians then score the assessments and determine the at-risk status of the patient. The SOFAS is scored based on the clinical interview. The patient is then informed of the outcome. The next day the EIS clinical team discuss the outcome of the assessment and agree the next steps. Normally patients with

a psychosis are offered case management by the EIS for a period of 3 years and patients at risk of psychosis for 1 year.

Following the assessment, the LEAD clinic places patients into one of 3 groups:

1. At-Risk Mental State (ARMS)
2. Not At-risk
3. Psychotic

The decision regarding group allocation is based upon the assessment outcome. People are placed in the at-risk group if they meet either SPI-A (COPER or COGDIS), or CAARMS criteria for at-risk mental states. If neither SPI-A nor CAARMS deem the patient to have an at risk mental state they are placed in the not at-risk group. Patients meeting the CAARMS psychosis threshold are placed in the psychosis group.

CAARMS Criteria

The CAARMS symptoms are rated on a global severity and a frequency/duration scale:

Global Rating

0 – Never, absent
1 – Questionable
2 – Mild
3 – Moderate
4 – Moderately severe
5 – Severe
6 – Psychotic and Severe

Frequency and Duration Rating

0 – Absent
1 – Less than once a month
2 – Once a month to twice a week – less than an hour per occasion
3 – Once a month to twice a week –more than an hour per occasion **OR** 3 to 6 times a week – less than an hour per occasion.
4 – 3 to 6 times a week more than an hour per occasion **OR** Daily – less than an hour per occasion
5 – Daily – more than an hour per occasion **OR** Several times a day
6 – Continuous

At-risk and psychosis status is determined by the following criteria:

1. Vulnerability
2. Attenuated Psychosis
3. BLIPS

Patients meeting any one or more of these criteria are deemed at-risk of psychosis.

Criterion 1: Vulnerability Group

This criterion combines trait factors (schizotypy and first degree family history of psychosis) with a significant deterioration in mental state and/or functioning

- A first-degree family history of psychosis **OR** a score of ≥ 39 on the SPQ-A.

PLUS

- A 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within the past 12-months **OR** SOFAS score of 50 or less for 12 months or longer.

Criterion 2: Attenuated Psychosis Group

This criterion identifies people with sub-threshold symptoms that do not yet meet the criteria for psychosis. This group includes two subgroups: Subthreshold intensity (the symptoms are not severe enough) and subthreshold frequency (the symptoms do not occur often enough).

2a: Subthreshold Intensity:

- Global rating scale score of 3-5 on Unusual Thought Content subscale, 3-5 on Non-Bizarre Ideas subscale, 3-4 on Perceptual Abnormalities subscale and/or 4-5 on Disorganised Speech subscales.

PLUS

- Frequency scale score of 3-6 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech subscales for at least a week

  OR

- Frequency scale score of 2 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and Disorganised Speech subscales on more than 2 occasions (experienced a minimum of 4 times in total).

2b: Subthreshold Frequency

- Global rating scale score of 6 on Unusual Thought Content, 6 on Non-Bizarre Ideas, 5-6 on perceptual Abnormalities and/or 6 on Disorganised Speech subscales

PLUS

- Frequency scale score 3 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech

PLUS for Both Categories

- Symptoms present in the past year

- 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within the last 12-months **OR** SOFAS score of 50 or less for the past 12-months or longer.

Criterion 3: BLIPS GROUP

This criterion identifies people at risk of psychosis due to a recent history of symptoms meeting psychosis criteria that resolved spontaneously without treatment within one week.

- Global rating scale of 6 on Unusual Thought Content subscale, 6 on Non-Bizarre Ideas, 5or 6 on Perceptual Abnormalities and /or 6 on Disorganised Speech.

PLUS

- Frequency scale score of 4-6 on Unusual Thought content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech Subscales.

PLUS

- Each symptom episode is present for less than one week and symptoms remit spontaneously on each occasion.

PLUS

- Symptoms occurred during the last year

PLUS

- 30% drop in SOFAS score from premorbid level, sustained for a month, occurred within the last 12-months **OR** SOFAS score of 50 or less for the past 12-months or longer.

Psychosis Threshold

In theory as all referrals to the LEAD clinic will have already received an assessment of psychotic symptoms using the PANSS (Kay et al., 1987), none of the patients should be psychotic at baseline assessment. Psychotic

patients should have already been accepted into case management and not referred to the clinic. However, the CAARMS does enable the presence of symptoms meeting the psychosis to be assessed. The threshold is as follows:

- Severity scale score of 6 on Unusual Thought Content, 6 on Non-Bizarre Ideas, 5 or 6 on Perceptual abnormalities and/or 6 on Disorganised Speech.

PLUS

- Frequency scale score of ≥ 4 on Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities and/or Disorganised Speech.

PLUS

- Symptoms present for longer than 1 week.

(Yung et al., 2006a)

Basic Symptom Criteria

The presence or absence of Basic Symptoms is rated on a 9-point scale as follows:

0 – Absent, never present

1 – Rare – Less than once in a month

2 – Mild – Short periods about once in a month

3 – Moderate – Several times in a month or weekly

4 – Moderately severe – several times in a week

5 – Severe – Daily, periods of improvement possible

6 – Extreme – Daily, but not necessarily continuously

7 – Has always been present in the same severity (trait)

8 – Definitely present, but severity unknown

9 – Symptom definition questionably met

The SPI-A uses two sets of overlapping criteria to determine at-risk of psychosis status – COPER and COGDIS

COPER Criterion

COPER criterion is determined by the presence of at least any one of the following ten basic symptoms with a SPI-A score of ≥ 3 within the last 3 months and first occurrence ≥ 12-months ago:

- Thought Interference
- Thought Perseveration
- Thought Pressure
- Thought Blockages
- Disturbance of receptive speech
- Decreased ability to discriminate between ideas/perception, fantasy/true memories
- Unstable ideas of reference
- Derealisation
- Visual perception disturbances (excluding hypersensitivity to light or blurred vision)
- Acoustic perception disturbances (excluding hypersensitivity to sounds)

COGDIS Criterion

The COGDIS criterion is determined by the presence of at least two of the nine following basic symptoms with a SPI-A score of ≥3 within the last 3 months:

- Inability to divide attention
- Thought Interference
- Thought pressure
- Thought blockages
- Disturbance of receptive speech

- Disturbance of Expressive Speech
- Unstable ideas of reference
- Disturbances of abstract thinking
- Captivation of attention by details of the visual field

5.3.8 Evaluation at Follow-up

Patients were categorised into 3 groups at baseline: at-risk, not at risk and psychotic. Patients who are psychotic or prescribed anti-psychotic medication at baseline will be excluded from follow-up analysis. Patients in both the at-risk and not at risk groups will be included in the follow-up analysis.

The follow-up evaluation will involve a review of the electronic care record of all patients in the at-risk and not at-risk groups to determine who did and did not develop a psychosis. Conversion to psychosis for the purposes of the evaluation is defined by:

1. Admission to hospital for a psychotic illness;
2. In receipt of prescription of anti−psychotic medication, for treatment of psychotic symptoms;
3. Documented presence of psychotic symptoms in the clinical record persisting for more than one week.

Given that Lancashire Care NHS foundation Trust is the only provider of mental health services in Lancashire, anyone developing a psychosis will likely receive care from one of the services within the Trust. Therefore a review of the clinical record should successfully identify anyone still residing in Lancashire who develops psychosis. However, patients who move to other areas of the country will be lost to follow-up.

5.3.9 Data Analysis

Analysis was conducted utilising SPSS for Windows (SPSS Inc., 2007, Version 19, Chicago, IL, US). Diagnostic efficiency measures such as sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Values (NPV), Likelihood Ratios (LR) and Odds Ratios (OR) were calculated using MedCalc software (Version 12.3.0, Mariakerke, Belgium). Statistical measures, means and standard deviations are explained for descriptive purposes. Receiver Operating Curve (ROC) analysis enabled the most predictive cut-off scores for measures to be determined.

The risk of conversion to psychosis was calculated by Kaplan-Meier survival analysis for calculating the cumulative hazard rate. The association between baseline measures and conversion to psychosis was determined by univarate chi squared analysis. Binary logistic regression was used to determine the most predictive combination of tests.

RESULTS

CHAPTER 6: Results of a Systematic Review with Meta-Analysis of the Accuracy of Psychopathology-Based Risk Assessments.

Chapter 6: Results of a Systematic Review with Meta-Analysis of the Accuracy of Psychopathology-Based Risk Assessments.

6.1 Introduction

Over the last two decades, researchers have increasingly shifted their attention from stabilisation and maintenance interventions for psychosis to earlier detection and possible prevention of the disorder. As a result, two main psychopathology based approaches to early detection have emerged; the UHR and Basic Symptom approaches. This chapter presents the results of a comprehensive synthesis of all available published studies of psychopathology-based instruments for the detection of the psychosis prodrome. The review methodology was explained in chapter 5 (section 5.1).

6.2 Search Strategy Results

The search strategy (outlined in chapter 5) identified 14,683 abstracts of which 168 were from papers that described studies potentially meeting the inclusion criteria. After reviewing the full-text of these papers, 103 were found to describe studies that were not relevant to the review. A further 41 papers described 21 studies that met some but not all of the inclusion criteria and were excluded from the review (see appendix 3). Six of these papers described data from the North American Prodrome Longitudinal study (NAPLS) (Addington et al., 2007, 2010, 2011a, 2011b, Cannon et al., 2008, Seidman et al., 2010).This study was excluded from the meta-analysis as it is difficult to determine whether studies included in NAPLS duplicated the individual study data from already included American studies and was itself essentially a meta-analysis. Seven papers described studies with no follow-up data (Addington et al., 2008, Heinimaa et al., 2006, Liu et al., 2010, Muller et al., 2010, Ord et al., 2004, Salokangas et al., 2013, Yung et al., 2009). Seven papers reported studies in a language other than English (Bechdolf et al., 1998, Cotte et al., 1980, Hasan et al., 2010, Klosterkotter et al., 2000a, 2000b, 2001c, Schafer et al., 2007). Four papers described intervention

studies (Bechdolf et al., 2004, 2007, Morrison et al., 2002, 2011) . Three papers described retrospective studies (Poustka et al., 2007, Schultze-Lutter et al., 2010b, Shioiri et al., 2007). One paper described a review (Bergman et al., 2000). Four papers were conference abstracts and did not contain sufficient data to include in the meta-analysis (Demjaha et al., 2010, Liu et al., 2010, Nelson et al., 2011, Schlosser et al., 2011). Two papers described a population survey of the prevalence and burden of at-risk criteria (Schultze-Lutter et al., 2010a, 2011). One study described a single case study (Winton-Brown et al., 2011)

The final sample consisted of 24 papers, describing 15 studies meeting all of the eligibility criteria (Bechdolf et al., 2010, Broome et al., 2005, Carr et al., 2000, Cornblatt et al., 2003, Haroun et al., 2006, Klosterkotter et al., 2001a, Lam et al., 2006, Lencz et al., 2003, Mason et al., 2004, Miller et al., 2003a, Miller et al., 2002, Riecher-Rossler et al., 2007, Ruhrmann et al., 2010, Schultze-Lutter et al., 2007b, Simon et al., 2006b, Simon and Umbricht, 2010, Yung et al., 2008, Yung et al., 1998a, Yung et al., 1998b, Yung et al., 2003a, Yung et al., 2004b, Yung et al., 2006c, Yung et al., 2007, Ziermans et al., 2011) . The flow diagram shown in figure 2 below shows the study selection process.

6.3 Included Study Characteristics

Across the included studies, the total number of participants was 1,573. The mean age was 20.57, 44.4% (n=698) were female, follow up periods ranged from 6 months to 9.6 years and studies were conducted worldwide in Europe, America, Australia and Asia. The characteristics of each study are summarised in table 5.

Figure 2: Flow Diagram of Included and Excluded Studies

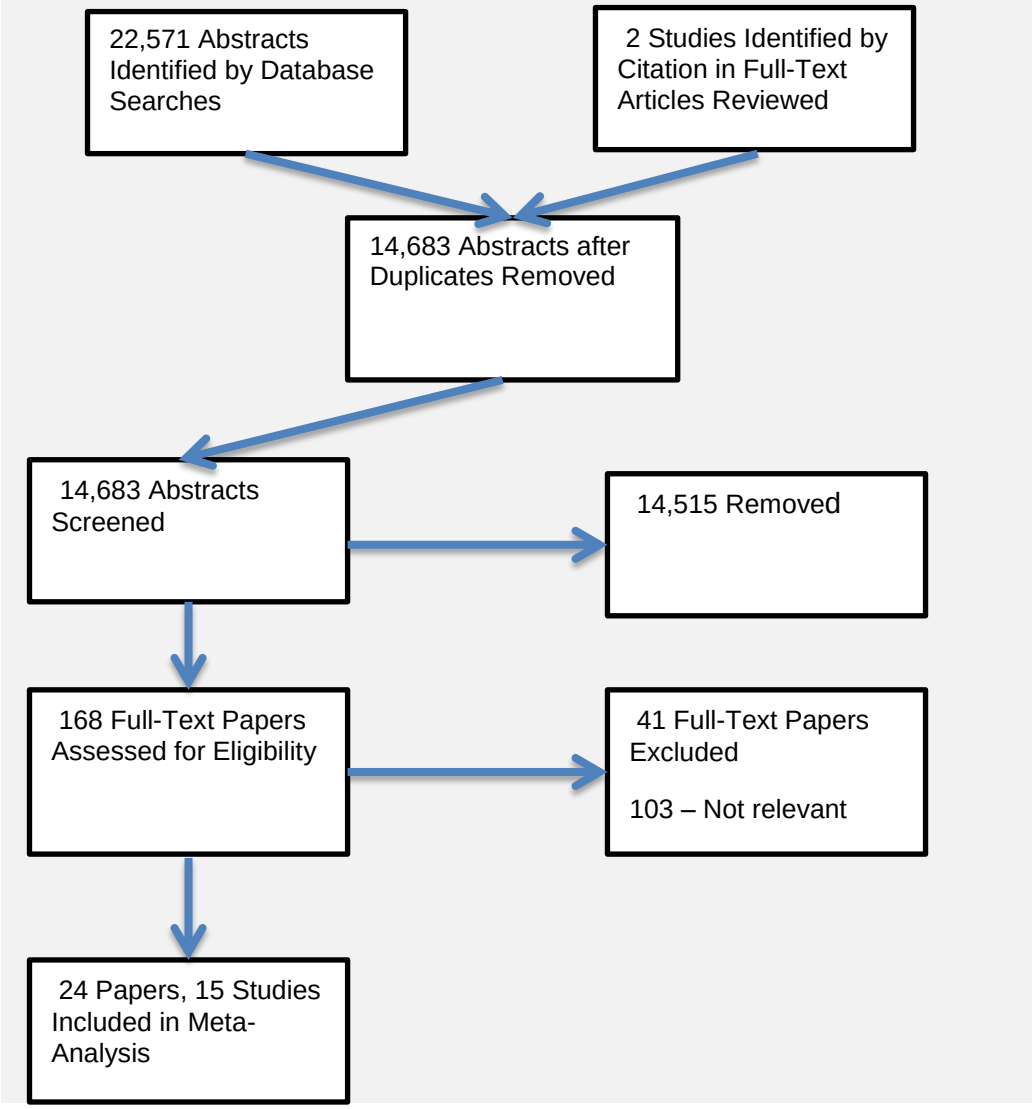


Table 6: Characteristics of Included Studies

Study Reference	Author	Year	Clinical Setting	N	Test(s) At Baseline	Test(s) At follow-up	Mean age	% Female
Bechdolf-Mebourne-2007	Bechdolf et al	2010	Specialist Early Detection Clinic for Young People Melbourne	92	CAARMS SOFAS GTQ	Evaluation by Psychiatrist and ICD-10 applied	18	65.2 (n=60)
Broome-London-	Broome et al	2005	Specialised inner city prodrome service London	58	CAARMS FIGS SCID-I SCID-II HRSD HRSA	Not reported	24.1	34.5 (n=20)
Carr-Newcastle, Aus - 1997	Carr et al Mason et al	2000 2004	First-episode psychosis and At-Risk service, Newcastle Australia	74	SANS, SAPS, BPRS-E, CASH, HRSD, HRSA, QLS, GAF, SOFAS	Clinical Evaluation and DSM-IV criteria applied	17.3	47.3 (n=35)
Cornblatt-NY-1998	Cornblatt et al Lencz et al	2003 2003	Specialist Prodrome Clinic (RAP Clinic).	62 (42 CHR+ 20 CHR-	SOPS	SOPS	16.44 SD. 2.3	40.5 (n=17)

Study Reference	Author	Year	Clinical Setting	N	Test(s) At Baseline	Test(s) At follow-up	Mean age	% Female
			New York USA	)				
Haroun-San Diego-	Haroun et al	2006	Specialist Prodrome Research Clinic (CARE) USA	50	SIPS, GAF, K-SADS, SCID, SANS SAPS BPRS	Repeat measures and DSM-IV criteria applied	18.7	42 (n=21)
Klosterkotter-Cologne- 1987	Klosterkotter et al	2001a	Specialist Prodrome Research Clinic University of Cologne Germany	160 110 with BS 50 without	BSABS and PSE9	DSM-IV at follow-up	29.3	47.5 (n=76)
Lam-HongKong-2002	Lam et al	2006	Specialist Early Assessment Service for Young people (EASY) Hong Kong	62	CAARMS, GAF	CAARMS	16.2	41.9 (n=26)
Miller-Yale-1998	Miller et al	2002 2003	Specialist Early detection clinic PRIME – Yale University USA	34	SIPS/SOPS	SIPS/SOPS	17.9	32.4 (n=11)
Reicher-Rossler-Basel-2000	Reicher-Rossler et al	2007	Specialist Early Detection clinic. University	50 At Risk 32 Not at	BSIP	BPRS	26.8	40 (n=20)

Study Reference	Author	Year	Clinical Setting	N	Test(s) At Baseline	Test(s) At follow-up	Mean age	% Female
			Hospital Basel Switzerland	Risk				
Ruhrmann-Europe-2001	Ruhrmann et al	2010	Six early-detection outpatient centres in Germany, Finland, the Netherlands, and England	245	SIPS, GAF-M, BDI, BSABS-P	SIPS and DSM-IV criteria applied	23	44.1 (n=108)
Schultze-Lutter-Cologne-2000	Schultze-Lutter et al	2007	Specialist Prodrome Research Clinic University of Cologne German	146	SPI-A	PANSS	24.4	30.8 (n=45)
Simon-Bruderholtz-2003	Simon et al	2006, 2010	Specialised outpatient clinic for the assessment of early psychosis	72	SIPS/SOPS	SIPS	20.3	40.3 (n=29)
Yung-Melbourne-1995	Yung et al	1998a, 1998b, 2003, 2004, 2007	Specialist Early Detection Clinic for Young People Melbourne	104	Modified BPRS, SCID DSM-IV-psychotic Disorders section, FIGS,	Repeat Baseline Measures SCID to confirm DSM-IV	19.3	51 (n=53)

Study Reference	Author	Year	Clinical Setting	N	Test(s) At Baseline	Test(s) At follow-up	Mean age	% Female
					SANS, HRSD HRSA, Young Mania Scale, QLS, GAF, SCAN CAARMS	diagnosis		
Yung-Melbourne-2003	Yung et al	2008	Specialist Early Detection Clinic for Young People Melbourne	292	CAARMS, GAF, CGAS, FIGS	CAARMS or review of medical records	18.1	51 (n=149)
Ziermans-Utrecht-	Ziermans et al	2011	Child and adolescent Department University Medical Centre	72	SIPS, SOPS BSABS-P	SIPS DSM-IV	15.3	38.9 (n=28)

6.3.1 Study Descriptions

Australian Studies

Bechdolf-Melbourne 2007 (Bechdolf et al., 2010) and Yung-Melbourne 1995 & 2003 (Yung et al., 2007, 2008) recruited subjects from the Personal Assessment and Crisis Evaluation Clinic (PACE) in Melbourne. The PACE clinic is a clinic designed to assess, manage and follow-up young people aged between 16 and 30, deemed to be at risk of psychosis. The mean age of the Bechdolf-Melbourne sample was 18 years with a standard deviation (SD) of 2.9 and 68% were female. The Yung-Melbourne 1995 sample combines 3 research cohorts from the PACE clinic (April 1995 – October 1996, October 1996 – January 1999, and February 1999 – August 2000). This combined sample had a mean age of 19.3 years (SD. 3.4). The Yung-Melbourne-2008 sample had a mean age of 18.1 years and 51% were female.

Carr-Newcastle (Carr et al., 2000) conducted their study at the Psychological Assessment Service (PAS) in New South Wales, Australia. The PAS programme is a clinical service for the assessment and treatment of young people at high risk of psychosis. The mean age of the sample was 17.58 and 38.3% were female.

European Studies

Broome-London (Broome et al., 2005) was conducted in the Outreach and Support in South London (OASIS) clinic. The OASIS service is a clinical service for young people aged between 14 and 35 thought to be at risk of psychosis. The mean age of the sample was 24 years (SD. 6.1) and 38.3% were female.

Klosterkotter-Cologne-1987 (Klosterkotter et al., 2008) recruited prodromal and non-prodromal participants from 5 German specialist outpatient clinics

between 1987 and 1991. The mean age of the sample was 29.39 (SD. 9.63) and 47.5% were female.

Schultze-Lutter-Cologne-2000 (Schultze-Lutter et al., 2007) recruited subjects from the Cologne Early Recognition and Intervention Centre for Mental Crisis (FETZ), a specialist clinic for the people aged between 16 and 40 years of age. The mean age of the sample was 24.4 (SD. 5.2) and 31% were female.

Simon-Bruderholtz (Simon and Umbricht, 2010) recruited patients aged between 14 and 40 referred to the Bruderholz Early Psychosis Outpatient Service in Switzerland. The mean age of the sample was 20.3 (SD. 4.9) and 40% were female.

Reicher-Rossler-Basel **(**Reicher-Rossler et al., 2007) recruited consecutive referrals to a specialised clinic for the detection of psychosis (FEPSY). The clinic is situated in the Psychiatric Outpatient department of the University Hospital, Basel, Switzerland. The mean age of participants was 26.8 years (SD. 8.9) and 41.4% were female.

Ruhrmann-Europe, the European Prediction of Psychosis Study (EPOS) (Ruhrmann et al., 2010) recruited prodromal people from six early detection clinics across Germany, Finland, the Netherlands, and England. The mean age of the sample was 23 years (SD. 5.2) and 44.1% were female.

Ziermans-Utrecht (Ziermans et al., 2011) recruited adolescents between the age of 12 and 18 from the Child and Adolescent department of the University of Utrecht. Participants were help-seeking individuals referred by their general practitioner (GP). The mean age of the sample was 15.3 years (SD.1.9) and 39% were female.

North American Studies

Cornblatt- New York (Cornblatt et al., 2003, Lencz et al., 2003) recruited at risk of psychosis subjects from the Recognition and Prevention Programme (RAP) in New York. The RAP clinic treats prodromal adolescents between the age of 12 and 22. The mean age of the sample was 16.4 years (SD. 2.3) and 40.5% were female.

Haroun-San Diego (Haroun et al., 2006) recruited subjects deemed at risk of psychosis from the Cognitive Assessment and Risk Evaluation Programme (CARE) at the University of California, San Diego, USA. The CARE programme aims to improve the early detection of psychosis in young people aged between 12 and 30. The mean age of the sample was 18.7 years and 42% were female.

Miller-Yale (Miller et al, 2003) conducted their study at the Prevention through Risk Identification, Management, and Education (PRIME) based at Yale University, USA. Subjects were recruited from consecutive help-seeking referrals. The mean age of the included sample was 17.9 years (SD. 5.8) and 32% were female.

Asian Study

Lam-Hong Kong (Lam, Hung and Chen, 2006) recruited UHR subjects from referrals to the Early Assessment Service for Young People (EASY) in Hong Kong. The mean age at first assessment was 16.2 years (SD. 3.7) and 42% were female.

6.3.2 Cohort Size

The Yung-Melbourne-2003 Cohort was the largest with 292 participants. The other studies had much smaller cohorts. In descending order of size the samples were as follows: Ruhrman-Europe (245), Schultze-Lutter-Cologne- (146), Yung-Melbourne-1995 (142), Klosterkotter-Cologne (110 prodromal, 50 not prodromal), Bechdolf-Melbourne (92), Ziermans-Utrecht, (72, 57 at

follow-up), Simon-Bruderholz (72, 42 at follow-up),Lam-Hong-Kong (62), Carr-Newcastle-Australia (60, 23 follow-up), Broome-London (58), Reicher-Rossler-Basel (58, 50 at follow-up), Haroun-San-Diego (50, 40 follow-up), Cornblatt-New York (42, 34 at follow-up) and Miller-Yale (34, 23 at 2-year follow-up).

6.3.3 Instruments

Lam-Hong Kong, Broome-London, Bechdolf-Melbourne and Yung-Melbourne-2003 all used the Comprehensive Assessment of At-Risk Mental states (CAARMS) (Yung et al, 1996). In the first cohort of her study Yung-Melbourne-1998 used the instruments from which the CAARMS was derived along with the CAARMS at-risk criteria (see table 3,). CAARMS was used in the later Melbourne cohorts. Carr-Newcastle-Australia used the original instruments from which the CAARMS was derived, and applied the CAARMS UHR criteria to these.

Cornblatt-NY used the Scale of Prodromal Symptoms (SOPS) (McGlashan, 1999). In addition, mid-way through recruitment the companion interview for the SOPS (the Structured Interview for Prodromal Symptoms; SIPS) was launched and introduced into the study. Haroun-San Diego, Simon-Bruderholz and Miller-Yale all used both the SIPS and the SOPS.

Klosterkötter-Cologne used the Bonn Scale for the Assessment of Basic Symptoms (BSABS) (Klosterkötter, 2001). Schultze-Lutter-Cologne used the Schizophrenia Proneness Instrument – Adult Version (SPI-A). Ruhrmann-Europe and Ziermans-Utrecht used SIPS, SOPS, and the BSABS. Reicher-Rössler-Basel conducted a step-wise screening procedure consisting of the Basel Screening Instrument for Psychosis (BSIP) (Reicher-Rossler, 2007) in combination with the Brief Psychiatric Rating Scale (BPRS) (Overall et al, 1962). The BSIP is a 46-item checklist derived from the DSM-III-R (American Psychiatric Association, 1987), developed specifically for the detection of patients at-risk of developing psychosis. The checklist includes criteria

derived from the literature pertaining to social decline, drug abuse, previous psychiatric disorders, and genetic risk. The authors assert that it is not designed for use in the general population, rather in help-seeking populations by experienced psychiatrists. It is used in combination with the BPRS to enable the classification of patients at risk of psychosis in accordance with the UHR at risk criteria (Yung et al., 1998b).

6.4 Quality Assessments

With the exception of three studies for which it was not clear (Haroun-San-Diego, Schultze-Lutter-Cologne and Ziermans-Utrecht), all study samples were consecutive recruits. Rutjes et al. (2006) found that studies using non-consecutive samples were associated with an overestimation of the diagnostic odds ratio by 50% compared with those that used a consecutive sample.

Index tests were applied appropriately and the thresholds were pre-specified. The application of the reference tests at follow-up, however, presented numerous opportunities for bias across a number of studies. Four studies (Broome-London, Carr-Newcastle-Australia, Simon-Bruderholz, and Haroun-San-Diego) did not clearly articulate how transition to psychosis was determined. Nine studies (Bechdolf-Mebourne, Cornblatt-NY, Lam-Hong-Kong, Miller-Yale, Reicher-Rössler, Simon-Bruderholz and Haroun-San-Diego, Yung-Melbourne-1995 & 2003) used psychosis anchor points on either SOPS or CAARMS to determine transition. The use of the same instrument at baseline and follow-up can introduce incorporation bias. Mower (1999) suggests that using the same tests at baseline and follow-up introduces a form of circular reasoning which inflates reasoning and introduces considerable bias.

None of the studies completed the follow-up assessment blind to the results of the baseline test. Haynes et al. (2006) assert that blinding the individual conducting or interpreting the test is critical for the validity of the study of

diagnostic tests. Table 6 summarises the QUADAS 2 assessment of methodological quality.

6.5 Data Analysis Results

Table 7 below provides a summary of the data extracted from the studies prior to meta-analysis. In studies that used both Basic Symptoms and UHR approaches, data was extracted separately wherever possible. Additional data was also provided by one of the study authors, Tim Ziermans (personal communication, 11th December 2011).

Of the 15 included studies only two UHR studies (Yung-Melbourne-2003, Miller-Yale) and one basic symptom study (Klosterkotter-Cologne) reported data on the follow up of both those at risk and those not at risk. Each study used a different instrument. Hence, it was not possible to model the data with a bivariate random-effects model. The remaining 12 studies followed-up only patients deemed to be at risk, thus restricting meta-analyses to estimating a positive predictive value, that is, the proportion at risk who transition to psychosis.

Six studies (Ziermans-Utrecht, Schultze-Lutter-Cologne, Klosterkotter-Cologne, Lam-Hong-Kong, Cornblatt-NY & Ruhrmann-Europe) used the DSM-IV (American Psychiatric Association, 1994) as a separate reference standard to confirm the psychosis status at follow-up. The use of a reference standard was added as a covariate to the logistic mixed effects model to analyse its effects on the overall performance. It was a not a significant covariate (*LRT = 0.02; df = 1; p = 0.87*)

Overall, seven studies (Haroun-San-Diego, Miller-Yale, Simon-Bruderholz, Ziermans-Utrecht, Broome-London, Yung-Melbourne-1995 & 2003) provided data on patients at either 12 months or 24 months follow up. The respective summary PPVs were 0.26 (95% CI: CI: 0.14, 0.43) and 0.21 (95% CI: 0.09, 0.43). Heterogeneity was present in both of these sub-groups (*Q =15.9; df = 3; p = 0.001 and* I^2 *= 81%*) and (*Q = 25.4; df = 3; p<0.001 and* I^2 *= 88%*), respectively.

Table 7: QUADAS 2 Results

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Bechdolf-Mebourne	☺	☺	☺	?	☺	☺	☺
Broome-London	☺	☺	**?**	**?**	☺	☺	**?**
Carr-Newcastle, Aus	☺	☺	**?**	☺	☺	**?**	☺
Cornblatt-NY	☺	☺	☺	☺	☺	☺	☺
Haroun-San Diego	**?**	☺	**?**	**?**	☺	☺	☺
Klosterkotter-Cologne	☺	☺	☺	☺	☺	☺	☺
Lam-HongKong	☺	☺	☺	☺	☺	☺	☺
Miller-Yale	☺	☺	☺	☺	☺	☺	☺
Reicher-Rössler-Basel	☺	☺	☺	☺	☺	☺	☺
Ruhrmann-Europe	☺	☺	☺	☺	☺	☺	☺
Schultze-Lutter-Cologne	?	☺	☺	☺	☺	☺	☺
Simon-Bruderholtz	☺	☺	**?**	**?**	☺	☺	☺
Yung-Melbourne-1995	☺	☺	☺	☺	☺	☺	☺
Yung-Melbourne-2003	☺	☺	☺	☹	☺	☺	☺
Ziermans-Utrecht	**?**	☺	☺	☺	☺	☺	☺

Table 8: Extracted Data from Included Studies

	Date study started	Date clinic opened	Instruments	Baseline N	Follow-up N	N = Test Positive	N = Psychosis at F/U	N = No Psychosis at F/U	N = Test Negative	N = Psychosis at Follow-up	N = No Psychosis at Follow-up	sensitivity	specificity	NPV	PPV	Likelihood Ratio	Length of Follow-up (Months)
Cornblatt-NY 1998	1998	1998	SOPS	62 42 CHR+ 20 CHR-	34 CHR+ 14 CHR-	34 14	9 0	25 14	n/a	n/a	n/a	n/a	n/a	n/a	0.26	n/a	Mean 24.7 (SD 5.9)
Haroun- San Diego-	2000	2000	SIPS, GAF, K-SADS, SCID, SANS/SAPS, BPRS	50	40	40	6	34	n/a	n/a	n/a	n/a	n/a	n/a	0.15	n/a	12
Miller-Yale 1998	1998-2000	?	SIPS/SOPS	34	34: 6/12 34: 12/12 27: 18/12 23: 24/12	14 14 13 12	6 7 8 8	8 7 5 4	20 20 14 11	0 0 0 0	20 20 14 11	1.0 1.0 1.0 1.0	0.71 0.74 0.74 0.73	1.0 1.0 1.0 1.0	0.43 0.50 0.62 0.67	3.45 3.85 3.85 3.70	6 12 18 24
Reicher-Rossler-Basel 2000	2000	1999	BSIP BPRS	58 at risk 32 Not at risk	50 at risk 32 not at risk	50	16	34	32	n/r*	n/r*	n/a	n/a	n/a	0.32	n/a	12-60
Simon-Bruderholtz	2003	2002	SIPS/SOPS	72	42	42	7	35	n/a	n/a	n/a	n/a	n/a	n/a	0.17	n/a	12-months
Kloster-kotter Cologne-1987	1987	?	BSABS and PSE9	385	110 with BS 50 without BS	110	77	33	50	2	48	0.98	0.59	0.96	0.70	2.39	Mean 9.6 years
Schultze-	2000	1997	SPI-A	146	146	146	51	95	n/a	n/a	n/a	n/a	n/a	n/a	0.35		Mean

	Date study started	Date clinic opened	Instruments	Baseline N	Follow-up N	N = Test Positive	N = Psychosis at F/U	N = No Psychosis at F/U	N = Test Negative	N = Psychosis at Follow-up	N = No Psychosis at Follow-up	sensitivity	specificity	NPV	PPV	Likelihood Ratio	Length of Follow-up (Months)
Lutter-Cologne 2000				Total													20.6 (SD 16.1)
				124 COGDIS	124	124	43	81	n/a	n/a	n/a	n/a	n/a	n/a	0.35		
				22 COPER	22	22	8	14	n/a	n/a	n/a	n/a	n/a	n/a	0.36		
Ziermans-Utrecht-	?	?	SIPS, SOPS BSABS-P	72	65 UHR inc. 39 BS	65 39	9 7	56 32	n/a	n/a	n/a	n/a	n/a	n/a	0.14 0.18	n/a	24
Ruhrmann-Europe 2002	?	2002	SIPS, GAF-M, BDI, BSABS-P	245	183 BS+ UHR-18 UHR+ BS-59 UHR+BS+ 106	245	37	208	n/a	n/a	n/a	n/a	n/a	n/a	0.15		18
Broome-London	2002	2002	CAARMS FIGS SCID-I SCID-II HRSD HRSA	58 UHR	58	58	6	52	n/a	n/a	n/a	n/a	n/a	n/a	0.10	n/a	12
Lam-Hong Kong 2002	2002	2001	CAARMS, GAF	62	62	62	18	44	n/a	n/a	n/a	n/a	n/a	n/a	0.29	n/a	6
Carr-	1997	1997	SANS, SAPS,	116	23 at-risk	23	2	21	n/a	n/a	n/a	n/a	n/a	n/a	0.09	n/a	Mean

	Date study started	Date clinic opened	Instruments	Baseline N	Follow-up N	N = Test Positive	N = Psychosis at F/U	N = No Psychosis at F/U	N = Test Negative	N = Psychosis at Follow-up	N = No Psychosis at Follow-up	sensitivity	specificity	NPV	PPV	Likelihood Ratio	Length of Follow-up (Months)
Newcastle, Aus 1997			BPRS-E, CASH, HRSD, HRSA, QLS, GAF, SOFAS	60 at-risk 56 FEP	27 FEP												14.6
Yung-Melbourne-1995	1995	1994	CAARMS, GAF, CGAS, FIGS, BPRS, SANS, HRSD, HRSA, Young mania scale, QLS, SCAN	142	142	142	51	91	n/a	n/a	n/a	n/a	n/a	n/a	0.36	n/a	12
Yung-Melbourne, 2003	2003	1994	CAARMS, GAF, CGAS, FIGS, BPRS, SANS, HRSD, HRSA, YMRS, QLS, SCAN	292	292	119	19	100	173	2	171	0.91	0.63	0.99	0.16	2.46	24
Bechdolf-Mebourne 2007	2007	1994	CAARMS	92 UHR	92	92	20	72	n/a	n/a	n/a	n/a	n/a	n/a	0.22	n/a	Mean 615 days (SD 282.7)

*not reported

6.5.1 Performance of the UHR Criteria in Predicting Psychosis

Ten studies used a prognostic instrument based on the UHR criteria (Yung-Melboune-1995 & 2003, Miller-Yale, Cornblatt-NY, Broome-London, Lam-Hong-Kong, Bechdolf-Melbourne, Haroun-San-Diego, Carr-Newcastle-Australia, Simon-Bruderholz,). Two further studies used both UHR and basic symptom approaches (Ruhrmann-Europe and Ziermans-Utrecht). UHR data was extracted and included in the meta-analysis. As expected there was widespread heterogeneity across these studies (*Q=86.9; df=11; p<0.001* and I^2 *= 87%*). The overall PPV from the random effects model was 0.25 (95% CI: 0.18, 0.33) (figure 2).

Yung-Melbourne-1995 reported declining transition rates between years 1995 and 2000. Kaplan-Meier estimates for 12-month transition rates over each successive year during this period were 0.50, 0.33, 0.32, 0.29, 0.21, and 0.12 respectively. Early studies by the Melbourne group did not involve follow-up of UHR negative patients, therefore the sensitivity and specificity is not available for this period. The cohort assembled between 1995 and 1999 consisted of 104 UHR patients, of which 41 developed a psychosis over the course of the follow-up period, giving a CAARMS PPV of 0.39 (95% CI: 0.30, 0.49) (Yung et al., 2004a). A later study in 2003, in the same Melbourne clinic (Yung-Melbourne-2003) did involve a follow-up examination of both UHR positive and UHR negative cohorts. This study found that the transition rate had further decreased to 16%, with the sensitivity of the CAARMS being 0.91, (95% CI 0.68, 0.98) and the specificity 0.63 (95% CI: 0.57, 0.69); the LR was 2.46.

Also in the Melbourne clinic, Bechdolf-Melbourne found that 21.7% (PPV, 0.22) of UHR patients developed a psychosis over a mean follow-up period of 615 days. Other studies using CAARMS UHR criteria (Broome-London & Lam-Hong-Kong) reported transition rates of 10% (PPV 0.10, 95% CI: 0.39, 0.21) and 29% (PPV, 0.29, 95% CI: 0.18, 0.42) respectively. Again, neither study completed follow-up observations of UHR negative patients so the sensitivity and specificity of CAARMS cannot be calculated.

The initial cohort in the Yung-Melbourne-1995 sample for which the Kaplan-Meier transition rate was 0.50 was assessed using the instruments from which the CAARMS was derived. Carr-Newcastle-Australia used the same instruments and found that only 2 (8.7%) of the 23 at-risk patients they followed-up converted to psychosis.

Studies using the SIPS/SOPS approach (Miller-Yale, Simon-Bruderholz, Haroun-San-Diego, Cornblatt-NY, Ziermans-Utrecht & Ruhrmann-Europe) reported transition rates of 67%, 17%, 15%, 14%, 26% and 21%, respectively. With the exception of Miller-Yale, performance across studies was similar to that of CAARMS. Miller-Yale conducted the only study of SIPS that conducted follow-up evaluations of both the UHR positive and UHR negative groups. After 24.month follow-up they report the sensitivity of the SIPS/SOPS was 1 (95% CI: 0.63, 1), specificity 0.73 (95% CI: 0.45, 0.92), PPV 0.67 (95% CI: 0.35, 0.90), NPV 1 (95% CI: 0.71, 1) and LR 3.70.

6.5.2 Performance of the Basic Symptom Criteria in Predicting Psychosis

Four studies evaluated a basic symptom approach to classifying at risk patients (Klosterkotter-Cologne, Schultze-Lutter-Cologne, Ruhrmann-Europe, and Ziermans-Utrecht). Although the overall PPV (0.34: 95% CI 0.15, 0.61) was greater than the UHR method, the results are not significant ($p > 0.05$). There was also significant heterogeneity ($Q=95.6; df=3; p<0.001$ *and* $I^2 =97\%$). Only one study Kloserkotter-Cologne reported follow-up data for both at-risk and not at-risk patients. With a transition rate of 49% the sensitivity of the BSABS was found to be 0.97 (95% CI: 0.90, 1), specificity 0.59 (95% CI: 0.48, 0.70), PPV 0.70 (95% CI: 0.60, 0.78), NPV 0.96 (95% CI: 0.85, 0.99).

Schultze-Lutter-Cologne achieved an overall transition rate of 36.4% for the SPI-A. As discussed in chapter 2 the SPI-A uses two overlapping criterions

for identifying subjects at risk of psychosis; COPER and COGDIS. The PPV for the COPER criterion was 0.36 (95% CI: 0.17, 0.59) and was 0.35 (95% CI: 0.26, 0.44) for COGDIS. Tim Ziermans (personal communication, 11th December 2011) reported that in the Ziermans-Utrecht study 39 people met the Basic Symptom criteria and of these 7 developed a psychosis by the end of the 2-year follow-up period. The Basic Symptom PPV was therefore 0.18 (95% CI: 0.08, 0.34).

6.5.3 Comparison of UHR and Basic Symptom Performance.

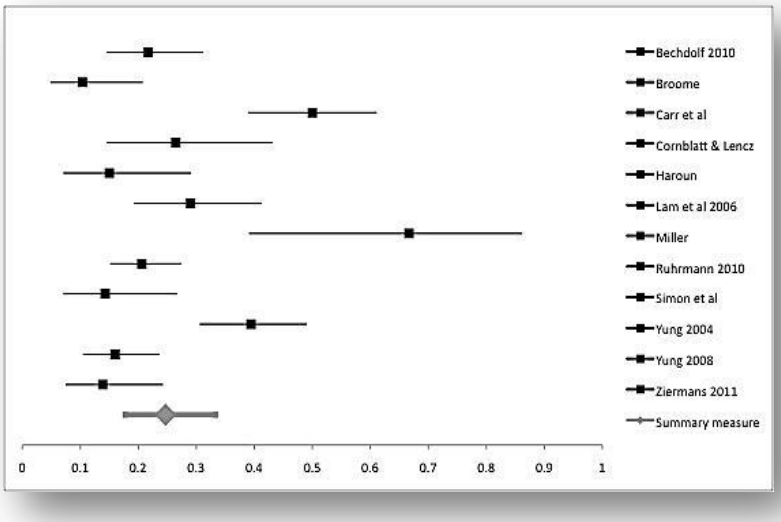
Two UHR and one Basic Symptom study completed follow-up analyses of both at-risk and not-at-risk patients. Yung-Melburne-2003 reports CAARMS sensitivity and specificity as 0.91 and 0.63 (NPV 0.99, PPV 0.16, and LR 2.46). Miller-Yale reports SIPS/SOPS sensitivity and specificity as 1.00 and 0.73 (NPV 1.00, PPV 0.67) and Klosterkotter-Cologne reports sensitivity and sensitivity as 0.98 and 0.59 (NPV 0.96, PPV 0.70, and LR 3.70).

Overall the PPV (0.34: 95% CI 0.15, 0.61) of the Basic Symptoms approach was greater than the UHR method (PPV 0.25 (95% CI: 0.18-0.33), however, the results are not significant ($p > 0.05$). Ruhrmann-Europe found that patients positive for both COGDIS and UHR criteria showed higher sensitivity (0.68) and specificity (0.88) in comparison to those who were COGDIS positive and UHR negative (sensitivity, 0.03, specificity 0.88) and those who were COGDIS negative and UHR positive (sensitivity, 0.30, specificity, 0.67). Although not high the positive likelihood ratio was higher for patients who met both UHR and Basic Symptom criteria (1.2) compared with those who just met COGDIS or UHR criteria alone (0.2 and 0.9 respectively). Ruhrmann et al. (2010) conclude that these findings signal a ‘methodological advancement’ in the early detection of psychoses.

6.5.4 A Step-Wise Screening Approach

Reicher-Rössler-Basel achieved transition rates of 32% over the course of the 5-year follow-up, with 14% having made the transition within the first 6 months of follow-up.. Kaplan-Meier survival analysis estimated the 6-month transition rate to be 0.13 (95% CI 0.05-0.21), 12-month as 0.23 (95% CI: 0.13-0.33) and 24-month transition to be 0.25 (95% CI: 0.15, 0.35).

Figure 3: Forest Plot of the PPV of UHR instruments



The Forest plot shows the range of PPVs for prognostic tools used to define UHR patients. Inspection reveals widespread heterogeneity.

6.6 Discussion

In a total sample size of 1573 participants, we found strong evidence for the consistent validity of high-risk criteria across the various psychopathology-based instruments. Two main approaches were identified the UHR and the Basic symptoms. One further approach was identified: a step-wise approach

known as the Basel Screening Instrument, however only one study was available in relation to this approach so meta-analysis was not possible. Meta-analysis of studies using either UHR or Basic Symptom approaches yielded similar results for both approaches; differences in the PPV between the two were not statistically significant (Basic Symptoms: 0.34: 95% CI: 0.15, 0.61, UHR: 0.25 95% CI: 0.18, 0.33). The study of the stepwise screening achieved results similar to the Basic symptom approach with a PPV of 0.32, (95% CI: 0.20, 0.47). It will be interesting to see whether this finding will be replicated across subsequent studies.

It is not obvious at this stage whether Basic Symptoms and UHR approaches are measuring different phenomenon as Schultze-Lutter et al. (2009) suggest. However, it must be noted that there is some overlap between the two approaches as the CAARMS does contain some Basic Symptoms.

There was considerable heterogeneity between studies. However, the forest plot showed that this could not be explained by the type of instrument used. We therefore explored other reasons for this degree of heterogeneity. Of particular interest was the high transition rates achieved in initial studies conducted by the authors of the instruments (Klosterkotter-Cologne, Miller-Yale, Yung-Melbourne-1995) when compared to subsequent studies of the same instruments. We considered whether transition rates are higher when clinics are newly established, as there may be a cohort of 'about to transit' patients waiting to be detected. However, this was not found to be an obvious trend across studies when we explored the relationship between the periods of time that the respective clinics had been open prior to commencement of the study (table 8). Yung et al. (2007) suggest that declining transition may in part be due to decreasing duration of symptoms prior to receiving help. They further suggest that the routine provision of treatments such as supportive therapy, anxiolytics, and antidepressants may avert transition in their clinics.

We also explored whether the instruments from which the CAARMS was derived yielded better transition rates than the CAARMS itself. The first cohort of Yung-Melbourne-1995 was assessed using among others the

BPRS, which was also used by Reicher-Rössler-Basel in their stepwise approach. Both of these cohorts yielded superior transitions to studies using CAARMS. However, Carr-Newcastle-Australia also achieved a low transition rate of 9%.using the instruments from which CAARMS (including BPRS) was derived. This raises some doubts about this hypothesis. However, it certainly merits further investigation.

The main limitation of the review was the inability to perform meta-analysis of sensitivity and specificity due to the small number of studies providing follow-up data of both at-risk and not-at-risk patients. Only published studies were included in the analysis so the potential for publication bias could not be excluded. The strength of the review was the quality of the meta-analysis: the authors did not try to calculate sensitivity and specificity in the absence of full-follow up data (i.e. both test positive and test negative). A similar review by Chuma and Mahadun (2011) calculated sensitivities and specificities in the absence of this data. We also excluded treatment trials in order to exclude any biases introduced by both the treatment itself and the selection biases often introduced in randomised controlled trials. A large multi-centre study in North America (NAPLS; Woods et al, 2009) was also excluded to prevent double counting with studies likely to have been included in this study. This may however, have resulted in some important data being missed.

The findings of the review indicate that Basic Symptoms and UHR approaches can predict onset of psychosis. However, they appear to generate high levels of false-positive results ranging from 33% - 91%. This makes treatment options for prevention of psychosis difficult to determine. The majority of the included studies were conducted in highly specialised clinics and several by the authors of the instruments. It would be beneficial to conduct a service evaluation of both approaches in a representative mainstream Early Intervention service. Such a study would serve as a reference point for further studies and enable the two approaches to be evaluated both head-to-head and combined.

CHAPTER 7: Service Evaluation: Baseline Findings

Chapter 7: Service Evaluation: Baseline Findings

7.1 Introduction

Over the last 20 years two main approaches to the prediction of psychosis onset have emerged – the Ultra High Risk (Yung et al., 1998b, Miller et al., 2003a) (Chapter 2) and the Basic Symptom Approach (Klosterkotter et al., 2001a, Schultze-Lutter et al., 2007a) (Chapter 3). The systematic review with meta-analysis of these approaches in chapter 6 yielded promising results; the Basic Symptom approach accurately predicted transition to psychosis in 34% of cases compared with 25% with the UHR approach. However, the majority of the studies were conducted in highly specialised clinics often by the authors of the instruments and there was significant heterogeneity between studies. Little is known about the performance of the instruments in representative mental health services. This service evaluation is to our knowledge one of the first evaluations of how well these instruments perform in a representative UK mental health setting.

This chapter of the thesis presents the baseline findings the service evaluation. The aims, objectives, and full methodology of the study are outlined in chapters 4 and 5. Statistical analysis of the data was performed using SPSS for Windows (IBM SPSS Statistics, Released 2011, Version 20.0, Armonk, NY: IBM Corp.), statistical measures, means and standard deviations are quoted for descriptive purposes.

7.2 Methods

The sample consists of consecutive referrals to the LEAD clinic; a clinic for the assessment of at-risk mental states, within the Lancashire EIS. All referrals to the clinic have undergone prior assessment by EIS case managers who use the PANSS assessment (Kay et al., 1987) to determine psychosis status. All patients found to be psychotic according to the PANSS assessment are referred to the LEAD clinic.

The following instruments are administered at the LEAD clinic: CAARMS, SPI-A, SPQ-A and SOFAS. Based on the assessments patients are grouped as: At-Risk Mental State (ARMS), not ARMS or psychotic. The EIS offers case management to ARMS and psychotic patients for periods of 1 and 3 years respectively. All not ARMS patients are referred on to appropriate services.

Patients who were aged between 14 and 35, not currently psychotic and did not have a history of psychosis were deemed eligible for the service evaluation. Patients found to be psychotic or receiving a therapeutic dose were excluded from the follow-up evaluation.

7.3 Results

One hundred and seventy-four help-seeking young people attended the LEAD clinic between January 2008 and December 2011. Of these 103 were found to meet the inclusion criteria. Sixty-five people meeting the inclusion criteria were found to have an at-risk mental state (ARMS) and 38 did not. Fifty-seven met CAARMS criteria for psychosis so were excluded from the follow-up evaluation, however this group is relevant to the overall service evaluation so is examined in this chapter. A further 14 had been prescribed antipsychotic medication at a dose deemed therapeutic for the treatment of psychosis and were therefore excluded (see section 7.23).

All referrals completed a CAARMS and SOFAS assessment, 173 completed a SPI-A assessment and 155 completed the SPQ-A. As the assessments are a routine part of the service, there was no obligation for patients to complete all assessments. Likewise, the service evaluation method does not require a detailed investigation of why the patient chose not to complete some assessments. However, the most common reason for non-completion of the SPQ-A was literacy problems. The SPQ-A requires a good level of literacy to complete it. In the case of the one person who did not complete SPI-A, I was the assessor and chose not to complete the SPI-A for clinical

reasons. The patient met CAARMS criteria for psychosis and presented as agitated and distressed. They would not have tolerated an assessment lasting 2½ hours.

7.3.1 Sample Characteristics

Sixty (58.25%) of the included cohort were male and 43 (41.75%) were female. The psychosis group comprised of slightly more females than males with 27 (47.37%) male and 30 (52.63%) female patients. The ARMS group however comprised of more male patients, with 37 (56.92%) male and 28 (43.08%) female patients. The not ARMS group consisted of 23 (60.53%) males and 15 (39.47%) females.

The mean age for the included cohort was 21.30 (SD 5.08, 95% CI: 20.31, 22.29). The mean age of the ARMS group was 21.09 (SD 4.92, 95% CI: 19.87, 22.31) and the not ARMS group was 21.66 (SD 5.39, 95% CI: 18.88, 23.43). The mean age of the psychosis group was slightly lower 20.91 (SD 5.08, 95% CI: 19.56, 22.26). The age range for the ARMS group, $D(65) = 0.17$, $p < 0.001$, the not ARMS group $D(38) = 0.15$, $p < 0.05$ and the psychosis group $D(57) = 0.19$, $p < 0.001$ was significantly non-normal. The relationship between age and ARMS status was not found to be significant X^2 (21, N = 103) = 19.25, $p = 0.569$.

The ethnic origin of the patients assessed was broadly in line with the demographic profile of Lancashire with 9.8% being from Black and Minority Ethnic backgrounds (compared with 9% for the general population). Of those meeting ARMS criteria 7.69% (n=5) were from minority ethnic backgrounds. This was slightly higher in the psychosis group where 10.53% (7) were from minority ethnic backgrounds. The relationship between ethnicity and ARMS status was not found to be significant $X^2(2, N=103) = 1.61$, $p = 0.45$. Table 8 below outlines the demographic characteristics of the cohort. Figure 4 shows the gender profile of the at-risk, not at risk and psychosis groups.

We did not employ any culturally specific approaches to assessment within the clinic, other than to provide an interpreter for a Polish man who did not speak English. All other attendees at the clinic had an excellent command of English.

Figure 4: Gender Profile of the Follow-Up Cohort and the Psychosis Group

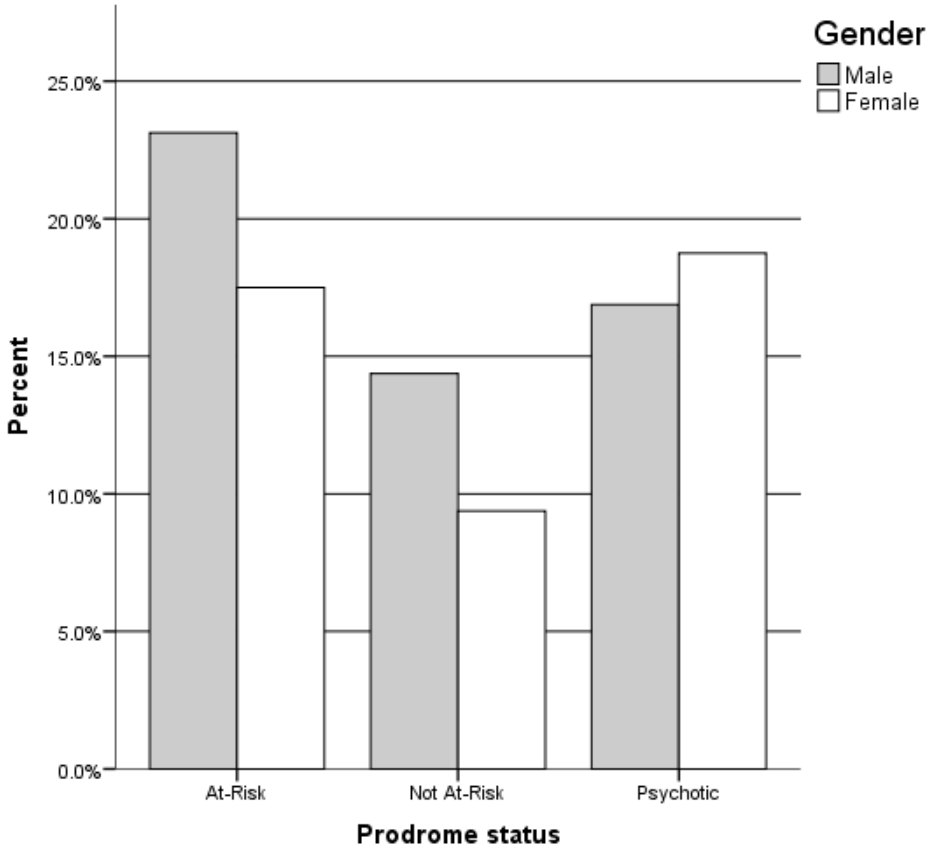


Table 9: Demographic Profile of Referrals

		All Referrals	Included At-Risk	Included Not At-Risk	Psychosis
N		174	65	38	57
Age in years (SD)		21.30 (5.06)	21.09 (4.92)	21.66 (5.39)	20.91 (5.08)
% Males (n)		54.02	56.92	60.53	49.10
Ethnicity: % of cases	**White British**	90.2	92.31	0.87	89.5
	White Irish	0.6	0	0	1.8
	Mixed – White and Black African	1.1	0	5.26	0
	Mixed –White and Asian	1.1	0	0	3.5
	Mixed – any other	1.1	3.08	0	0
	Asian or Asian British Pakistani	0.6	0	0	1.8
	Asian or Asian British Bangladeshi	1.1	1.54	5.26	0
	Asian or Asian British any other background	1.7	0	0	1.8
	Black or Black British Caribbean	0.6	1.54	0	0
	Black or Black British African	1.1	1.54	2.63	0
	Any other Ethnic Group	0.6	0	0	1.8

7.3.2 Substance Misuse Profile

Cannabis was the most frequently used drug, with 40.78% (n = 42) of the included cohort admitting lifetime use. Table 9 shows the substance use profile of the cohort. More patients in the ARMS group admitted lifetime cannabis use when compared with those in the not ARMS group (49.23% versus 26.32). Chi-square analysis showed that the relationship between lifetime cannabis use and ARMS status is significant X^2 (1, N=103) = 5.21, p = 0.02.

Females reported slightly higher levels of lifetime cannabis use than males (39.29%, for females compared with 30% for males). However, in contrast the not ARMS group males reported higher cannabis use than females (30.43% for males compared with 20% for females). Poly drug use (2 or more substances) in the ARMS group was reported in 27.02% of males and 14.29% of females. Figure 5 shows the substance use profile of the included sample by gender. The relationship between gender and substance use was not found to be significant X^2 (6, N=103) = 6.15, p = 0.41.

Patients meeting criteria for schizotypy as assessed by the SPQ-A, admitted increased levels of cannabis use than those who did not. Lifetime use of cannabis was reported in 44% of high schizotypes and in 34.88% of low schizotypes. However, the relationship between cannabis use at the time of assessment and schizotypy was not found to be significant X^2 (1, N=93) = 3.41, p = 0.065.

Lifetime Class A (i.e. cocaine, heroin, ecstasy and LSD) drug use was reported by 27.69% of the ARMS group compared with 21.05% of the not ARMS group. At the time of assessment, 7.69% of the ARMS group reported current class A use. Only one person from the ARMS group reported current amphetamine use, however 8 (12.30%) reported lifetime use in this group.

Of the 57 people found to be psychotic at baseline 21.05% (n=12) reported using cannabis at the time of the assessment and 40.35% (n=23) reported

lifetime use. The substance use profile of psychotic patients is shown in figure 6.

According to Home Office (2012) statistics, 15.7% of young people in Britain aged between 16 and 24 admit a lifetime use of cannabis. The lifetime cannabis use of the LEAD clinic cohort was substantially higher. Seventy five percent of referrals (n=131) were aged 16-24 and 42% (n=55) of them admitted lifetime cannabis use. The Class A substance use profile of this age group is similar to the national average at 16% (National average 15.1%), however lifetime ecstasy use was higher compared to the national average (8.4% compared with 3.3%).

Table 10: Substance use profile of the cohort

		All Referrals (n=174) % (n)	Included At-Risk (n=65) % (n)	Included Not At-Risk (n-38) % (n)	Psychosis (n=57) % (n)
Cannabis	Current	22.41 (39)	29.23 (19)	15.79 (6)	21.05 (12)
	Past	18.39 (32)	20 (13)	10.53 (4)	19.30 (11)
Cocaine	Current	4.02 (7)	4.61 (3)	0	5.26 (3)
	Past	9.20 (16)	6.15 (4)	7.89 (3)	12.28 (7)
Heroin	Current	0.57 (1)	0	0	0
	Past	4.60 (8)	6.15 (4)	0	5.26 (3)
Ecstasy	Current	2.30 (4)	1.54 (1)	0	5.26 (3)
	Past	7.47 (13)	7.69 (5)	10.53 (4)	12.28(7)
Amphetamines	Current	0.57 (1)	1.54 (1)	0	0
	Past	8.62 (15)	12.31 (8)	7.89 (3)	5.26 (3)
LSD	Current	0.57 (1)	1.54 (1)	0	0
	Past	1.72 (3)	0	2.63 (1)	0
Mephedrone	Current	1.72 (3)	1.54 (1)	2.63 (1)	1.75 (1)
	Past	0	0	0	0
Ketamine	Current	1.15 (2)	3.08 (2)	0	0
	Past	1.15 (2)	3.08 (2)	0	0

Figure 5: Substance Use History of the At-Risk Cohort by Gender

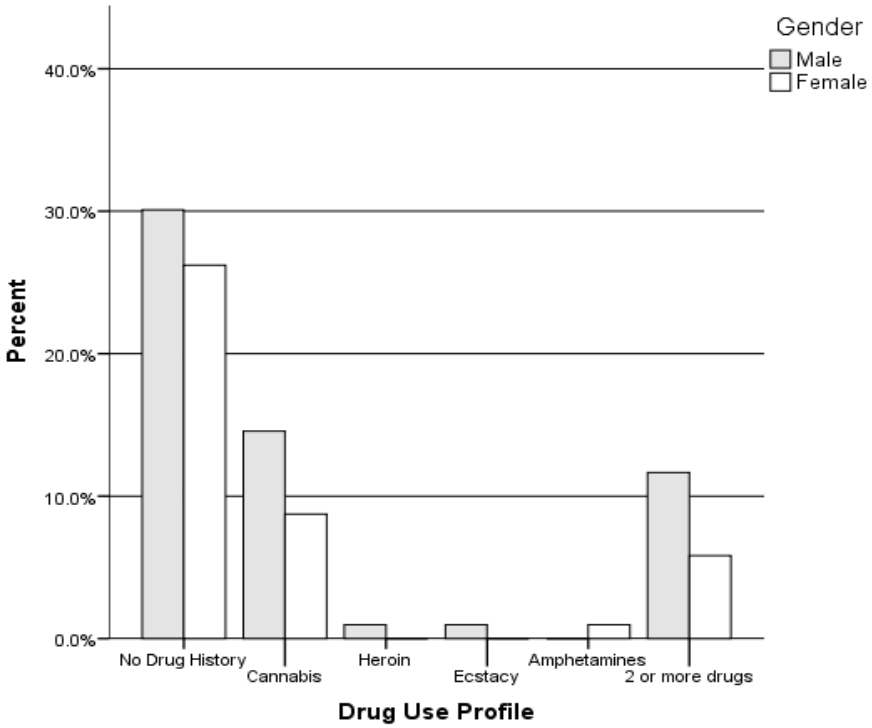
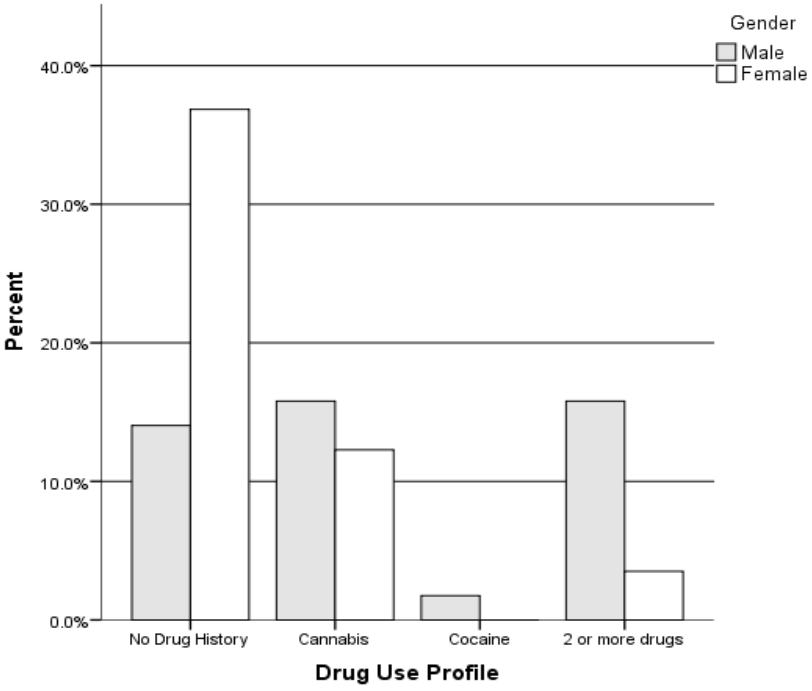


Figure 6: Substance Use History of the Psychotic Cohort by Gender



7.3.3 Medication Use Profile of the Cohort at Baseline

Fifteen people (19.5%) deemed to be at risk of developing psychosis by either SPI-A or CAARMS, were prescribed an atypical antipsychotic at baseline. Three people who did not meet at-risk criteria were also prescribed atypical antipsychotics. Twelve people from the at-risk group and two from the not at-risk group were subsequently excluded from the service evaluation as they were prescribed antipsychotics at a dose within the therapeutic range for the treatment of psychosis.

Fifteen people (19.5%) meeting the at-risk criteria were prescribed Selective Serotonin Re-uptake Inhibitor (SSRIs) antidepressants and 3 were prescribed Noradrenergic and Specific Serotonergic antidepressants (NaSSAs) prior to baseline assessment. Nine (22.5%) people not at-risk of psychosis were prescribed SSRIs and one person (2.5%) was prescribed NaSSAs (Table 11).

7.3.4 CAARMS At-Risk Status

Thirty-one people were identified as having an ARMS by CAARMS UHR criteria. This accounted for 47.69% (n=20) of the follow-up sample (n=103). Of these 20 people (64.51%) met both the Attenuated Psychosis and Vulnerability Trait criteria of CAARMS. Two people (6.45%) met the Vulnerability Trait criteria alone, seven (22.58%) only met the Attenuated Psychosis criteria and 2 (6.45%) met both BLIPS and attenuated psychosis criteria. Figure 7 below shows the CAARMS criteria met.

Fourteen people (63.64%) had schizotypal traits as determined by an SPQ-A score of ≥ 39. Six people (27.27%) met the SPQ-A schizotypy threshold and also had a first-degree relative with psychosis and 2 people (9.09%) had a first-degree relative with psychosis but did not meet schizotypy criteria. Twenty-seven people satisfied the attenuated psychosis criterion. Figure 8 below shows the subgroups met in order to satisfy the attenuated psychosis criterion.

Table 11: Baseline Medication Profile of the Cohort

	None (n)	SSRI Antidepressant (n)	NaSSA (n)	Atypical Antipsychotic (n)	Typical antipsychotic (n)	Mood Stabilizer (n)	Mood Stabilizer and Atypical (n)	Methadone (n)	Atypical and SSRI (n)	Beta blocker (n)	Benzodiazepine (n)	Atypical and Subutex (n)	Atypical and NaSSA (n)
All referrals	87	36	6	24	2	3	2	2	6	1	3	1	1
CAARMS criteria only	6	1	0	3	0	1	0	0	0	0	0	0	0
SPI-A Criteria only	23	6	1	5	0	1	0	0	2	0	0	0	0
Both SPI-A and CAARMS Criteria met	12	8	2	2	0	0	1	0	1	0	1	1	0
Not At-Risk Group	27	9	1	2	0	0	1	0	0	0	0	0	0
Psychosis Group	21	14	3	6	2	1	1	2	3	1	2	0	1

Figure 7: CAARMS At-Risk Criteria Subgroups (N)

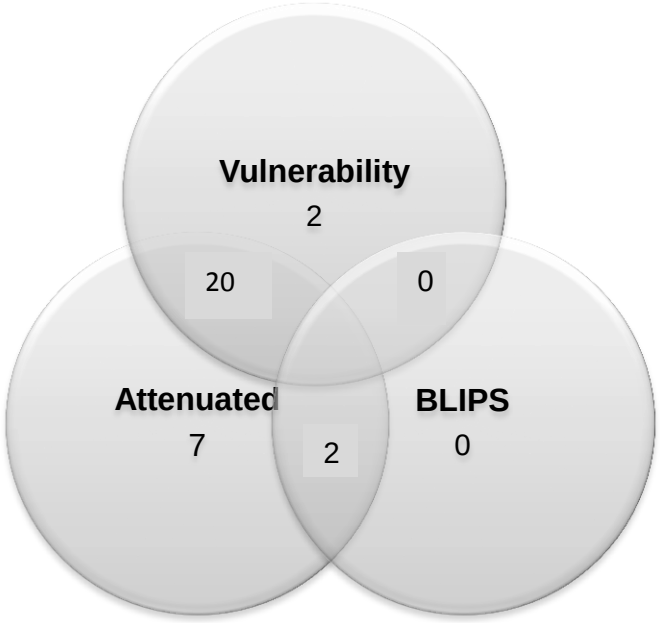
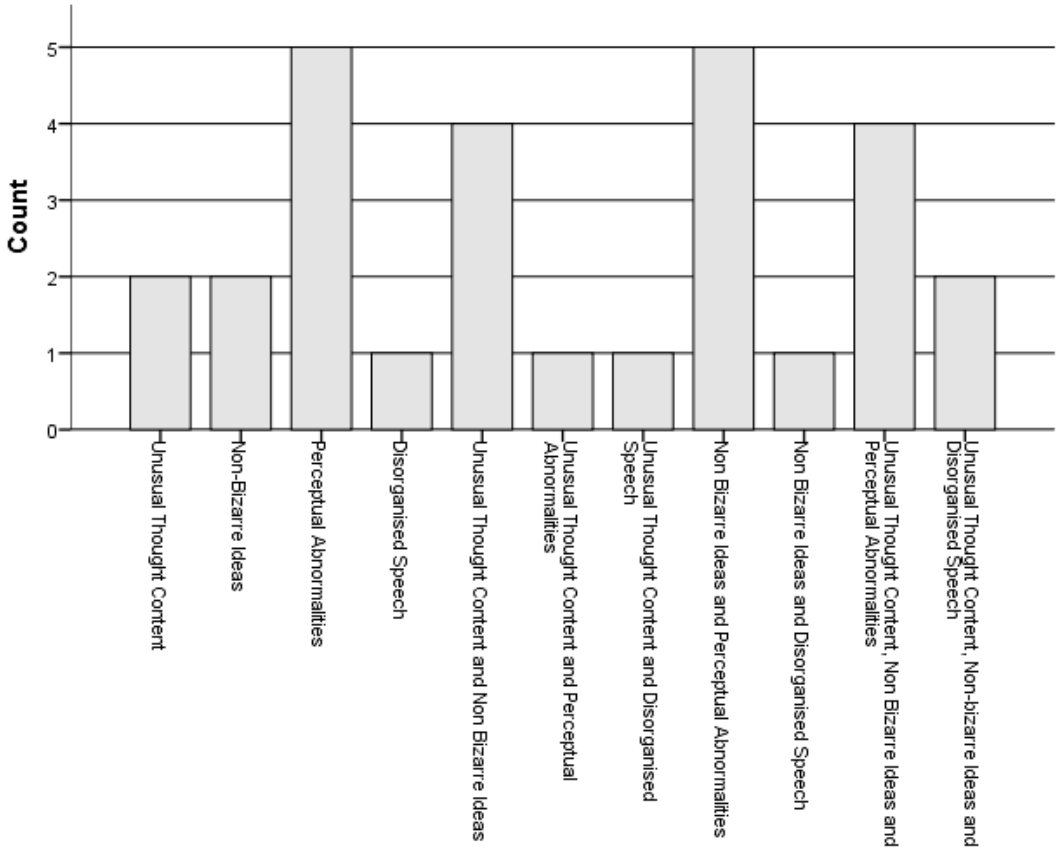


Figure 8: Attenuated Symptom Subgroups Met



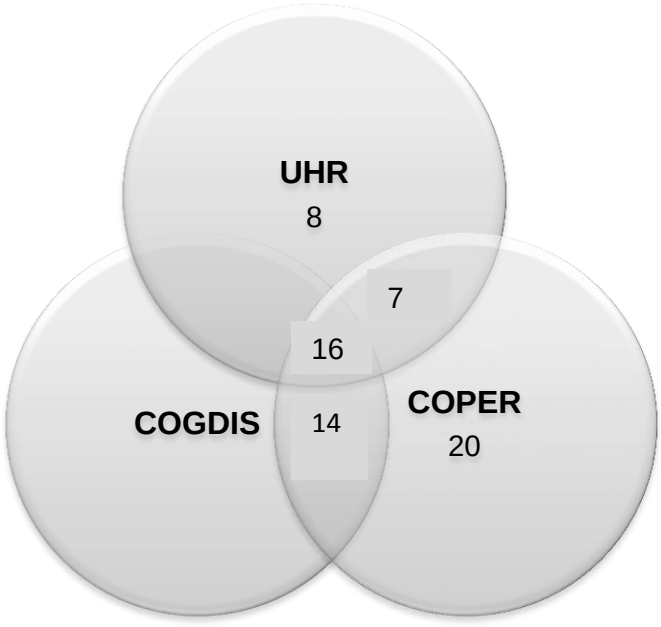
7.3.5 SPI-A At-Risk Status

The SPI-A identified more patients as having an ARMS than the CAARMS, with 57 patients (87.69%) meeting either COPER or COGDIS criteria. Of these, 27 (47.37%) met COPER criteria and 30 (52.63%) met COGDIS criteria. The mean total scores for SPI-A in the follow-up cohort (n=103) were 13.67 (SD 14.55, 95% CI: 10.83, 16.51). COGDIS was 30.08 (SD 13.48, 95% CI: 25.76, 35.84, skewness 0.23, kurtosis -1.02) and COPER was 13.19 (7.57, 95% CI: 10.19, 16.18, skewness 0.46, kurtosis -0.90). A lower mean total score for COPER can be expected, as only one Basic Symptom is required to fulfil the COPER criterion compared with two or more for COGDIS.

7.3.6 SPI-A and CAARMS At-Risk Status Overlap

There was a degree of overlap between the people identified by the SPI-A and CAARMS as having an ARMS. Twenty-three patients (35.38%) of the ARMS group fulfilled both criteria; eight people (12.31%) only met CAARMS criteria and 34 (52.31) only met SPI-A criteria. Figure 9 below shows overlap between three criterions.

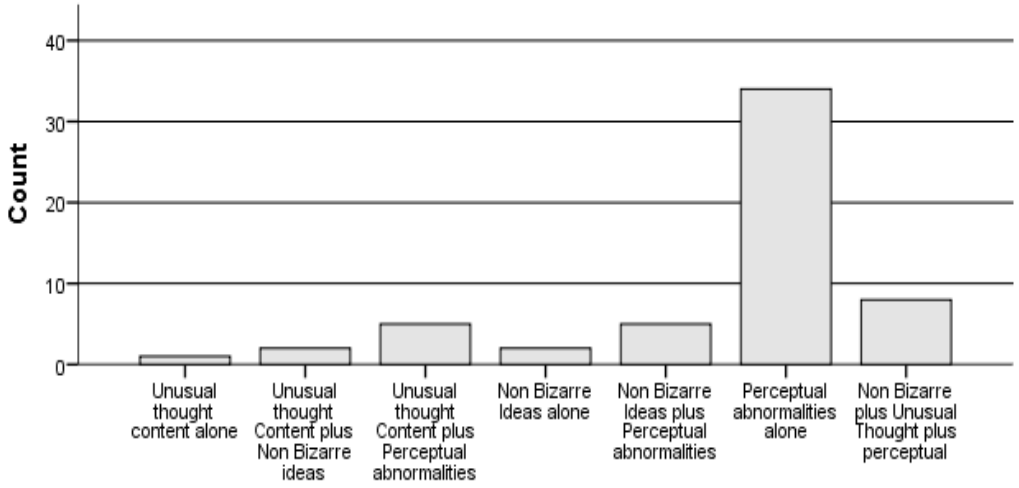
Figure 9: COPER, COGDIS and UHR Status



7.3.7 Psychosis Status

At baseline assessment, 57 (33%) people were found to meet the CAARMS threshold for psychosis. Perceptual abnormalities were the most commonly occurring psychotic symptoms occurring in 71.93% (n= 41) of cases. Figure 10 below shows the frequency by which psychosis thresholds were met in the CAARMS subgroups.

Figure 10: Psychosis Thresholds Met In the CAARMS Subgroups



Basic symptoms as assessed by SPI-A were also found to be present within the psychosis group; fifty patients (87.72%) met either COPER or COGDIS criteria. Twenty-two patients (38.6%) met COPER criteria and 28 (49.12%) met COGDIS criteria. The mean total SPI-A score for the psychosis group was 20.79 (SD 16.44, 95% CI: 16.38, 25.19).

7.3.8 Schizotypal Personality Traits

SPQ-A Schizotypy assessments were available for 93 (90.29%) of the follow-up cohort. The mean SPQ schizotypy score for the cohort was 42.14 (SD 16.307, 95% CI: 39.58, 44.77). The three subscales cognitive perceptual, Interpersonal had means of 15.93, 19.19, and 9.38 respectively (see table 12). Overall the mean SPQ score was higher for those meeting CAARMS at

risk criteria (M=44.72 SD. 15.67, 95% CI: 39.44) compared with those not (M= 35.42 SD 16.302, 95% CI: 31.42, 39.43). This difference was significant *t* (102) = 2.795, *p*= 0.006, with an effect size of 0.27. This is as would be expected given that the SPQ-A was used to inform the vulnerability trait criterion of CAARMS. Those found to be psychotic had a mean SPQ score of 49.44 (SD 13.20, SE 1.867). The difference in mean SPQ-A scores between those who were psychotic and those who were at-risk was significant *t*(120*)* = -2.51*, p* = 0.014.

On average patients meeting SPI-A COPER criteria scored lower on the SPQ-A (M = 38.96, SD 14.45, 95% CI: 32.99, 44.93) than patients meeting COGDIS criteria (M = 47.18, SD 14.13, 95% CI: 41.70, 52.66). This difference was found to be significant *t* (51) = 2.09, *p* = 0.042. However, the difference between the two means was not statistically significant *t*(102) = -1.66, *p* = 0.10.

Table 12: The Means and Standard Deviations of SPQ-A Total and Subscale Scores

	Maximum	Mean	Std. Deviation	Variance	Skewness		Kurtosis	
SPQ-A total score	70	37.96	16.92	286.368	-.347	.261	-.723	.517
SPQ-A Cognitive Perceptual	50	15.93	8.96	80.281	.448	.261	1.045	.517
SPQ-A Interpersonal	33	19.19	8.16	66.631	-.481	.261	-.578	.517
SPQ-A Disorganised	26	9.38	5.28	27.833	-.075	.261	-.245	.517

7.3.9 Social Functioning

SOFAS social functioning assessments were available for the entire included cohort. On average the ARMS group experienced a lower level of SOFAS functioning at baseline assessment (M=57.77, SD 13.01, 95% CI: 54.55,

60.99) than the not ARMS group (M= 67.37, SD 11.73, 95% CI: 63.51, 71.22). This difference was significant $t(103) = -3.75$, $p < 0.001$ with a small effect size of 0.12. Table 13 shows the mean baseline SOFAS according to CAARMS, SPI-A and SPQ-A status.

Table 13: Means and Standard Deviations of SOFAS Scores According to CAARMS, SPI-A and SPQ-A Status.

		N	Mean	Std. Deviation	Std. Error	95% Confidence interval for the mean	
						Lower Bound	Upper Bound
CAARMS	Positive	31	48.35	6.83	1.23	45.83	50.88
	Negative	72	66.89	11.42	1.35	64.21	69.57
	Psychosis	57	52.06	11.61	1.54	49.52	55.68
SPI-A	COPER	27	61.85	12.14	2.34	57.05	66.65
	COGDIS	30	56.50	13.84	2.53	51.33	61.67
	Negative	46	64.13	13.05	1.92	60.25	68.01
SPQ-A	Positive	50	59.52	13.03	1.84	55.82	63.22
	Negative	43	62.88	13.92	2.12	58.06	67.17

On average ARMS patients also experienced a greater decline in functioning prior to assessment, (determined by the difference between SOFAS premorbid and current scores) (M = 13.28, 15.45, 95% CI: 9.45, 17.10) compared with the not ARMS group (M=7.92, SD 8.95, 95% CI: 4.98, 10.86). This difference was also significant $t(101) = 2.23$, $p = 0.028$ with a very small effect size of 0.05. Table 12 shows the mean decline in functioning according to CAARMS, SPI-A and SPQ-A status.

As can be seen in tables 13 and 14 patients meeting SPI-A COPER had higher levels of functioning at baseline (M = 61.85) than those meeting COGDIS criteria (M = 56.50). However the difference between the two

groups in relation to baseline SOFAS score was not found to be significant *t* (55) = 1.54, *p* = 0.126. While high schizotypes (SPQ-A positive) had lower levels of functioning (59.52) than low schizotypes (SPQ-A negative) (M = 62.88), low schizotypes had a slightly greater degree of decline in functioning. This difference was not however, significant *t* (55) = -1.626, p = 0.110.

Table 14: Means and Standard Deviations of the Decline in SOFAS Scores from Pre-Morbid Levels of Functioning, According to CAARMS, SPI-A and SPQ-A Status.

		N	Mean	Std. Deviation	Std. Error	95% Confidence interval for the mean	
						Lower Bound	Upper Bound
CAARMS	Positive	31	20.81	18.26	3.28	14.11	27.50
	Negative	72	7.21	8.31	0.98	5.25	9.16
	Psychosis	57	20.11	17.29	2.29	15.52	24.69
SPI-A	COPER	27	9.30	11.96	2.30	4.57	14.03
	COGDIS	30	15.40	16.25	2.97	9.33	21.47
	Negative	46	9.80	12.32	1.82	6.15	13.46
SPQ-A	Positive	50	10.96	13.58	1.92	7.10	14.82
	Negative	43	12.35	14.18	2.16	7.98	16.71

7.4 Discussion

The Cohort of people attending the LEAD clinic was young with a mean age of 21.30. The peak age range for onset of first episode psychosis is late teens to early twenties (Kessler et al., 2007), therefore, those attending the clinics are representative of people likely to develop a first episode psychosis.

The gender mix of the cohort with 54.6% males is similar to the findings the meta-analysis in chapter 6, which found that the combined cohort comprised of 55.6% males. This suggests that the gender mix of the population is broadly representative of those attending early detection services.

The cannabis use profile of the cohort although higher than the national average is within the range reported in a systematic review of 53 psychosis treatment studies and 5 epidemiological studies by Green et al (2005). They found lifetime cannabis use to be 42.1%, which is slightly higher than the lifetime use of the included cohort that was 40.78% but almost identical to the 16-24 age group, whose lifetime use was 42%. A review of five prospective studies of cannabis and psychosis (Arseneault et al., 2004) found that cannabis use conferred a two-fold increase in relative risk for psychosis but concluded that it was only a 'component part' of a number of casual factors in the development of psychosis. It will be interesting to see whether cannabis use is a factor in psychosis development in the follow-up analysis.

The social functioning of the whole cohort was poor, indicating that all of the young people accessing our services are experiencing mental health problems to a degree that their functioning is considerably impaired. The difference in mean SOFAS scores between the not-at-risk and at-risk population was statistically significant, indicating that those at risk were significantly more impaired. Greater impairment in social functioning has been previously found to increase the positive predictive power of the assessment of psychosis risk (Cannon et al., 2008) and it will be interesting to see if this is the case in the follow-up analysis of this cohort.

Although not significant, patients meeting the SPI-A COPER criterion showed higher levels of functioning than either COGDIS or CAARMS UHR positive patients. We hypothesized that as functioning levels are higher in the COPER group the risk of transition to psychosis is not as imminent; therefore, conversion in the COPER group will occur later than the COGDIS

group. This would support the initial findings of Schultze-Lutter et al. (2006), who found that COGDIS patients converted earlier than COPER patients.

While there is some overlap between SPI-A and CAARMS criteria, SPI-A would seem to capture a broader section of the cohort. SPI-A deems 57 people at risk compared with 31 by CAARMS. The overlap between the two is 28 cases. It will be interesting to see at follow-up whether those fulfilling both SPI-A and CAARMS criteria have an increased likelihood of developing psychosis, compared with those meeting the respective test results in isolation.

One of the unexpected benefits of the LEAD clinic is the detection of 57 cases of psychosis at baseline assessment, which accounted for 32.76% of referrals. This was higher than the experience of the Outreach and Support Service in South London (OASIS) who found 21% of those assessed to psychotic (Broome et al., 2005). OASIS is a specialised prodrome service and not part of an EIS therefore; we would anticipate the rate of psychosis in the LEAD clinic to be lower as all cases have been assessed by the EIS prior to attending the clinic using the PANSS (Kay et al., 1987). It was not our expectation to find a third of the cohort to be already experiencing a psychosis. Had the clinic not detected this cohort of young people they would have likely been discharged back to their General Practitioner and would have experienced a longer than necessary duration of untreated psychosis.

The SPQ-A was used as a self-report measure of schizotypy, to inform the vulnerability criteria of the CAARMS. This tool is not currently used by the authors of the CAARMS; instead, they use the Structured Clinical Interview (SCID) for DSM-IV (American Psychiatric Association, 1994). The difference in the SPQ-A scores for those at-risk and not-at-risk of psychosis was statistically significant. Those psychotic at baseline also had mean scores above the threshold for schizotypy (a score ≥39). We hypothesize that rather than a true measure of schizotypal traits the SPQ-A is actually a self-report measure of psychotic symptoms and may be benefitting the predictive ability

of the CAARMS. It will be interesting to see if this is the case in our follow-up analysis.

CHAPTER 8: Results of the Service Evaluation Follow-up Analysis

Chapter 8: Results of the Service Evaluation Follow-up Analysis

8.1 Introduction

Over the last 20 years and two main psychopathology based approaches to the detection of the psychosis prodrome have emerged; the Ultra-High Risk approach (UHR) (Miller et al., 2002, Yung et al., 1998a, Yung et al., 2003b) (Chapter 2) and the Basic Symptom approach (Huber and Gross, 1989, Klosterkotter et al., 2001a, Schultze-Lutter et al., 2007a) (Chapter 3).

Both approaches were shown by the meta-analysis in chapter 6 to have similar positive predictive values; Basic Symptoms: 0.34 (95% CI: 0.15, 0.61) compared to UHR: 0.25 (95% CI: 0.18-0.33). However, to our knowledge, neither approach has been tested in a routine clinical setting in the UK. To date research has been conducted in highly specialised prodrome clinics. The purpose of this thesis is to conduct a service evaluation in order to investigate how well these two approaches perform in LEAD clinic which uses both the Basic Symptom and UHR approaches to detection; i.e. the CAARMS (Yung et al., 2006a) and the SPI-A (Schultze-Lutter et al., 2007b).

The previous chapter (chapter 7), presented the baseline findings of the service evaluation and this chapter presents the follow-up results for the cohort. The chapter address all five aims of the service evaluation:

1) to determine how many people assessed in the clinic between January 2008 and December 2011 subsequently developed psychosis
2) to establish the accuracy of our current predictions concerning which non−psychotic patients will develop psychosis
3) to improve the efficiency of the assessment process by identifying redundant or inaccurate techniques
4) to determine whether combining UHR and BS instruments has an additive effect and improves predictive ability

5) to determine time to transition and inform the duration of care co-ordination follow-up offered by the Lancashire EIS.

We hypothesise that combining the SPI-A assessment with the CAARMS will result in greater sensitivity and specificity than when the CAARMS or SPI-A are evaluated individually. We also hypothesise that the use of the SPQ-A as a measure of schizotypy will increase the overall sensitivity and specificity of the CAARMS.

8.2 Methods

This section gives a summary of the methods used to determine psychosis risk within the LEAD clinic. Chapter 5 outlines the study design and general methodology of the service evaluation and chapter 7 describes the method of the baseline service evaluation and the sample characteristics. The current chapter describes the included patients (detailed in chapter 7) who did and did not convert to psychosis by the end of the follow-up period. The predictive ability of the baseline measures was examined by comparing the results of the baseline evaluation, with the results of the follow-up evaluation. The overall aim was to improve the efficiency of the service.

8.2.1 Procedure

The study evaluates the ability of the baseline measures (CAARMS, SPI-A and SPQ-A) to predict conversion to psychosis in a consecutively assembled cohort of non-psychotic help-seeking young people. At the end of the follow-up period, the electronic care records of all included patients were reviewed to establish conversion to psychosis. Conversion to psychosis was defined by:

- Admission to hospital for a psychotic illness;
- In receipt of prescription of anti-psychotic medication, for treatment of psychotic symptoms;
- Presence of psychotic symptoms documented in the clinical record, persisting for more than one week.

While from a methodological point of view casenote evaluation is clearly a less rigorous method of follow-up evaluation than face-to-face interview, it does enable all patients still residing within the Lancashire area to be evaluated. It is not subject to the same problems of attrition that inviting patients back for follow-up assessment would have; it is also a cost effective method of follow-up. Lancashire Care NHS Foundation Trust is the primary provider of mental health care in Lancashire, so unless the patient moved out of the county, their mental health records would be accessible. If residing in Lancashire patients who converted to psychosis would receive care from a Lancashire Care NHS Foundation Trust service.

At the end of the follow-up period, CJ reviewed the electronic case notes of all included patients against the conversion criteria. To ensure the correct interpretation of the records an EIS psychiatrist reviewed the clinical records of those whom CJ deemed to have converted.

8.2.2 Analyses

SPSS for Windows (SPSS Inc., 2007, Version 19, Chicago, IL, US) was used to analyse the data. Diagnostic efficiency measures such as sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Values (NPV), Likelihood Ratios (LR) and Odds Ratios (OR) were calculated using MedCalc software (Version 12.3.0, Mariakerke, Belgium). Statistical measures, means, and standard deviations are explained for descriptive purposes. Receiver Operating Curve (ROC) analysis enabled the most predictive cut-off scores for measures to be determined. Spearman's correlations will be used to measure relationship with different continuous variables.

The risk of conversion to psychosis was calculated by Kaplan-Meier survival analysis for calculating the cumulative hazard rate. The association between baseline measures and conversion to psychosis was determined by univarate chi squared analysis. Multivariate logistic regression was used to determine the most predictive combination of tests.

8.3 Planned (A-Priori) Analysis

One hundred and seventy four people attended the LEAD clinic for assessment between January 2008 and the end of December 2011. At baseline, patients were categorised as either ARMS, not At-Risk or Psychotic. We excluded fifty-seven patients from the follow-up analysis as they met the CAARMS threshold for psychosis at baseline. A further 14 patients were excluded as they were prescribed and concordant with antipsychotic medication at a dose within the therapeutic range. We excluded one further patient at the follow-up analysis stage as they had converted to psychosis within 2 weeks of the initial assessment. Given that conversion occurred so soon following assessment we deemed them to have been psychotic at baseline. The remaining 102 patients were included in the follow-up evaluation. Of these 64 met at-risk criteria and 38 did not.

8.3.1 At-Risk Status of the Cohort

Sixty-four people (62.75%) satisfied ARMS criteria as determined by either SPI-A (COPER or COGDIS) or CAARMS. Of these 30 people (46.88%) fulfilled CAARMS UHR criteria. Twenty-seven people (42.19%) met COPER criteria and 29 (45.31%) met COGDIS criteria There was some overlap between the CAARMS and the SPI-A; with 22 people (34.38%) meeting both criteria. Eight people (12.5%) only met CAARMS criteria and 34 (53.13%) only met SPI-A criteria (table 15). The mean age of the ARMS and not ARMS groups was 21.11 years (SD 4.96, SE 0.62) and 21.66 years (SD 5.39, SE 0.88) respectively. The majority of both the ARMS and not ARMS group were of white British origin (92.19% and 92.11% respectively). Chapter 7 describes the demographic characteristics of the cohort in more detail.

The mean baseline score on the SOFAS for those who converted was 52.35 (SD. 12.64, SE, 3.07) compared with 63.33 (SD 12.98, SE, 1.44) for those who did not. This difference was statistically significant t (96) = -3.19, p = 0.002. The mean drop in functioning at baseline for those who converted was 18.68 (SD 16.15, SE, 3.70) compared with 9.75 (SD 12.53, SE 1.38) for

those who did not. Again this difference was statistically significant t (100) = 2.65, p = 0.009

Table 15: Characteristics of Converted and Non-Converted Patients

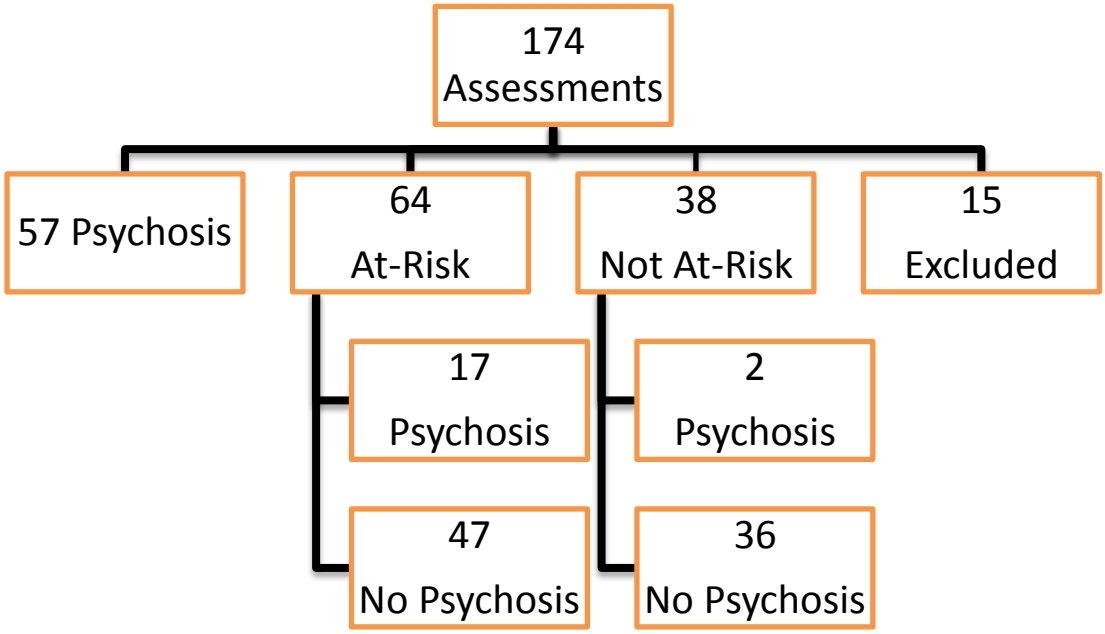
	Total (N=102)	Converters (N=19)	Non-Converters (N=83)	Converters v Non-Converters (*p* value)
Age (years, mean, SD)	21.31 (5.11)	20.79 (4.13)	21.43 (5.32)	0.622[a]
Male (n, %)	59 (57.8)	10 (52.63)	49 (59)	0.617[b]
Ethnicity (% White British)	90.2	100	88	0.864[c]
At-Risk by either CAARMS or SPI-A (n,%)	64 (62.75)	17 (89.47)	47 (56.63)	0.008[b]
CAARMS UHR Positive	30 (29.41)	11 (57.89)	19 (22.89)	0.005[b]
SPI-A Positive (COGDIS or COPER) (n,%)	56 (54.9)	16 (85)	40 (48.2)	0.005[b]
COPER Positive (n,%)	26 (25.49)	3 (15.79)	23 (27.71)	0.387[b]
COGDIS Positive (n,%)	30 (29.41)	13 (68.42)	17 (20.48)	0.000[b]
Both SPI-A and CAARMS UHR positive	22 (21.57)	10 (52.63)	12 (14.5)	0.002[c]
Both COGDIS and CAARMS UHR	15 (14.71)	8 (42.11)	7 (8.43)	0.001[b]
Either COGDIS or CAARMS or both	44 (43.14)	17 (89.47)	28 (33.73)	0.000[b]
Lowest SOFAS score in last 12-months (mean, SD)	61.43 (13.52)	52.35 (12.64)	63.33 (12.98)	0.002[a]
Mean baseline SPQ-A score (0nly 92 available)	38.56 (16.77)	49.65 (15.45)	36.01 (16.10)	0.002[a]

a. **T-test.**
b. **Fisher's exact test (2-sided)**
c. **Pearson Chi Square (2-sided**

8.3.2 Transition to Psychosis

The mean length of the follow-up period was 30.44 months (SD. 13.68 months, 95% CI: 27.75, 33.13, median 32 months). By the end of this period, 19 people (10 males and 9 females) had developed psychosis, 17 of whom had been categorised at baseline as having an ARMS (by either SPI-A or CAARMS) and two had not. This represents a 26.56% conversion rate within the ARMS group and a 5.26% conversion rate in the not at-risk group. The mean time to conversion was 8.68 months (SD 8.75 months, 95% CI: 4.47, 12.90, median, 6 months). Figure 11 below shows the number of conversions by baseline group.

Figure 11: Conversion to Psychosis by Baseline Group



Kaplan-Meier survival analysis showed that all transitions occurred within 25 months of follow-up. The incidence rate of conversion after 6, 12, 18, 24 and 30 months for ARMS patients was 14%, 19%, 22%, 22% and 27% (figure 10). Conversions for the not at-risk patients occurred within the first 18 months, therefore the incidence rate of conversion for this group after 6, 12 and 18 months was 2.63%, 2.63%, 5.26%, respectively. Figure 10 below shows the Kaplan- Meier survival plot for the ARMS and not ARMS groups.

The estimate mean survival time for the ARMS group is 41.07 months (SE 2.52 months (95% CI: 36.12, 46.02) and for the not at risk group 53.42 months (SE 1.79 months, 95% CI: 49.92, 56.93). The difference between the survival curves of the ARMS and not ARMS groups is significant (log-rank test p=0.008, Breslow test p=0.009) (figure 12). The mean time to transition for males was 6.30 months (SD 8.08 months, 95% CI: 0.52, 12.08) and for females was 11.33 months (SD 9.15 months, 95% CI: 4.30, 18.37). While males converted earlier than females the difference between the survival curves was not significant (log-rank test p = 0.716) (Figure 13).

The sensitivity of meeting either SPI-A or CAARMS ARMS criteria was 0.89 (95% CI: 0.65, 0.98) and the specificity was 0.43 (95% CI: 0.33, 0.55), PPV 0.27 (95% CI: 0.17, 0.39), NPV 0.95 (95% CI: 0.81, 0.99), likelihood ratio (LR) was 1.56. Table 16 below shows the sensitivity and specificity of the various tests and combinations of tests.

Figure 12: Kaplan-Meier Cumulative Hazard Plot for the Follow-Up Cohort

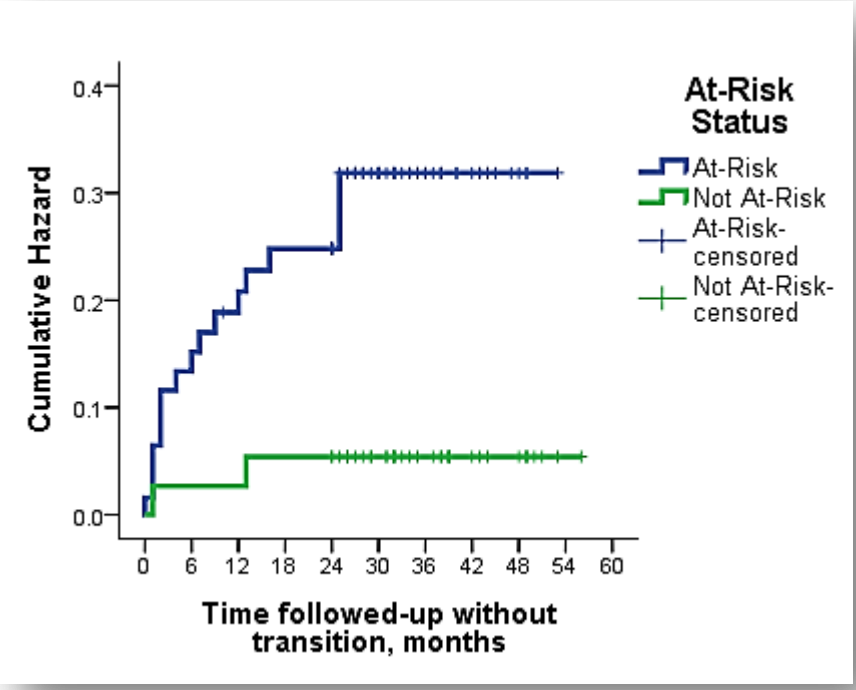


Figure 13: Kaplan-Meier Survival Plot for the Follow-Up Cohort

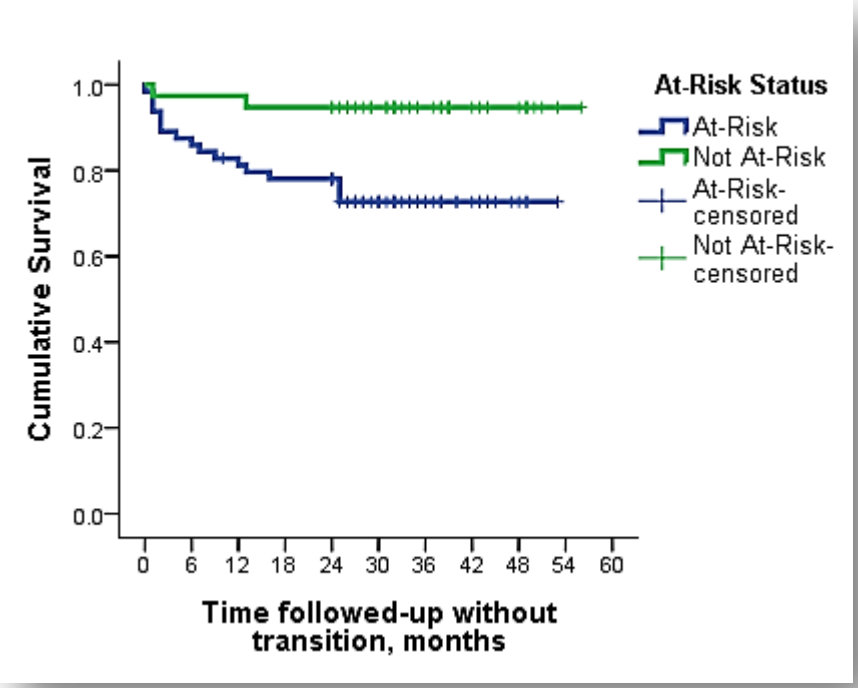


Figure 14: Kaplan-Meier Plot for the Follow-Up Cohort: Converted Males and Females

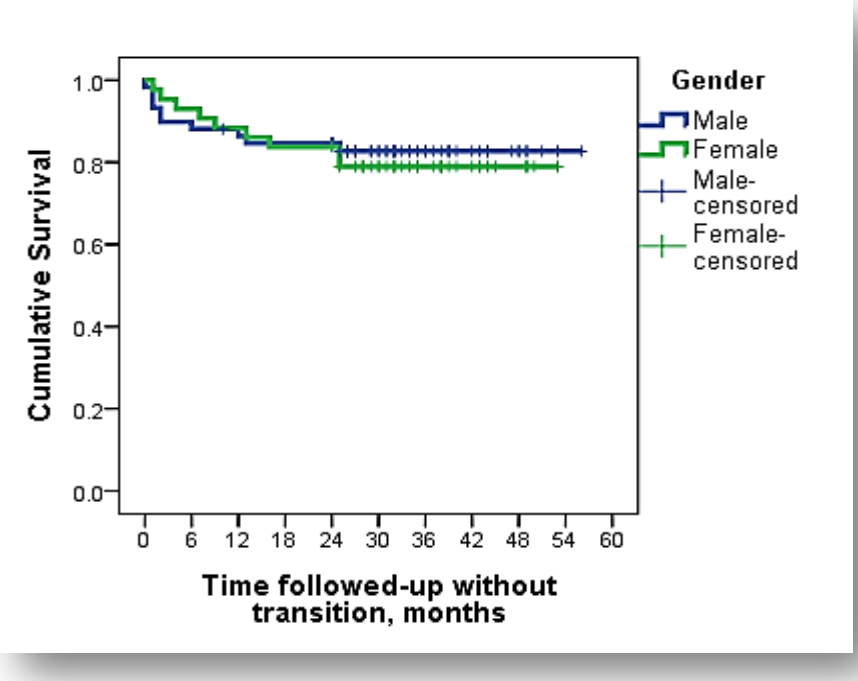


Table 16: Sensitivity and Sensitivity of the Baseline Tests and Combinations of Tests.

Test	Sensitivity	Specificity	Likelihood ratio
CAARMS	0.58	0.77	2.48
SPI-A (either COPER or COGDIS)	0.84	0.51	1.71
COPER	0.16	0.72	0.56
COGDIS	0.68	0.80	3.4
SPQ-A only (data available for 92 people)	0.88	0.54	1.91
SOFAS (with 30-point drop in the last year sustained for ≥ 1 month or score ≤ 50 for 1 year or more)	0.63	0.75	2.6
SPI-A (either COPER or COGDIS) and CAARMS	0.53	0.86	3.79
SPI-A (COPER or COGDIS) or CAARMS	0.89	0.43	1.56
COGDIS and CAARMS	0.42	0.92	5.25
Either COGDIS or CAARMS or both	0.84	0.66	2.47

8.3.3 Effect of CAARMS Criteria on Conversion

Thirty patients met CAARMS UHR criteria at baseline and 72 did not. Eleven (36.67%) UHR positive (UHR+) and 8 (11.11%) UHR negative (UHR-) converted to psychosis by the end of the follow-up period. Those in the UHR+ group converted sooner than the UHR- group. The mean time to conversion for the UHR+ cohort was 6 months (SD 7.316, 95% CI: 1.09, 10.91) compared with 12.38 months (SD 9.68, 95% CI: 4.285, 20.47) for the UHR- group. Just under two thirds (63.64%, n = 7) of UHR+ conversions occurred within 6-months of follow-up. By 12-month follow-up 11 (90.91%) had converted. The incidence rates of conversion after 6, 12, 18, 24 and 30 months for the UHR+ group were 23.3%, 33.5%, 33.5%, 33.5% and 37.7% respectively and for the UHR- group were 4.2%, 4.2%, 8.3%, 8.3% and

11.3% respectively (figure 15). The difference in survival curves between the UHR+ and UHR- patients was significant (log-rank test $p < 0.001$) (figure 16).

The sensitivity of the CAARMS was 0.58 (95% CI: 0.34, 0.79) and the specificity was 0.77 (95% CI: 0.66, 0.85), PPV 0.37 (95% CI: 0.21, 0.56), NPV 0.89 (95% CI: 0.79, 0.95), positive LR 2.53 (95% CI: 1.46, 4.39) and negative LR 0.55 (95% CI: 0.32. 0.93).

Psychosis at follow-up was significantly associated with UHR positive status at baseline (X^2 (1, N= 102) = 9.12, p = 0.003). Those who met UHR+ criteria at baseline had significantly greater odds of developing psychosis than those deemed UHR- (Odds Ratio (OR), 4.63, 95% CI: 1.63, 13.17).

Figure 15: Kaplan-Meier Cumulative Hazard Plot for CAARMS

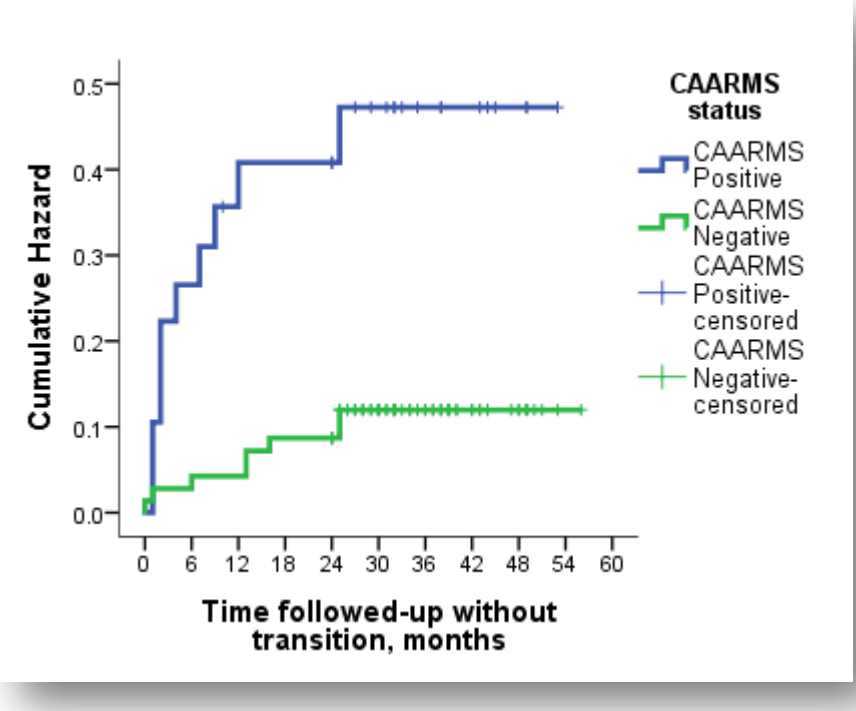
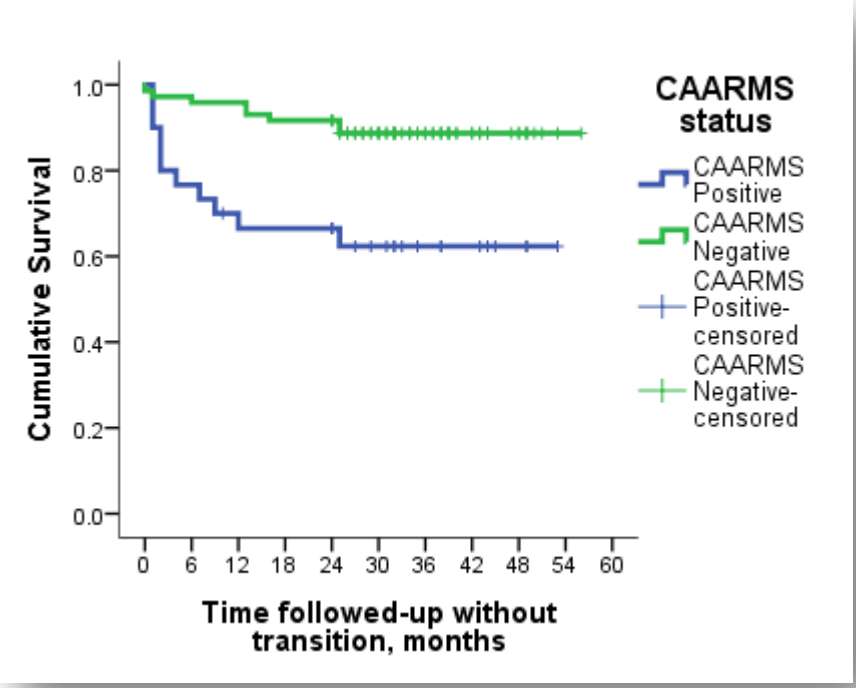


Figure 16: Kaplan-Meier Survival Plot of CAARMS UHR+ and UHR- groups.



All 11 of the UHR+ patients who converted to psychosis, had attenuated symptoms at baseline and nine of them had vulnerability traits. All nine met the vulnerability criterion through a positive result on the SPQ-A (total SPQ-A ≥ 39) and three patients had a first-degree relative with psychosis in addition to schizotypy. None of the patients who converted to psychosis met the BLIPS group criterion at baseline. Of the three CAARMS criterions attenuated symptoms and vulnerability traits were statistically significant predictors of psychosis conversion (the attenuated group, X^2 (1, N = 102) = 10.87, p = 0.003, and the vulnerability group, X^2 (1, N = 102) = 10.34, p = 0.006), BLIPS was not significant X^2 = (1, N= 102) = 0.467, p = 0.494).

The attenuated symptom group comprises four subgroups, unusual thought content, non-bizarre ideas, perceptual abnormalities, and disorganised speech. Of these the only statistically significant predictor of psychosis conversion was the perceptual abnormalities subgroup, X^2 (1, N= 102) = 4.22, p = 0.04.

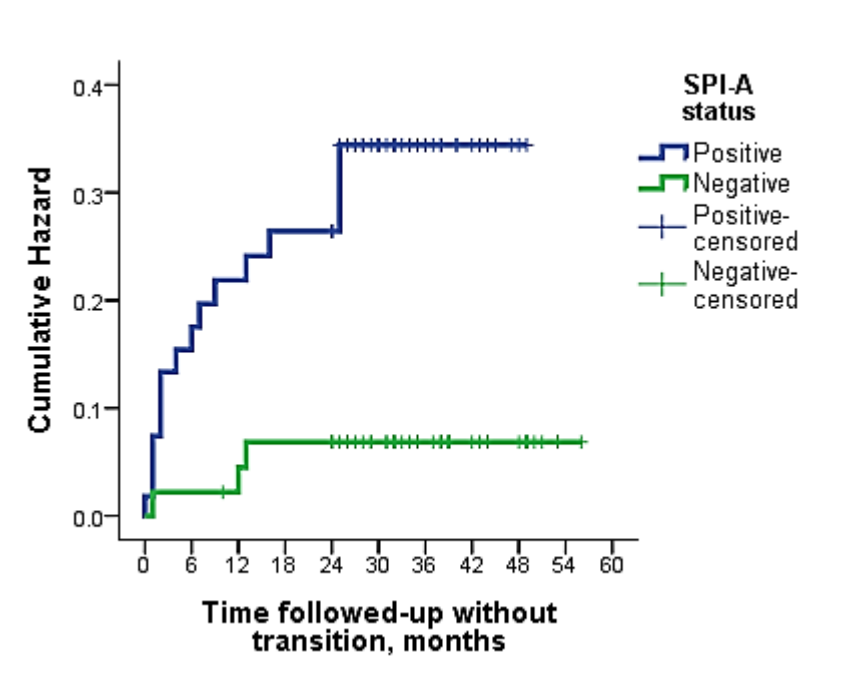
8.3.4 Effect of SPI-A Criteria on Conversion to Psychosis

Of the 56 people who satisfied SPI-A at risk criteria (COPER or COGDIS) at baseline, 16 (28.57) had converted by the end of the follow-up period. Three people (6.5%) not deemed at risk by SPI-A also converted. The mean total SPI-A score for those who developed psychosis was 28.11 (SD 17.80, 95% CI: 19.53, 36.68) compared with 10.34 (SD 11.59, 95% CI: 7.81, 12.87) for those who did not. The difference between the mean total SPI-A scores of the converted and not converted groups was significant t (100) = 4.16, P < 0.001.

A significant difference was found in the Kaplan-Meier survival times for those meeting SPI-A criteria at baseline and those not (log-rank test p = 0.005, Breslow test, p= 0.005) (figure 17). The incidence rates of conversion for after 6,12,18,24 and 30 months for patients meeting SPI—A at risk criteria (COPER or COGDIS) were 16.1%, 19.6%, 23.2%, 23.2, 29.1%, with two thirds (68.75%) of conversions occurring within the first 12-months of follow-up (figure 15). The sensitivity of the SPI-A was 0.84 (95% CI: 0.60, 0.96) and the specificity was 0.51 (95% CI: 0.41, 0.63), PPV was 0.29 (95% CI: 0.18, 0.42), NPV 0.93 (95% CI: 0.81, 0.98) and LR 1.71.

Psychosis at follow-up was significantly associated with a positive baseline SPI-A result) (X^2 (1, N = 102) = 8.10, p = 0.004). Those who were deemed to have an ARMS by SPI-A had significantly greater odds of developing psychosis than those who were not (OR 5.73, 95% CI: 1.55, 21.17).

Figure 17: Kaplan-Meier Cumulative Hazard Plot for the SPI-A



When the performance of the two SPI-A at-risk criterions (COPER and COGDIS) are compared, COPER was not found be a statistically significant predictor of psychosis (X^2 (1, N= 102) = 1.16, p = 0.282), COGDIS however was (X^2 (1, N=102) = 17.11, p < 0.001). COPER identified 26 people as having an ARMS at baseline and of these three (11.54%) developed psychosis by the end of the follow-up period. In comparison, COGDIS identified 30 people as having an ARMS and 13 (43.33%) subsequently developed a psychosis. The sensitivity of COPER criteria was 0.16 (95% CI: 0.12, 0.28), Specificity was 0.72 (95% CI: 0.61, 0.81), PPV was 0.12 (95% CI: 0.03, 0.31), NPV was 0.79 (95% CI: 0.67, 0.87) and the LR was 0.56. The sensitivity of the COGDIS criteria was 0.68 (95% CI: 0.43, 0.86), the specificity was 0.80 (95% CI: 0.69, 0.87), PPV was 0.43 (95% CI: 0.26, 0.62), NPV was 0.92 (95% CI: 0.82, 0.97) and the LR was 3.4.

The mean time to transition for the COPER positive cohort was 11 months (SD 12.49 months, 95% CI: -20.03, 42.03). Kaplan-Meier survival analysis indicates that all COPER positive conversions occurred within the first 25-months of follow-up. The mean time to transition for those meeting COGDIS criteria was 8.15 months (SD 8.93 months, 95% CI: 2.76, 13.55), with all transitions occurring within 25 months. After six months five (38.46%) COGDIS patients had converted and at 12-months nine (69.23%) had converted. The difference between the survival curves of those meeting COPER, COGDIS or neither criteria is significant (log-rank test p=0.000, Breslow test p=0.000) (figure 18).

With over two thirds (69.23%) of the conversions occurring in the first 12-months of follow-up, the incidence rate for conversion for the COGDIS group at 6, 12, 18, 24 and 30 months was 26.7%, 30%, 36.7%, 36.7% and 44.1% respectively (Figure 19).

Schultze-Lutter et al (2010) suggest that when unaccompanied by attenuated psychotic symptoms the COPER criterion represents the early stage of the psychosis prodrome. To test this we analysed the data to determine how many of the of the COPER and COGDIS patients in both the converted and non-converted group also experienced attenuated symptoms. As shown in table 16 the vast majority (80.77%) of those who met COPER criteria did not experience attenuated psychotic symptoms compared with 46.67% of the COGDIS group. The majority (86.96%) the non-converters in the COPER group did not have attenuated symptoms. This would seem to suggest that Schutze-Lutter et al (2010) may be correct in their hypothesis that COPER in the absence of attenuated symptoms represents the early stage of the psychosis prodrome.

Table 17: Overlap Between COPER & COGDIS Criterions and Attenuated Symptoms in the Converted and Non-Converted Groups

	COPER		COGDIS	
	Plus Attenuated Symptoms	No Attenuated Symptoms	Plus Attenuated Symptoms	No Attenuated Symptoms
Converted	2	1	8	5
Non-Converted	3	20	8	9

Figure 18: Kaplan-Meier Survival plot – COPER and COGDIS Criteria

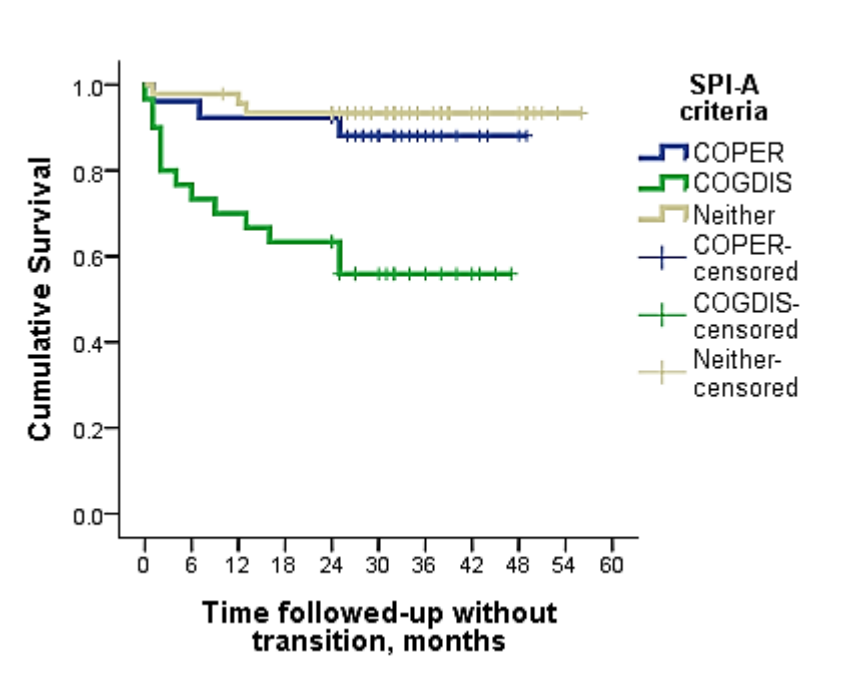
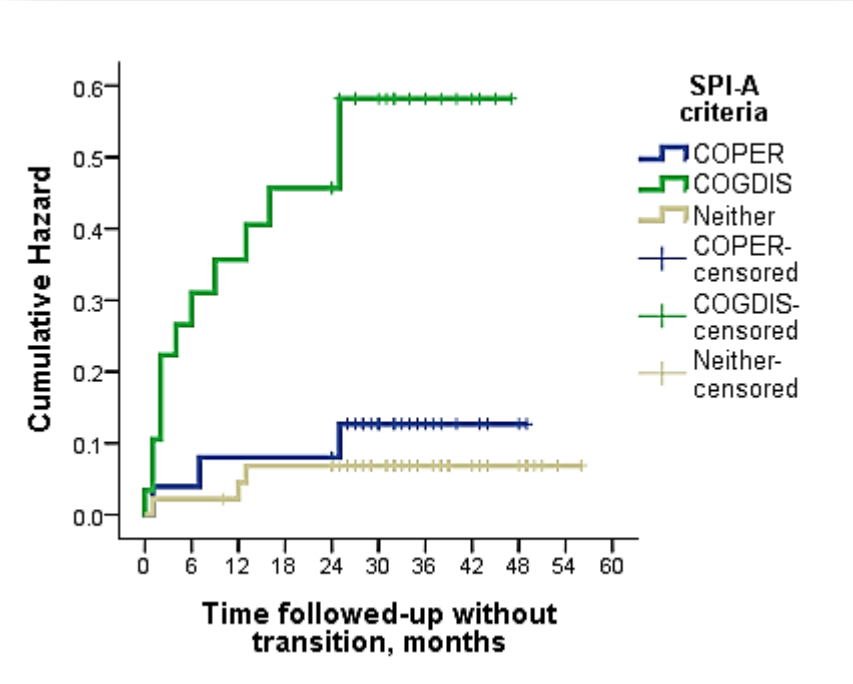


Figure 19: Kaplan-Meier Cumulative Hazard Plot for COPER and COGDIS



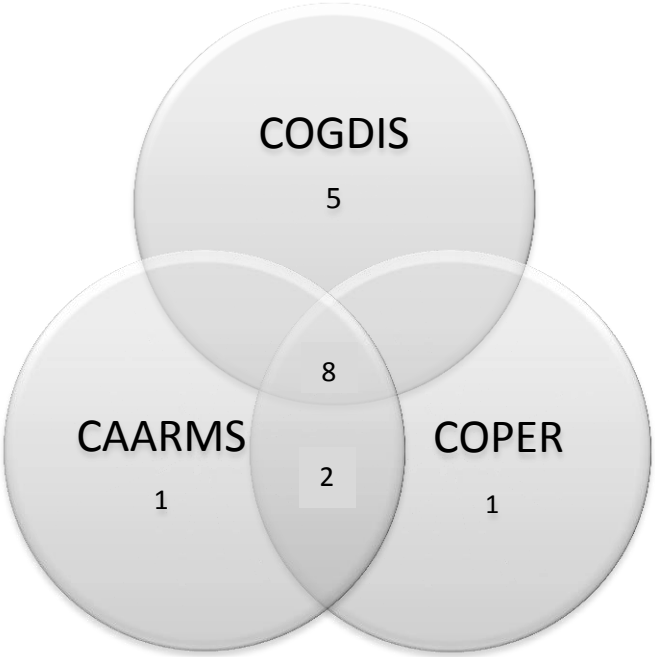
8.3.5 Effect of combining both SPI-A and CAARMS Criteria

At baseline twenty-two people satisfied both SPI-A (COPER and/or COGDIS) and CAARMS at-risk criteria and 10 (45.45%) had converted to psychosis by the end of the follow-up period. Figure 20 below shows the overlap between CAARMS and SPI-A criteria in those who converted to psychosis. The mean time to transition for people meeting both CAARMS and SPI-A criteria was 7.80 months (SD 9.44 months, 95% CI: 1.05, 14.05). Kaplan-Meier survival analysis indicates that all transitions occurred within 25 months of the baseline assessment and 80% occurred within the first 9 months. The sensitivity of the combined criteria was 0.53 (95% CI: 0.29, 0.75), specificity was 0.86 (95% CI: 0.76, 0.92), PPV was 0.45 (95% CI: 0.25, 0.67), NPV was 0.89 (955 CI: 0.79, 0.94), the positive LR was 3.93 and the negative LR was 0.57.

Psychosis at follow-up was significantly associated with a positive result on both CAARMS and SPI-A (X^2 (1, 102) = 13.32, $p < 0.001$). The odds ratio for

those meeting both SPI-A and CAARMS at-risk criteria, subsequently developing a psychosis was 6.57 (95% CI: 2.21, 19.53). This represents an increased odds ratio compared with when CAARMS (OR, 4.63) and SPI-A (COGDIS OR, 5.73) were considered individually.

Figure 20: Conversion by Baseline At-Risk Criteria



We tested the finding of Ruhrmann and colleagues (2010) that a positive result on both COGDIS and CAARMS results in greater sensitivity. Fifteen patients were deemed at risk by both CAARMS and COGDIS criteria at baseline, of these eight (53.33%) developed a psychosis and seven (43.75%) did not. The sensitivity of the combined COGDIS and CAARMS was 0.42 (95% CI: 0.20, 0.66), the specificity was 0.92 (95% CI: 0.83, 0.97), PPV was 0.53 (95% CI: 0.27, 0.79), NPV was 0.87 (95% CI: 0.79, 0.94), the positive LR was 4.99 and the negative LR was 0.63. Unlike Ruhrmann et al (2010) we did not find an increase in sensitivity with this combination of tests when compared with CAARMS or COGDIS individually (CAARMS 0.58, COGDIS 0.68), rather we found sensitivity reduced considerably. We did however find an increase in the specificity of the test (0.92) compared with CAARMS (0.77) and COGDIS (0.80). The positive likelihood was also

improved however, a likelihood ratio of 10 is considered to be the level at which a positive result would significantly indicate the presence of the disorder (Akobeng, 2007), therefore as the likelihood ratio remains low a positive result on both COGDIS and CAARMS cannot be seen as significantly indicating that conversion will occur.

Kaplan-Meier survival analysis of the COGDIS and CAARMS combination showed that six (75%) of those deemed at risk by CAARMS and COGDIS at baseline made the transition within 6-months, a further conversion occurred at month nine and the remaining patient converted at month 25.

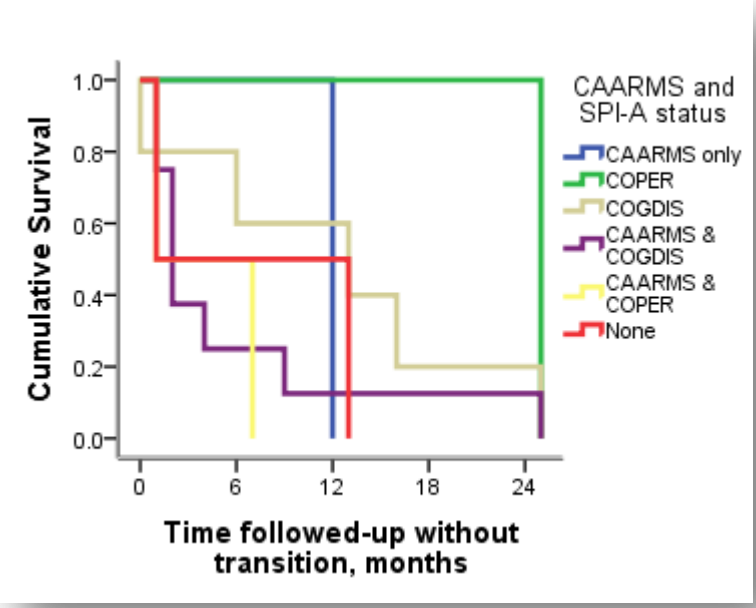
Psychosis at follow-up was significantly associated with a positive result on both CAARMS and SPI-A (COGDIS), X^2 (1, N = 102) = 137.98, $p < 0.001$. The odds ratio of patients meeting both COGDIS and CAARMS criteria developing a psychosis was 7.90 (95% CI: 2.39, 26.09) which was greater than for CAARMS (4.63) but less than for COGDIS alone (8.4).

When either the COGDIS or CAARMS at-risk criteria were satisfied the sensitivity of the test did improve. Forty-four patients were categorised as at-risk by either criteria and of these 16 (36.36%) converted to psychosis. Only three people not deemed to present a risk converted. The sensitivity was 0.84 (95% CI: 0.60, 0.95), specificity was 0.66 (95% CI: 0.55, 0.76), PPV was 0.36 (95% CI: 0.23, 0.52), NPV was 0.95 (95% CI: 0.85, 0.99) and the LR was 2.47.

Given that there was considerable overlap between the COGDIS and CAARMS criteria, we examined the baseline tests of converted cases more closely. There was only one converted patient deemed UHR+ that did not also satisfy either the COPER or COGDIS criterions. When their scores on the individual SPI-A items were examined, we noticed that quite a number were identified as traits rather than Basic Symptoms. It is possible therefore that there may have been an error in scoring the test. If this were the case, all transitions would have met either SPI-A COPER or COGDIS at baseline.

Kaplan-Meier survival analysis for the converted patients showed that those who met COGDIS and CAARMS criteria converted earliest, with 75% of patients meeting this criteria converting within 6 months, compared with 40% of those meeting COGDIS only. The only converted patient who did not meet SPI-A criteria at baseline converted at month 12 and the 2 patients who met the COPER criterion converted at 6 and 12 months (figure 21).

Figure 21: Kaplan-Meier Survival Curve by Baseline criteria



8.3.6 Influence of Schizotypy on Conversion

SPQ-A data was only available for 93 people and of these 49 people met criteria for schizotypal personality traits (an SPQ-A score of ≥ 39). Of these 15 converted to psychosis within the follow-up period and 34 did not. Two people deemed not to have schizotypal traits also developed a psychosis. The sensitivity of the SPQ-A was 0.88 (95% CI: 0.62, 0.98) and the specificity was 0.54 (95% CI: 0.43, 0.66), PPV was 0.31, (95% CI: 0.19, 0.46), NPV was 0.95, (95% CI: 0.83, 0.99) and the LR was 4.5. Psychosis at follow-up was significantly associated with a score of ≥ 39 on the SPQ-A X^2 (1, N=92) = 10.25, p = 0.001.

The mean SPQ-A score for those who converted to psychosis was 49.65 (SD 15.45, SE 3.74), higher than for those who did not convert (M = 36.01, SD 16.10, SE 1.87). The difference between the two means was statistically significant $t(89) = 3.17$, p = 0.002.

The mean time to conversion for schizotypal patients was 9.33 months (SD 9.45 months, SE 2.44) and 34.50 months (SD 8.07 months, SE 1.38) for non-schizotypal patients. This difference in mean conversion times was statistically significant, $t(47) = -9.55$, $p < 0.001$. Kaplan-Meier survival analysis showed that all transitions occurred within 25 months of the baseline assessment (figure 22) and the difference between the survival times of schizotypal and non-schizotypal patients was statistically significant (log-rank test, $p = 0.001$). The incidence rate for conversion for schizotypal patients at 6,12,18,24 and 30 months was 16.3%, 20.4%, 24.5%, 24.5% and 31.6% respectively (figure 23).

Figure 22: SPQ-A Kaplan-Meier Survival Analysis

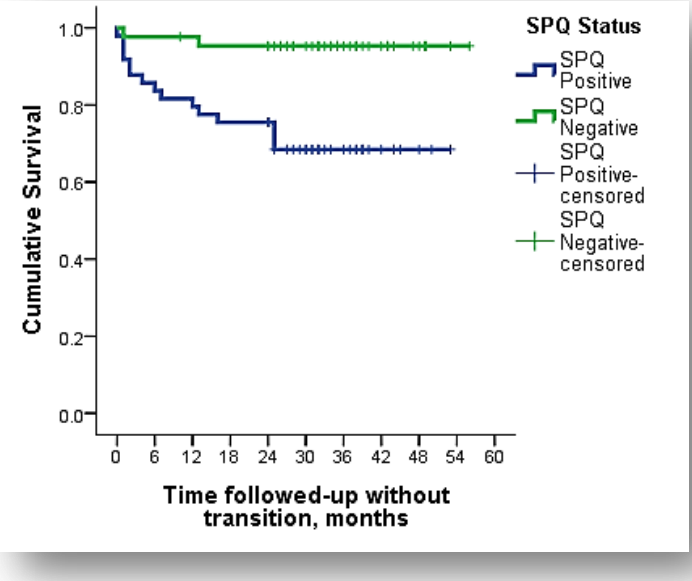
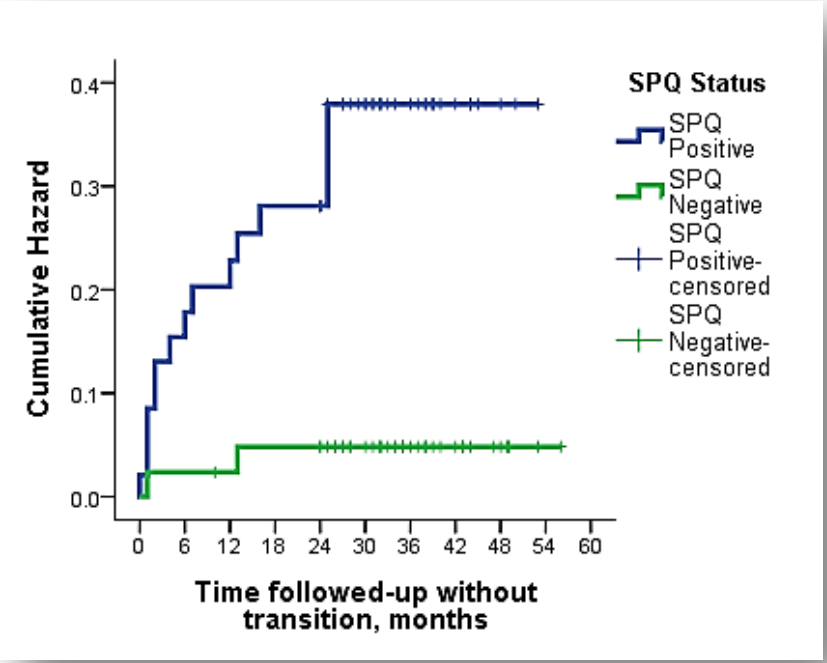


Figure 23: SPQ-A Kaplan-Meier Cumulative Hazard Plot



We conducted a Mann-Whitney U test to determine whether the mean scores in each of the SPQ-A factors (cognitive perceptual, interpersonal and disorganised) differed between those who converted and those who did not. The test showed that there was a highly significant difference between the mean Interpersonal and Disorganised factor scores in those who converted and those who did not (U= 288, p = 0.007, U = 298.50, p = 0.10). The difference between mean scores in the Cognitive Perceptual factor were not significant (U = 368, p = 0.081).

To test whether using SPQ-A to inform the vulnerability trait criterion of CAARMS improves the overall sensitivity and specificity of CAARMS, we removed the SPQ-A as a decision rule. This did not have any effect on the overall sensitivity, which suggests that the SPQ-A does not improve the sensitivity and specificity of the CAARMS.

8.3.7 Influence of Social Functioning on Conversion

The mean SOFAS scores at baseline were lower for those who converted (M = 52.63, SD 12.06, SE 2.77) than for those who did not (M = 63.13, SD 12.92, SE 1.45). The difference between the SOFAS baseline score of those who converted and those who did not was significant $t(97) = -3.22$, $p = 0.002$. The mean drop in functioning at baseline from premorbid level was greater for those who converted (M = 17.75, SD 16.26, SE 3.64) than for those who did not (M = 9.75, SD 15.53, SE 1.38). The difference in the mean drop in function between those who converted and those who did not was statistically significant $t(101) = 2.06$, $p = 0.05$. When the SOFAS decision rule was considered as a predictor of conversion in the absence of other instruments, it classified 32 patients as having an ARMS, of which 12 (37.5%) converted. The sensitivity of the SOFAS was 0.63 (95% CI: 0.39, 0.83), specificity was 0.76 (95% CI: 0.65, 0.84), PPV was 0.38 (95% CI: 0.22, 0.56), NPV was 0.90 (95% CI: 0.80, 0.96) and the LR was 2.63. The sensitivity and specificity of the SOFAS was superior to that of the CAARMS which were 0.58 and 0.77 respectively. When the SOFAS decision rule is removed from the CAARMS the sensitivity of CAARMS increases to 0.89 (95% CI: 0.65, 0.98) but the specificity drops considerably to 0.41 (95% CI, 0.30, 0.52). This indicates that SOFAS reduces the number of false positive predictions. Yung and Nelson (2011) explain that the 'close in' approach of combining state and trait factors within the CAARMS seeks to prioritise specificity over sensitivity, which the inclusion of SOFAS as a decision rule clearly does.

8.4 Post Hoc Exploratory Analysis

Post Hoc analysis of the data is important to enable new hypotheses to be developed and tested in subsequent research (Elliott, 1996). As these hypotheses only arise from this dataset, we cannot determine whether they can be generalised to the wider at-risk population. This can only be

established by further research, hence the rationale for separating this section from the main analysis.

8.4.1 Further Analysis of the Attenuated Symptom Criterion of CAARMS

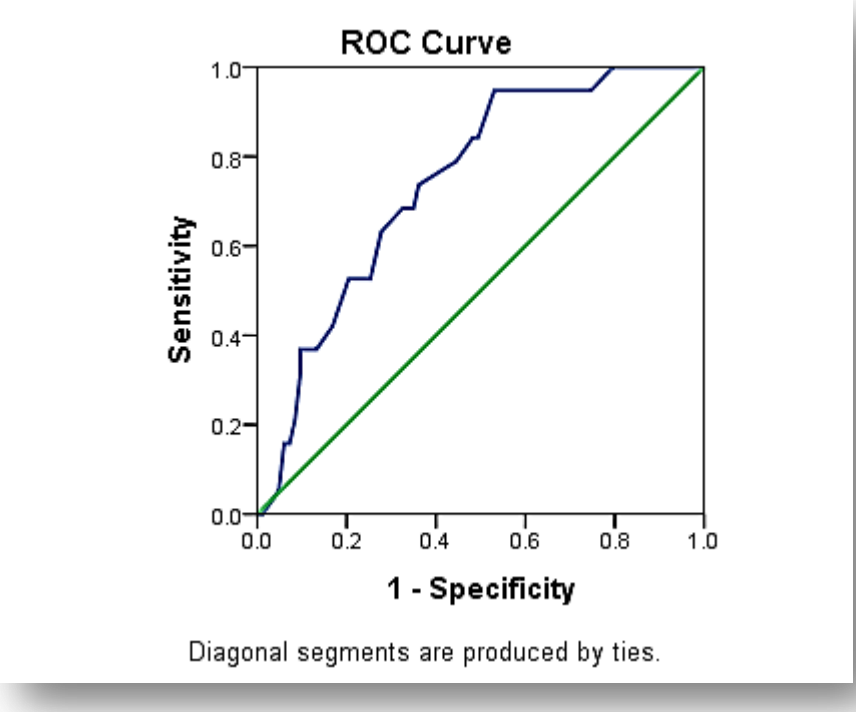
The attenuated symptom criterion of CAARMS is determined by a combination of scores on the global and frequency scales of four symptom subscales, unusual thought content, non-bizarre ideas, perceptual abnormalities, and disorganised speech. Currently, the attenuated criterion is satisfied if one of the subgroups meets defined thresholds in combination with a drop in functioning. We sought to investigate whether we could improve the sensitivity and specificity of the CAARMS by calculating the total score across all subscales and applying the most predictive cut-off score. Cut-off scores were established using ROC curve analysis. A ROC curve plots sensitivity versus 1-specificity and provides a visual representation of a tests accuracy. When interpreting a ROC curve the closer the curve is to the upper left corner, the greater the overall accuracy of the test. This also provides the optimum balance between sensitivity and specificity. The closer the curve gets to the 45° diagonal line the less accurate the test.

We calculated the sum of the global severity and frequency scores to determine the total attenuated symptom score. Using ROC curve analysis we were able to determine that a score of greater than or equal to 20.50 (figure 24) was the cut-off score that was closest to the upper left corner of the diagram and offered the optimum balance between sensitivity and specificity. The sensitivity of a score of ≥ 20.50 gave a sensitivity of 0.63 and a specificity of 0.72. When this new attenuated symptom threshold was used as part of the overall CAARMS, 28 people were identified as being UHR+. Of these 11 developed, a psychosis and 17 did not. The sensitivity of these new CAARMS criteria did not alter from previously (0.58) but the specificity increased slightly to 0.80 (95% CI: 0.69, 0.87). The new likelihood ratio increased slightly from 2.48 to 2.9.

A cut-off score of 20.5 would imply that more than one subgroup is required to predict onset as the maximum score is 11 for a subgroup category.

Currently, the CAARMS requires only one subgroup, in combination with a drop in functioning to meet the attenuated at-risk criterion. When we categorised patients as meeting 2 or more, 3 or more or 4, attenuated symptom subgroups, the two or more category was the only statistically significant predictor of conversion X^2 (1, N=102) = 4.39, p = 0.04. When this new criteria was included within the overall CAARMS decision rules the sensitivity and specificity were the same as the results for the cut-off score of 20.5, indicating that either criterion can be used. However, given that the new cut off score only resulted in a slight improvement in specificity it would not be worthwhile conducting a replication study. The current CAARMS attenuated symptom criterion decision rule yields almost the same results and is already validated.

Figure 24: ROC Curve of the CAARMS Attenuated Subgroup Total Scores.



8.4.2 Analysis of the Social Functioning Decision Rules of CAARMS

In order to determine the most predictive SOFAS cut-off scores we plotted two separate ROC curves for SOFAS functioning at baseline and drop in

functioning from pre-morbid level (figures 25 and 26). Again, we sought to determine a balance between sensitivity and specificity when determining the best cut-off score. A baseline SOFAS score of ≤ 52.50 a drop in SOFAS scores from pre-morbid level of ≥ 17.50 were found to provide the best balance between sensitivity and specificity. A baseline SOFAS score gave a sensitivity of 0.59 and a specificity of 0.73 and a drop in functioning of ≥ 17.50 gave a sensitivity of 0.58 and a specificity of 0.75. We then applied this to the CAARMS data in place of the existing SOFAS decision rules. In doing so, the new CAARMS identified 38 patients as UHR+ and 64 UHR- (the original CAARMS identified 30 as UHR+). Of these, 15 UHR+ and 4 UHR- patients converted to psychosis. The sensitivity of the CAARMS with the new SOFAS decision rule increased from 0.58 to 0.79 (95% CI: 0.54, 0.93) but the specificity decreased from 0.77 to 0.72 (95% CI: 0.54, 0.93), the PPV was 0.39 (95% CI: 0.24, 0.57), NPV was 0.94 (95% CI: 0.84, 0.98) and the LR was 2.82, OR 9.78. Overall, the revised SOFAS decision rule did improve the predictive ability of the CAARMS. However, whether the findings are generalizable beyond our dataset is unknown, only a replication study would determine this.

Figure 25: ROC Curve Analysis of SOFAS Scores at Baseline

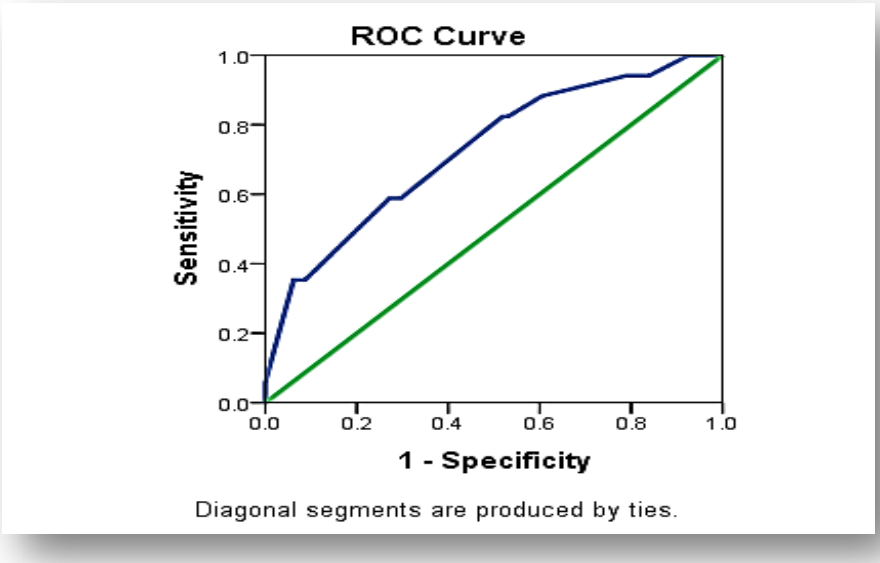
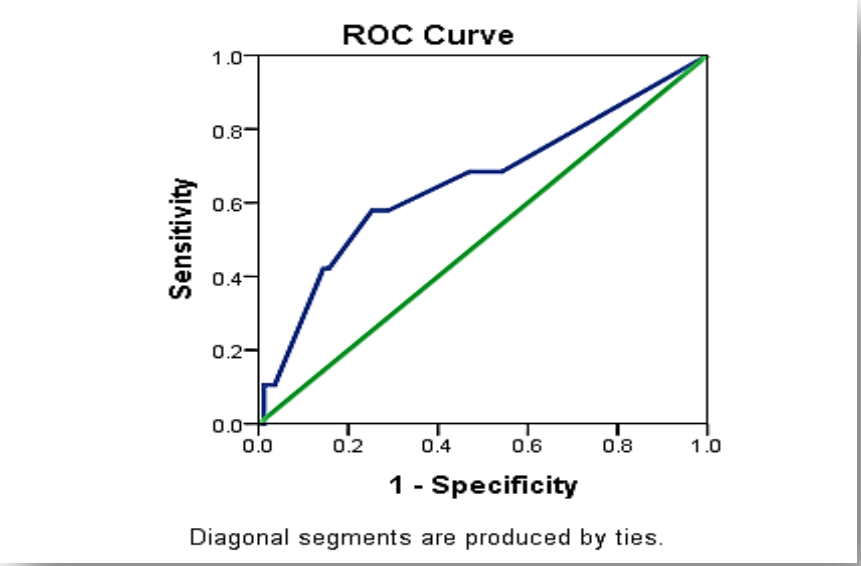


Figure 26: ROC Curve Analysis of Drop in Functioning At Baseline



8.4.3 Analysis of the Interaction between the SPQ-A and the CAARMS Attenuated symptoms

As discussed in section 8.3.3 eleven of the patients who converted to psychosis met the attenuated psychosis subgroup criteria. Of these, nine were also deemed to have schizotypal personality traits by the SPQ-A. We tested the difference between the mean SPQ-A total score and the mean total scores of the three SPQ-A factors (cognitive perceptual, interpersonal and disorganised) in those for whom the CAARMS attenuated symptom criterion was met or not met. Only the SPQ-A cognitive perceptual factor was found to have statistically significant higher scores in the attenuated symptom 'threshold met' group (p = 0.029) (table 18). The means of total SPQ-A scores in the attenuated symptom met and not met groups were 43.92 (SD 16.73, SE 3.21) and 36.42 (SD 16.57, SE 2.06) respectively.

Table 18: SPQ-A scores and Attenuated Symptoms

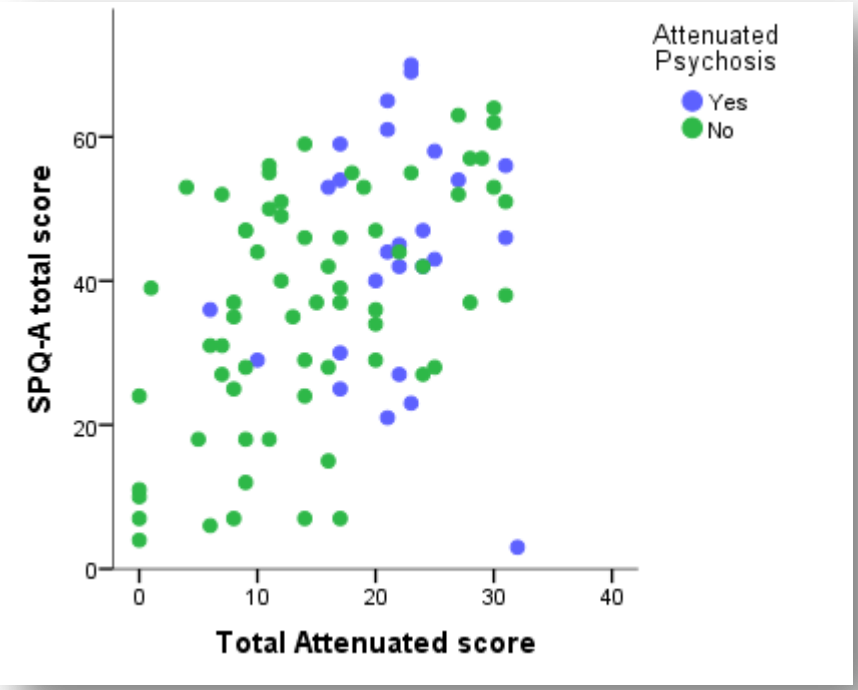
Attenuated Symptom Status	Sum of Squares	Mean Square	F	Sig.
SPQ-A Total Score	1046.787	1046.787	3.839	.053
SPQ-A Cognitive Perceptual	377.272	377.272	4.939	**.029**
SPQ-A Disorganised	72.845	72.845	2.675	.106
SPQ-A Interpersonal	178.612	178.612	2.703	.104

SPQ-A scores across the attenuated symptom subgroup scores showed a trend of higher rates with higher scores on attenuated symptoms. Total SPQ-A scores were significantly correlated with the attenuated symptom total score ($p < 0.001$, Spearman's *rho* = 0.449). The cognitive perceptual factor of SPQ-A significantly correlates with all the attenuated symptom subgroups (unusual thought content, $p < 0.001$, non-bizarre ideas, $p < 0.001$ perceptual abnormalities, $p = 0.009$ and disorganised speech, $p = 0.003$) (table 19). However, the disorganised and interpersonal SPQ-A factors did not significantly correlate with the perceptual abnormalities ($p = 0.344$ and $p = 0.126$ respectively).Higher scores on SPQ-A appear to show a trend for being positive on CAARMS attenuated symptoms (figure 27).

Table 19: Correlations between CAARMS Attenuated Symptom Subgroups and SPQ-A Factors

Spearman's rho		Total SPQ-A Score	Total SPQ-A Interpersonal	Total SPQ-A Disorganised	Total SPQ-A Cognitive Perceptual
Total CAARMS Attenuated Symptoms	Correlation coefficient	.449	.414	.439	.589
	Sig. (2-tailed)	.000	.000	.000	.000
	N	91	84	84	84
Total CAARMS Unusual Thought Content	Correlation coefficient	.365	.305	.415	.505
	Sig. (2-tailed)	.000	.005	.000	.000
	N	91	84	84	84
Total CAARMS Non-Bizarre Ideas	Correlation coefficient	.392	.381	.302	.471
	Sig. (2-tailed)	.000	.000	.005	.000
	N	91	84	84	84
Total CAARMS Perceptual Abnormalities	Correlation coefficient	.179	.168	.105	.283
	Sig. (2-tailed)	.089	.126	.344	.009
	N	91	84	84	84
Total CAARMS Disorganised Speech	Correlation coefficient	.292	.282	.362	.323
	Sig. (2-tailed)	.005	.009	.001	.003
	N	91	84	84	84

Figure 27: Scatter Plot of total SPQ-A Score and Total Attenuated Positive Scores in the Attenuated Psychosis Group



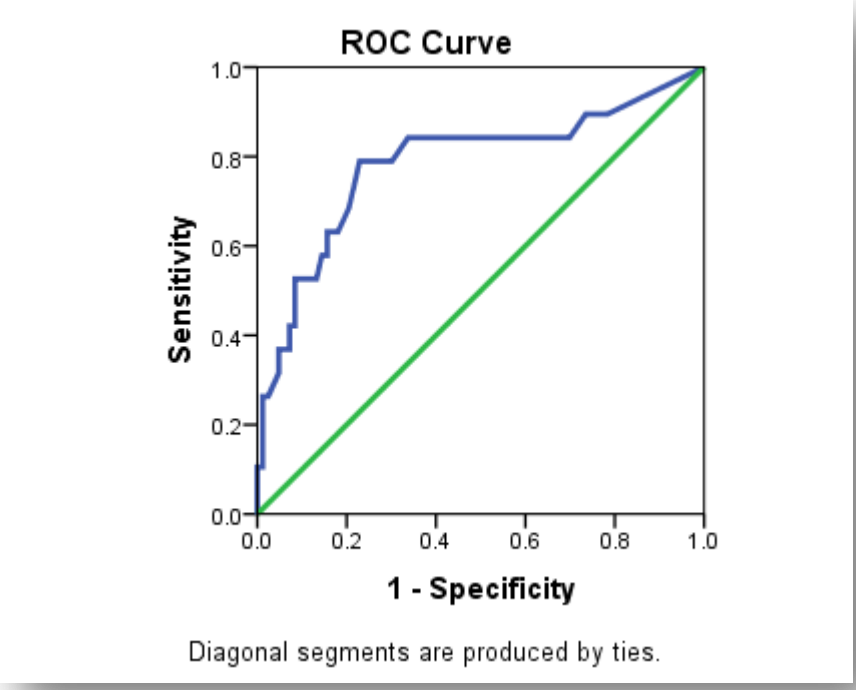
8.4.4 Analysis of SPI-A Total Scores

Currently, the SPI-A determines at-risk status through the satisfaction of either COPER or COGDIS criteria. However, given that, it is possible to calculate a total SPI-A score we wanted determine firstly whether the total SPI-A score is predictive of psychosis and secondly what the most predictive cut-off score for SPI-A would be.

Each SPI-A item is rated on a 0 to 9 scale, although only scores between 0 and 6 are used to determine basic symptom presence. The sum of scores between 0 and 6 gives the total SPI-A score. Psychosis at follow-up was found to be significantly associated with the SPI-A total score $t(100) = 3.47$, $p = 0.001$.

ROC curve analysis of the total SPI-A score found the area under the curve to be 0.78 (SE 0.07) and the optimum cut-off point for psychosis prediction was a score of 16.5 or greater (figure 28). The sensitivity of a cut-off score of ≥ 16.5 was 0.79 and specificity 0.77. This new cut-off score identified 34 people as having an ARMS and correctly predicted fifteen transitions. Four transitions were from the group deemed not to be at risk. The sensitivity of the new cut-off score is 0.78 (95% CI: 0.54, 0.93), specificity 0.77 (95% CI: 0.66, 0.85), PPV 0.44 (95% CI: 0.28, 0.62), NPV 0.94 (95% CI: 0.85, 0.98), LR 3.39. The original SPI-A criteria (either COPER or COGDIS), had a sensitivity of 0.84 and specificity of 0.51. While our new SPI-A total score cut-off score results in reduced specificity, sensitivity is considerably improved. This would offer a good balance between being able to detect those who will develop a psychosis and those who will not. Further research is required however, to test the generalizability of this new cut-off score, as it may only be relevant to our data.

Figure 28: ROC Curve of SPI-A Total Scores



8.4.5 Analysis of the SPQ-A Cut-Off Score

Raine (1991) asserts that cut-off scores can vary according to the population within which the SPQ-A is used. He suggests that researchers should establish their own cut-off points for the population. A ROC curve analysis (figure 29) showed that the most predictive cut-off point for the SPQ-A was a score of ≥ 51.50, which gives a sensitivity of 0.65 and a specificity of 0.78. However, the scatterplot in figure 30 shows that a cut-off score of ≥ 39 captured all but two conversions (17) with a sensitivity of 0.88 and specificity of 0.54; whereas the new cut off only captured 11 conversions. The challenge for the LEAD clinic is the balance between capturing all those at risk and ensuring the service is cost efficient. The cut-off score of ≥39 would potentially lead to a greater number of people being offered case management for a year than would actually convert to psychosis. The new cut-off of ≥ 50.50 offers a balance between sensitivity and specificity, which would seem sensible for the context within which it is used. However, the findings would need to be replicated in further studies before firm conclusions can be drawn.

Figure 29: ROC Curve Analysis of SPQ-A Scores

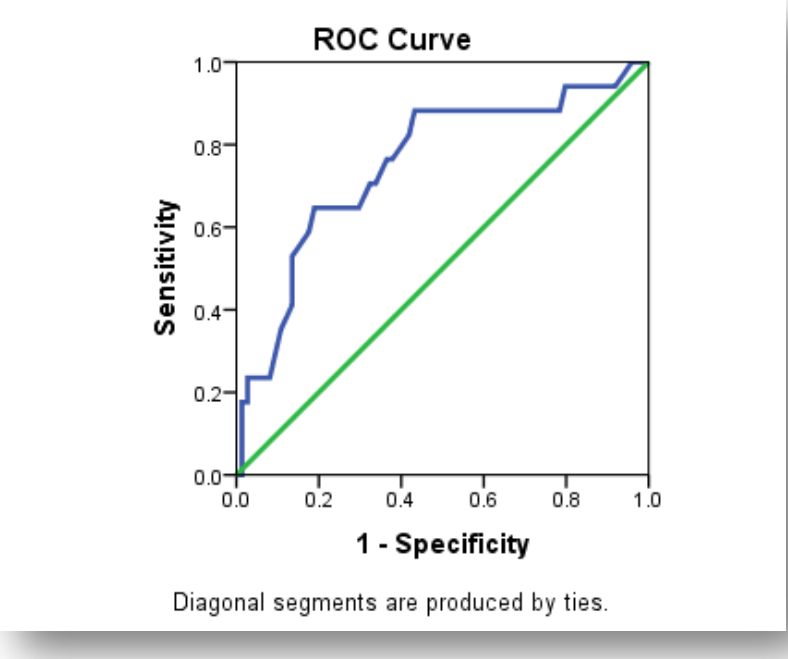


Figure 30: Scatter Plot of SPQ-A Scores and Transition

8.4.6 Influence of Cannabis use on Conversion

Cannabis use at baseline was not found to be a statistically significant predictor of psychosis, X^2 (1, N = 102) = 0.841, p = 0.359. However, when cannabis use was accompanied by an SPQ-A score of 39 or greater, conversion to psychosis could be significantly predicted, b = -1.52, Wald $X^2(1)$ = 0.581, P = 0.016. No other substances were found to significantly predict conversion, either by themselves or in combination with the SPQ-A.

8.4.7 Effect of the new cut-off scores for SPQ-A, SOFAS and Attenuated Symptoms on the Sensitivity and Specificity of the CAARMS

The new cut-off scores for SPQ-A (score ≥ 51.5), SOFAS (current score ≤ 52.5 and a drop in function from pre-morbid of ≥ 17.5) were tested as part of the overall CAARMS. To aid comparison the original CAARMS results are in brackets. The new CAARMS classified 33 (30) people as UHR+, of which 14(11) converted to psychosis. Five (8) people deemed UHR- also converted. The sensitivity of the new CAARMS was 0.74 (0.58) (95% CI: 0.49, 0.90), specificity was 0.77 (0.77) (95% CI: 0.66, 0.85), PPV 0.42 (95% CI: 0.26, 0.61), NPV 0.93 (95% CI: 0.83, 0.97) and the LR was 3.22. The revised CAARMS increases sensitivity without compromising specificity, which is a promising result and certainly merits further study to determine whether the results can be replicated.

8.4.8 Antidepressant Prescription at Baseline and Conversion

We explored whether we could detect similar findings to those of Cornblatt et al (2007), who in a naturalistic study found that none of the patients prescribed antidepressants developed psychosis. It is important to note at this stage that we did not track prescribing of and concordance with antidepressants over the course of the follow-up period. This analysis is only of prescription at baseline, which will clearly limit our findings. At baseline, 72 people were already prescribed either SSRI or NaSSa antidepressants by their General Practitioner (GP), 30 were not. Seventeen (23.61%) of the antidepressant group developed a psychosis compared with two (6.67%) of the no antidepressant group. This would not seem to suggest that antidepressants can delay or prevent conversion, however what we cannot possibly know is who would have converted but did not due to the effects of the antidepressant.

8.5 Improving the Efficiency of the LEAD Clinic Assessments

We used binary logistic regression with the aim of improving the efficiency of the LEAD clinic through the identification of the most efficient model of assessment. We performed the first analysis using the existing instruments and their established decision rules and cut-off scores. The second analysis aimed to explore the possibility of developing a new model of assessment based upon our post-hoc analysis. The new models of assessment could then form the basis of a future replication study.

8.5.1 Regression Analysis 1: Determining the Most Efficient Combination of Tests Using Established Decision Rules and Cut-off Scores

The first analysis aimed to determine whether any of the demographic factors (age, gender and ethnicity) or substance use history were associated with conversion to psychosis. We forced these interaction terms into the model using the enter method; with conversion to psychosis as the dependent variable. Removal from the model was set at $p < 0.1$. None of these variables were included in the final model as they were not statistically significant predictors of psychosis conversion.

Next we entered CAARMS, the SOFAS decision rule, SPI-A (COPER or COGDIS or both), COPER, COGDIS and SPQ-A (score ≥ 39) in a logistic regression analysis, using a forward stepwise method. Two statistically significant variables remained in the final model, a score of ≥ 39 on the SPQ-A and SPI-A COGDIS. The Nagelkerke R square for the model was 0.266, indicating that 26.6% of the variance can be explained by the model. COGDIS was the most significant predictor with an Exp(B) of 3.799 $b = 1.34$, Wald X^2 (1) = 4.75, $p = 0.029$. SPQ-A ≥39 also predicted psychosis with an Exp(B) of 5.760 $b = 1.75$, Wald $X^2(1) = 4.54$, $p = 0.033$.

We tested the new model on the data in two ways, firstly we tested the performance of the tests if both the SPQ-A and COGDIS criterions were met (combination 1) and then secondly if either were met (combination 2). Combination 1 identified 23 patients as having an ARMS of which 11 converted. Combination 2 identified 56 people as having an ARMS and 17 converted to psychosis. There are pros and cons of both combinations. Commination 1 has a good level of specificity but lower sensitivity and combination 2 has a higher sensitivity but a lower specificity. Combination 1 is similar to the performance of the CAARMS but the downside of this combination is the reliance of the SPQ-A on the literacy levels of the patient given that it is a self-report measure. Around 9% of our referrals do not have sufficient literacy skills to complete the SPQ-A. Combination 2 would be subject to the same limitation as combination 1 with the additional negative consequence of 69.64% of the people deemed to have ARMS by the criteria never converting. This would not improve the efficiency of the clinic. It would make it less efficient.

Table 20: Summary Table for Test Combinations (SPQ-A and COGDIS)

	Sensitivity	Specificity	PPV	NPV	LR
SPQ-A and COGDIS	0.57	0.86	0.48	0.90	4.07
SPQ-A or COGDIS	0.89	0.53	0.30	0.96	1.89

8.5.2 Regression Analysis 2: Determining the Most Efficient Combination of Tests Using New Decision Rules and Cut-off Scores

The next step was to determine whether we could construct a new model based upon our post hoc analysis. We used a forward likelihood ratio method and entered the following into the regression model:

1. CAARMS Attenuated symptoms (total score cut-off of ≥ 20.5)
2. SPI-A (total score cut-off of ≥ 16.5)
3. COGDIS
4. New SOFAS decision rule (current functioning score of ≥ 52.5 or a drop of ≥ 17.50 SOFAS points from pre-morbid level)
5. SPQ-A (total score cut-off of ≤ 51.5)
6. First degree relative
7. BLIPS
8. SPQ-A (cut-off of ≥ 39) with an interaction with current cannabis

The variables that remained in the final model were SPQ-A (with a cut-off of ≥ 51.5), SPI-A (with the total score cut-off of ≥ 16.5) and the new SOFAS decision rule (table 21). The Nagelkerke R square for the model was 0.446, indicating that 44.6% of the variance could be explained by the model.

Table 21: Logistic Regression Model

	B	df	Wald	ExpB	Sig.
SPQ-A ≥ 51.5	-1.85	1	7.58	0.157	0.006
SPI-A Total Score ≥ 16.5	-1.88	1	7.36	0.152	0.007
New SOFAS Decision Rules	-1.51	1	3.92	0.221	0.048

We tested four combinations of the model to determine their sensitivity, specificity, PPV, NPV and likelihood ratios:

- **Combination 1:** All three criterions met (SPI-A, **and** SOFAS **and** SPQ-A)
- **Combination 2:** SPQ-A **and** SPI-A criterions met but SOFAS thresholds are **not**
- **Combination 3:** SPQ-A **or** SPI-A criterions met **and** the SOFAS thresholds are met
- **Combination 4:** SPQ-A **or** SOFAS criterions met but the SOFAS thresholds are **not**.

The results are summarised in table 22. As can be seen from the table, patient's meeting combination 1 criteria (SPI-A total score and SPQ-A and SOFAS thresholds) are 53 times more likely to develop a psychosis than those who do not. While promising this is only applicable to our dataset, whether it is generalizable to the wider at-risk population can only be determined through further research. It is likely that only small numbers of people will satisfy this criterion; given that in our sample collected over 3 years only 10 people met this criteria.

When SOFAS thresholds are not satisfied the likelihood ratio reduces to 8.7, indicating that SOFAS plays a key role in improving the specificity of the tests. Combination three (SPQ-A or SPI-A and SOFAS) offers the best sensitivity and specificity for determining which patient's should receive case management from the EIS. This combination of tests would result in only 14 people who did not develop a psychosis receiving case management; slightly less when compared with the current LEAD protocol, which uses CAARMS to determine case management. The use of the CAARMS resulted in 19 people receiving case management who did not develop a psychosis.

Table 22: Summary Table for Test Combinations

	Sensitivity	Specificity	PPV	NPV	LR
Combination 1	0.53	0.99	0.90	0.90	53
Combination 2	0.52	0.94	0.69	0.89	8.7
Combination 3	0.79	0.83	0.52	0.95	4.65
Combination 4	0.89	0.61	0.37	0.96	2.28

8.6 Discussion

This chapter presented the follow-up analysis of 102 non-psychotic help-seeking patients referred to the LEAD clinic between January 2008 and December 2011. The analysis addressed all five of the service evaluation aims. Firstly, we established that 18.63% (n=19) of patients who fulfilled the criteria for inclusion developed a psychosis by the end of the follow-up period. Of these 17 were deemed to have an ARMS at baseline and two were not. SPI-A correctly identified 16 (84.21%) of the conversions compared with CAARMS which correctly identified 11 (57.89%). The sensitivity and specificity of CAARMS were 0.58 and 0.77 respectively and for SPI-A were 0.84 and 0.51 respectively. As can be seen SPI-A demonstrated greater sensitivity but CAARMS had superior specificity. When examined individually the COPER criterion was not a significant predictor of psychosis conversion while the COGDIS criterion was. The sensitivity and specificity of COGDIS were 0.68 and 0.80 respectively. From this part of the analysis, we can determine that the COPER criterion appears to be a redundant part of the overall SPI-A examination. If we only used the COGDIS criteria, we could reduce the test to nine questions, which would considerably improve the time efficiency of the clinic. However, an earlier study by the author of the SPI-A (Schultze-Lutter et al., 2007b) does not support these findings as she found no difference in the overall percentage of conversions predicted by either criterion.

We examined whether combining UHR and BS instruments has an additive effect and improves predictive ability. The results of this part of the analysis found that when patients satisfied both the CAARMS and COGDIS criteria the specificity increased to 0.92, and the sensitivity reduced to 0.42. When either COGDIS or CAARMS criteria were satisfied, the sensitivity increased to 0.89. However, the specificity reduced to 0.53. This analysis did not fully support our first hypothesis that combining the SPI-A assessment with the CAARMS will result in greater sensitivity and specificity than when the CAARMS or SPI-A are evaluated individually; an increase in one is at the expense of the other. The COGDIS and CAARMS combined criteria does

however have clinical utility, if used to determine the nature of the follow-up offered to patients. Patients who meet both criteria have a 56% probability of converting to psychosis compared with 19% for patients who do not meet any of the criteria, 37% for those who satisfy the CAARMS criteria, and 43% for those who satisfy the COGDIS criterion.

We tested our second hypothesis that the SPQ-A as a measure of schizotypy would improve the overall sensitivity of the CAARMS. In order to test this we removed the SPQ-A from the CAARMS decision rules and found no change in sensitivity and specificity. We therefore concluded that our hypothesis was incorrect. However, we did find a statistically significant correlation between the attenuated symptoms criterion and the SPQ-A ($p < 0.001$, Spearman's *rho* = 0.449). It appears that rather than contributing to the assessment of vulnerability SPQ-A is in fact tapping into attenuated symptoms.

When the SPQ-A is examined as a predictor of psychosis onset 15 (78.95%) conversions were correctly identified with a sensitivity of 0.88 and specificity 0.54. This was similar to the overall performance of the SPI-A when patients met either of the COPER or COGDIS criterions (0.84, 0.51). Logistic regression analysis of the original clinic instruments and their respective decision rules found that only COGDIS and the SPQ-A remained in the final model as statistically significant predictors of psychosis. However, when we tested the model on our dataset the resultant sensitivity (0.56) was lower than when COGDIS was considered individually (0.68). Specificity slightly improved from 0.80 to 0.86, as did the likelihood ratio (from 3.4 to 4.07).

To determine whether we could develop a more predictive model for use in the clinic we conducted a logistic regression analysis of the data using the new cut-off scores established by the post-hoc analysis for SOFAS, SPI-A and SPQ-A. The only statistically significant variables that remained in the final model were SPQ-A (with a cut-off of ≥ 51.5), SPI-A (with the total score cut-off of ≥ 16.5) and the new SOFAS decision rule (table 19). We tested four combinations of the tests and found that the sensitivities and specificities all had clinical utility. When the patients met all of the criteria the sensitivity was

0.53 and sensitivity 0.99, which gave a likelihood ratio of 53. While promising, further testing of this model is required before any firm conclusions can be drawn; it may be of no use beyond this dataset. However, it certainly merits further investigation. The most clinically promising combination of tests was either SPQ-A (with a cut-off of ≥ 51.5) or SPI-A (with the total score cut-off of ≥ 16.5) and the new SOFAS decision rule. This combination had a sensitivity of 0.79 and 0.83, which would offer a good balance between detecting those at risk and not offering care co-ordination to too many people that are false positives.

In order to ensure the appropriate duration of the 'watching brief' (Department Of Health, 2001) period, the final aim of the service evaluation was to determine time to transition. All transitions occurred within 25 months of follow-up; however, 70% occurred within the first 12-months. It would therefore seem reasonable to continue the current EIS policy of a 12-month follow-up period for those deemed to present a risk of psychosis.

Discussion

CHAPTER 9: Discussion and Conclusions

Chapter 9: Discussion and Conclusions

9.1 Introduction

The thesis set out to determine how well the Basic Symptoms and Ultra-High Risk approaches are able to predict psychosis onset. The first part of the thesis involved a systematic review with meta-analysis of the literature. The aim of the review was to identify all available psychopathology-based instruments for the detection of at-risk mental states and evaluate the sensitivity and specificity of the instruments through meta-analysis. The second part of the thesis concerned a service evaluation of the accuracy of the current predictions made within the Lancashire Early Assessment and Detection (LEAD) clinic, which uses both the Basic Symptom and UHR approaches.

This chapter aims to discuss the findings of both the systematic review and service evaluation from both a research and clinical perspective. The discussion will also address the two service evaluation hypotheses a) that combining the SPI-A assessment with the CAARMS will result in greater sensitivity and specificity than when the CAARMS or SPI-A are evaluated individually, b) the use of the SPQ-A as a measure of schizotypy will increase the overall sensitivity and specificity of the CAARMS.

9.2 Summary of Findings

9.2.1 Study One: The systematic Review with Meta-Analysis

The systematic review with meta-analysis described in Chapter 6 addressed the first aim of the thesis, which was to identify all available psychopathology based instruments for the detection of at risk mental states and evaluate the sensitivity and specificity of the instruments through meta-analysis.

The review included fifteen studies, describing three approaches to psychosis prediction: the Basic Symptom, Ultra-High Risk and a Stepwise

Screening approach. The Stepwise Screening approach (Riecher-Rossler et al., 2007), uses the Basel Instrument for Psychosis (BSIP) in conjunction with the BPRS (Overall and Gorham, 1962). The BSIP is a 46-item checklist based on the DSM-III-R (American Psychiatric Association, 1987) criteria for prodromal symptoms and other factors drawn from the literature such as social decline, substance use, genetic risk, and previous psychiatric disorders. Meta-analysis of this approach was not possible as the literature search only located one study reporting PPV of 0.32.

It was not possible to model the data with a bivariate random-effects model as only two UHR studies (Yung et al., 2006b, 2008, Miller et al., 2003a), and one basic symptom study (Klosterkotter et al., 2001b) reported data on the follow up of both those at risk and those not at risk. The remaining 12 studies only completed follow-up evaluations on patients deemed to be at risk, which restricted meta-analyses to estimating a positive predictive value.

Considerable heterogeneity was found across studies (UHR: Q=86.9*; df*=11*; p*<0.001 and I^2 =87% and Basic Symptoms*: Q*=95.6*; df=3; p*<0.001 *and* I^2 =97%). Overall, the meta-analysis found that the differences in the PPV between Basic Symptom and UHR approaches were not statistically significant (Basic Symptoms: 0.34: 95% CI: 0.15, 0.61, UHR: 0.25 95% CI: 0.18, 0.33). There was also emerging evidence that combining the two approaches improves the sensitivity and specificity. Ruhrmann et al. (2010) found that the sensitivity for patients meeting both COGDIS and UHR criteria was higher than for patients meeting either COGDIS or UHR criteria individually (COGDIS = 0.03, UHR = 0.30, both = 0.68).

9.2.2 Study Two: The LEAD Clinic Service Evaluation

The service evaluation discussed in chapters 7 and 8 addressed the second broad aim of the thesis i.e. to establish the accuracy of the current predictions made within the Lancashire Early Assessment and Detection (LEAD) Clinic, which uses both the Basic Symptom and UHR approaches.

We also sought to test two hypotheses 1) Combining the SPI-A assessment with the CAARMS will result in greater sensitivity than when CAARMS or SPI-A are evaluated individually, 2) the use of the SPQ-A as a measure of schizotypy will increase the overall sensitivity and specificity of the CAARMS.

The LEAD clinic conducted 174 assessments between January 2008 and December 2011. Fifty-seven patients were excluded from the follow-up evaluation as they already met the CAARMS threshold for psychosis and a further 14 were excluded as they were prescribed a therapeutic dose of an antipsychotic mediation. One patient was excluded at follow-up as they developed a psychosis within two weeks of assessment. Sixty-four at-risk and 38 not at-risk patients were subject to the follow-up evaluation.

Overall, the findings of the service evaluation were promising with 26.56% of referrals to the LEAD clinic correctly identified as being at risk of psychosis. The SPI-A COGDIS criterion had the best conversion rate of 43.33% with a sensitivity of 0.68 and specificity of 0.80, compared with a conversion rate of 36.67% for CAARMS UHR+. The sensitivity of the CAARMS was 0.58 and specificity 0.77. The COPER criterion was not found to be a statistically significant predictor of psychosis conversion $X^2(1, N = 102) = 1.16$, $p = 0.282$. The sensitivity of COPER was 0.16 and sensitivity 0.72. When patients met both the COGDIS and CAARMS criteria, the conversion rate was 53.33% overall sensitivity was 0.42 and specificity was 0.92. This represented a reduced sensitivity when compared to both COGDIS and CAARMS individually. This did not support our hypothesis that a combination of both approaches would improve sensitivity.

All conversions occurred within 25 months of the baseline examination with 70% occurring in the first 12-months. The mean time to conversion in the UHR group was 6 months, with 63.64% of transitions occurring before 6 months and 90.01% (10) before 12 months. The mean time to conversion was slightly longer for COGDIS, 8.15 months with only 38.46% (5) converting before 6 months. By 12-month follow-up 69.23% (9) had converted.

We found a correlation between the SPQ-A and the attenuated symptom criterion of CAARMS.($p < 0.001$, Spearman's *rho* = 0.449). A SPQ-A total score greater than or equal to 39 was also significantly associated with psychosis at follow-up X^2 (1, N=92) = 10.25, $p = 0.001$.The sensitivity of the SPQ-A was 0.88 and the specificity was 0.54. However, we were not able to prove our hypothesis that the SPQ-A would improve the sensitivity and specificity of the CAARMS. When the SPQ-A was removed as a decision rule within the CAARMS the sensitivity and specificity of the CAARMS did not alter.

In order to improve the efficiency of the clinic, we performed a Logistic regression analysis of all the instruments used in the clinic (CAARMS, SOFAS, SPI-A and SPQ-A). This analysis found that only COGDIS and SPQ-A (score ≥ 39) were statistically significant predictors of conversion ($p = 0.029$ and $p = 0.033$ respectively). CAARMS and SOFAS did not remain in the model. When tested on the data, the sensitivity for patients satisfying both SPQ-A and COGDIS criteria was 0.57 and the specificity was 0.86. When either of the two criterions was satisfied, the sensitivity was 0.89 and specificity 0.53. Neither of the two combinations performed better than COGDIS alone (Sensitivity 0.68, Specificity 0.80).

While cannabis use at baseline was not found to be a statistically significant predictor of psychosis at follow-up (X^2 (1, N = 102) = 0.841, $p = 0.359$), when accompanied by an SPQ-A score of 39 or greater, conversion to psychosis could be significantly predicted, $b = -1.52$, Wald $X^2(1) = 0.581$, $P = 0.016$, indicating an important interaction effect.

ROC curve analysis of the SPI-A total score found the most predictive cut-off score for our dataset was greater than or equal to 16.5. When tested on our dataset the sensitivity of the new cut-off score was 0.78 and specificity 0.77. If replicated in further research this cut-off would have considerable clinical

utility, as it would offer a good balance between being able to detect those who will develop a psychosis and those who will not.

ROC curve analysis was also used to establish the most predictive cut-off scores for the SOFAS. These were found to be a baseline score of ≤ 52.5 or a drop in functioning from pre-morbid level by ≥ to 17.5 points. When these cut-off scores were used as new decision rules for the CAARMS the sensitivity increased from 0.58 to 0.74 and specificity remained the same (0.77) was 0.77. We then tested the sensitivity and specificity of the CAARMS when the new cut off scores for SPQ-A and SOFAS were used. This reduced the sensitivity to 0.74 and specificity again remained the same at 0.77.

Finally, based upon our post hoc analysis we constructed a new predictive model. We entered all the new cut-off scores for the instruments into a binary logistic regression, (forward likelihood ratio method) and the following variables were found to be the most predictive:

- SPQ-A (with a cut-off of ≥ 51.5),
- SPI-A (with the total score cut-off of ≥ 16.5)
- SOFAS (a baseline score of ≤ 52.5 or a drop in functioning from pre-morbid level by ≥ to 17.5 points)

We tested the new model on our dataset and found the sensitivity of the model when all three criteria were satisfied to be 0.53 and the specificity to be 0.99, which gave a likelihood ratio of 53. This means that patients meeting all three criteria are 53 times more likely to develop a psychosis than those who do not. If replicated in future studies this finding could offer possible opportunities for treatments of the prodrome. However, it is likely that this is not generalizable beyond our dataset so further research is required to test the model. When SOFAS thresholds were not satisfied the likelihood ratio of the model decreases to 8.7, indicating that social functioning is a likely mediating factor in conversion.

9.3 Strengths and Limitations of the Systematic Review with Meta-Analysis

The main limitation of the review was the inability to perform a meta-analysis of sensitivity and specificity due to the small number of studies providing follow-up data of both at-risk and not-risk patients. A further limitation of the review was the finding of considerable heterogeneity across studies. To test the percentage of total variation across studies resulting from heterogeneity we used the I^2 statistic (Higgins et al., 2003); this was 81% for the Basic symptoms studies and 87% for the UHR studies. There are a number of possible explanations for the sources of this heterogeneity for example, sample sizes, age of subjects, variation of instruments and reference tests, the interpretation of results and socio-demographic factors. To account for this high degree of variability between studies a random effects method of meta-analysis was used. Dinnes et al. (2005) assert that it is particularly important to use methods that take account of variability when conducting systematic reviews of diagnostic test accuracy as considerable variation often exists between studies.

Only published studies written in English were included in the analysis so the potential for publication bias could not be excluded. Publication bias arises as studies reporting positive results have a better chance of being submitted and subsequently published. An analysis of publication bias in a sample of reviews from the Cochrane Database of Systematic Reviews found a clear indication of publication bias with a fifth having a strong indication (Sutton et al., 2000). The Cochrane Collaboration suggests that funnel plots should be used to investigate the extent of publication bias in the review (The-Cochrane-Collaboration, 2002). Funnel plots were not used in the review therefore the extent to which it is subject to publication bias is unknown.

The strength of the review was the quality of the meta-analysis; the authors did not try to calculate sensitivity and specificity in the absence of data for the test negative group. A recent similar review of the same studies (Chuma and

Mahadun, 2011), calculated sensitivities and specificities in the absence of this data from factors such as demographic data, family history and functioning.

Treatment trials were excluded from the review to avoid the selection biases often introduced in randomised controlled trials. In addition, a large multi-centre study in North America (NAPLS; Woods et al, 2009) was excluded to prevent double counting with studies likely to have been included in this study. However, this can also be seen as a limitation as some valuable data may have been missed as a result.

9.4 Strengths and Limitations of the Service Evaluation

The main limitation of this study is the choice of a service evaluation methodology. Service evaluations are not scientifically robust methodologies that can prove any findings definitively. We did not conduct a power analysis to determine the sample size; rather the sample was collected between two clinic time points. The author of this thesis carried out the notes-based follow-up analysis, which could have introduced researcher bias. She was not blind to the outcome of the initial baseline assessment and had conducted a large proportion of them.

To check the accuracy of the decision regarding conversion the author (CJ) asked an EIS psychiatrist to double check the records of patients she deemed to have converted. As the psychiatrist did not evaluate the case notes of non-converters, some conversions may have been missed. The use of a notes-based methodology can also be subject to recording error and the subjectivity of the entry author. This again could have introduced bias. Face-to-face evaluation of the patients using a reference standard would have been preferable.

The assessments carried out by the LEAD clinic did not include a measure of affect. A recent study of attachment and emotional dysregulation in UHR young people (Gajwani et al., 2013), found that 80% were insecurely

attached and mainly expressed anxiety regarding relationships, such as a fear of being rejected or unloved. Overall, the findings of study found that the UHR sample may resemble an affectively disturbed cohort. The Netherlands Mental Health Survey and Incidence Study (NEMESIS) (Krabbendam et al., 2005), also found that conversion to psychosis in those who reported hallucinatory experiences was higher for those who reported depression than for those who did not. Given that depression could indicate an increased risk of psychosis and is one of the 10 symptoms identified by the ABC Schizophrenia Study (Hafner et al., 1998) to precede psychosis onset, it would have been useful to include a measure of affect.

Patients deemed to present a risk of psychosis were offered 12-months case management by the EIS, which also included access to CBT. We did not examine how many people received CBT for affective disorders during the course of the follow-up period; however, clinically I am aware several did. CBT has been found to reduce depression and fear associated with voice hearing resulting in a subsequent reduction in psychotic symptoms (Chadwick and Birchwood, 1994), therefore, this could have possibly prevented or delayed conversion in some cases. However, a recent multisite randomised controlled study of CBT for people at risk of psychosis (Morrison et al., 2012) found that CBT did not significantly reduce conversion to psychosis.

One of the benefits of using a service evaluation methodology is that it is not subject to the selection biases faced by research studies. All of the patients assessed in the clinic that met the inclusion criteria were subject to follow-up evaluation. As the Lancashire Care NHS Foundation Trust is the primary provider of secondary mental health services in Lancashire, anyone residing in the area who converted would have received care from one of our services. Therefore, their conversion would be captured in the clinical record. However, patients not remaining under the care of Lancashire Care NHS Foundation Trust who moved out of the Lancashire area may have been lost to follow-up; we would not know from their records that they had moved. Therefore, it is possible that we missed some conversions.

We considered the limitations due to the lack of reliability testing of the instruments used. We did not formally measure concordance levels across our assessors, which may have introduced variation in the assessment quality and resultant bias. However, both CJ and her supervisor Professor Max Marshall (MM) did receive training in the use of the SPI-A from Frauke Schultze-Lutter who found them both to be concordant with her assessment decisions. CJ and MM used the CAARMS training DVD to establish their concordance and CJ attended a master-class with the CAARMS author Alison Yung. CJ then trained all of the clinic assessors in the use of the instrument and either CJ or MM supervised the other assessors until they achieved concordance. However, concordance was not formally measured.

To date the majority of the studies of both UHR and basic symptom approaches have been conducted in highly specialised clinics. This is one of the first evaluations of the approaches in a representative UK mental health setting. While, not subject to the methodological rigour of research studies it does allow an evaluation of how valid the instruments are in routine clinical settings.

9.5 The Clinical and Research Context of the Overall Findings

This section reviews the findings of the meta-analysis and service evaluation in the context of current research knowledge, future research opportunities, and the implications for clinical practice.

9.5.1 The Context of the Findings from the Systematic Review with Meta-Analysis

Our findings from the meta-analysis differed slightly from two other reviews conducted in this field (Chuma and Mahadun, 2011, Fusar-Poli et al., 2012). Both of these studies included the NAPLS multi-centre study (Woods et al., 2009), which will have inevitably increased the sample size with which meta-analysis was conducted. Chuma and Mahadun (2011) reported sensitivity

and specificity calculated from adjunctive criteria such as demographic data, rather than a 2 x 2 table which makes comparison with our review difficult. However, like our review Fusar-Poli et al. (2012) calculated pooled PPVs. The overall PPV from our random effects model of UHR criteria was 0.25 (95% CI: 0.18, 0.33) compared with a similar result of 0.27 (95% CI: 0.26, 0.30) by Fusar-Poli et al. (2012). The estimate of PPV for basic symptom studies was considerably higher in the Fusar-Poli et al. (2012) review at 0.49 (95% CI: 0.42, 0.56) when compared with our estimate of 0.34 (95% CI: 0.15, 0.61). One explanation for this difference is that they located an additional study by Koutsouleris et al. (2009) that our search strategy missed.

There has been a suggestion that basic symptoms precede the onset of attenuated symptoms and characterise the earlier stage of the prodrome whereas attenuated symptoms characterise the later stage (Fusar-Poli et al., 2013, Schultze-Lutter, 2009b). Our review does not indicate that this is the case given that the transition rates between the two criteria are not statistically different, however, as we did not specifically examine the time to transition we cannot draw any firm conclusions.

The findings from all three reviews indicate that both the basic symptom and UHR approaches are valid predictors of psychosis conversion. In addition, their predictive ability is maintained in centres worldwide. There are fewer studies of the basic symptom approaches, which may slightly inflate the overall PPV, however it would seem that it performs at least as well as and if not better than the UHR approach. Further research into the basic symptom approach is required if we are to determine how well it compares to the performance of the UHR approach. In addition, to evaluate fully the diagnostic validity of both concepts follow-up studies of both at-risk and not at risk patients are required.

9.5.2 The Context of the Findings from the Service Evaluation

The main findings of the study relate to the predictive ability of the CAARMS UHR approach and the SPI-A Basic Symptom approach. The CAARMS PPV was 0.37, higher than the pooled estimate of 0.25 (95% CI: 0.18, 0.33) from the meta-analysis. Notably it also fell outside the confidence intervals for PPV in the meta-analysis. This supports the meta-analysis finding of considerable heterogeneity between studies. The PPV for the SPI-A varied dependent upon the criteria used, i.e. COPER or COGDIS or either. For COPER PPV was 0.12, COGDIS, 0.43 and when either criterion was satisfied, it was 0.29. The pooled Basic Symptom PPV from our meta-analysis was 0.34 (95% CI: 0.15, 0.61). With the exception of COPER, our results fell within the confidence intervals for the meta-analysis. It is worthy of note that two studies in the meta-analysis (Ruhrmann et al., 2010, Ziermans et al., 2011) used the COGDIS criterion which we found resulted in a higher PPV.

A comparison between the performance of the CAARMS and the COGDIS criterion appears to indicate that the COGDIS criterion is the most predictive. The sensitivity and specificity of CAARMS were 0.58 and 0.77 respectively and for COGDIS were 0.68 and 0.80 respectively. The COGDIS criterion also correctly predicted more conversions that the COPER criterion (13 compared with 3). These findings differed from those of Schultze-Lutter et al (2007b) who did not find any difference in the overall percentage of conversions between the two criterions.

Patients meeting CAARMS criteria for UHR had a 37% probability of developing psychosis compared with a probability of 43% for COGDIS. There was considerable overlap between the two criteria as 72.73% of converted CAARMS UHR+ patients also satisfied the COGDIS criterion and similarly 61.54% of converted COGDIS patients satisfied CAARMS UHR+ criteria. Further analysis showed that only one converted CAARMS UHR+

patient did not meet either the COPER or the COGDIS criterions at baseline. However, when we examined the SPI-A scores of this one CAARMS UHR+ patient we noticed that they had a considerable number of items rated as traits. Had this not been the case they would have satisfied at least the COPER criterion. This leads us to question whether the scoring was inaccurate for this person. Regardless, what is interesting is that at baseline examination we noted that while there was some degree of overlap between the two tests, SPI-A captured a broader cohort. This remained true for the converted cohort as five patients met COGDIS but not CAARMS and only one patient did not meet either of the SPI-A criterions. However, as we did not repeat any of our measures it is not possible to determine whether those in the COGDIS group went on to develop attenuated psychotic symptoms over the course of the follow-up period. Although we did establish that those who met SPI-A (COGDIS or COPER) and CAARMS converted sooner than those who met just the COGDIS criterion. By 6 months 2 out of 5 (40%) COGDIS patients had converted compared to 7 out of 10 (70%) patients satisfied both the CAARMS and SPI-A (either COPER or COGDIS) criteria. This would seem to suggest that patients experiencing both Basic and Attenuated Symptoms are closer to the point of transition i.e. in the Late Initial State of the prodrome, whereas those meeting the COGDIS and COPER criterions only are in the Early Initial State of the Prodrome.

When unaccompanied by attenuated psychotic symptoms, the COPER criterion is thought to characterise the Early Initial Prodrome State of psychosis (Schultze-Lutter et al., 2010b). To test whether this could account for the low number of transitions in this group we analysed how many COPER patients in the converted and non-converted group also had attenuated symptoms. We found that two out of three COPER patients who converted also had attenuated symptoms compared with 13.04% (n=3) of the 23 COPER patients who did not convert. In the COGDIS group eight out of 13 (57.14%) converted patients had attenuated symptoms.

Conversion to psychosis was later for COPER patients than for COGDIS patients with COPER patients converting within a mean of 11 months and

COGDIS within a mean of 8.15 months. The difference between the Kaplan-Meier survival curves of those meeting COPER and COGDIS criteria was significant (log-rank test, $p < 0.001$). The mean time to conversion for CAARMS patients was 6 months with 63.64% (n= 7) converting during this time. The majority (90.91%) of conversions in the CAARMS UHR group occurred within 12 months of follow-up. Our results would appear to support the model proposed by Schultze-Lutter et al (2010) for the development of psychosis. Their model suggests that COPER characterises the Early Initial Prodrome State with a move towards attenuated symptom development in the Late Initial Prodrome state. If this model were accurate, we would expect further transitions from the COPER group over a longer period of follow-up. The mean duration of the follow-up period for the original study from which the COPER criterion was derived was 9.6 years and 70% of patients converted to psychosis (Klosterkotter et al., 2001b), thus suggesting the need for longer follow-up in this group.

The EPOS study (Ruhrmann et al, 2010) found that when both UHR and COGDIS criterions were satisfied the sensitivity was better than when the criterions were considered individually. We found the reverse to be true for our data. The sensitivity decreased but specificity improved considerably. When both CAARMS and COGDIS criterions were satisfied, the sensitivity and specificity were 0.42 and 0.92 respectively. Patients meeting both criteria have a 53% chance of conversion, and are over 5 times more likely than patients who test negative for the criteria to convert to psychosis. This would provide the clinic with a useful guide when determining the nature of the follow-up offered to patients following assessment. We would almost certainly want to provide case management to this group of patients. When either COGDIS or CAARMS were satisfied, there was an increase in sensitivity to 0.89 but a reduction in specificity to 0.53. With an NPV of 0.96 and a negative likelihood ratio of 0.2, we can have a high level of confidence that a negative test for both CAARMS and COGDIS will rule out conversion.

Nelson et al. (2008) argue that the distinction between the UHR and Basic symptom approach may be overstated. They suggest that it is plausible that

a symptom may be rated as both an attenuated symptom and a subjective basic symptom. Subjective experiences are not well represented in the UHR approaches. This raises the question of whether basic symptoms are indeed distinct from UHR or whether they a phenomenon of attenuated symptoms. The degree of overlap between UHR and Basic symptoms in those who converted in our sample would indicate that it is unlikely that they are completely distinct phenomenon.

In our study we used the SPQ-A to inform the vulnerability trait criterion of the CAARMS. We found that psychosis at follow-up was significantly associated with an SPQ-A score of greater than or equal to 39 (p = 0.001). Two logistic regression analyses found SPQ-A remained as a significant predictor in both of the final models. This is similar to the experience of Mason et al (2004) who found that when logistic regression was applied to the data, schizotypal personality traits remained as the only significant predictor of psychosis.

The difference between the mean SPQ-A total scores of those who converted and those who did not was statistically significant t (89) = 3.17, p = 0.002, this was also the case for the difference between mean SPQ-A scores for prodromal and psychotic patients at baseline (t(120) = -2.51, p = 0.014). This suggests that there may be an increase in SPQ-A scores when people convert. However, as we did not repeat our assessments at follow-up we cannot test this hypothesis.

Salokangas (2013) found an association between conversion and two subscales of the SPQ-A, ideas of reference and no close friends. The ideas of reference subscale is within the Cognitive Perceptual factor which was the only one of the three factors that we did not find a difference in mean scores between those who converted and those who did not (U = 368., p = 0.081). Our data did not enable analysis of individual subscales so we cannot determine whether any particular subscales were associated with conversion. We did however, find that the SPQ-A Cognitive Perceptual factor significantly correlated with the attenuated symptom criterion of CAARMS

(p= 0.029). This was similar to the findings of Bedwell and Donnelly (2005) who found that the cognitive perceptual factor showed the strongest correlation with the Youth Psychosis at Risk Questionnaire (YPARQ, ORD et al 2004) which is modelled on the CAARMS. This could possibly suggest that rather than simply being a stable measure of schizotypal personality traits, when used in symptomatic help-seeking patients the SPQ-A also detects attenuated psychotic symptoms. All of the converted patients who met the CAARMS attenuated symptom criterion also met the SPQ-A criterion, which would further support this suggestion.

Our hypothesis that the use of the SPQ-A to inform the CAARMS vulnerability criterion would improve the overall sensitivity and specificity of the CAARMS was not supported. When we removed the SPQ-A as a decision rule from the CAARMS neither the sensitivity nor the specificity of the CAARMS altered. This was because all of the patients that the SPQ-A identified as schizotypal also met the attenuated symptom subscale of CAARMS. This further supports our emerging hypothesis that in symptomatic help-seeking patients the SPQ-A elicits attenuated symptoms. Whether this is in addition to already present stable schizotypal traits is unknown. It would be interesting to conduct a prospective study of the SPQ-A to determine whether patients who were deemed schizotypal scored higher at the point of conversion.

If this hypothesis is correct and SPQ-A does indeed detect changes in symptomology, it could prove a useful and cost effective tool in measuring symptom development. The SPQ-A is a self-report measure and is reasonably quick to administer and score. It would be easy to train Case Managers to administer the questionnaire, for use on a regular basis. The only drawback would be its reliance on the literacy skills of the patient. Around 9% of the patients who attended our clinic were unable to complete the SPQ-A due to literacy issues.

ROC curve analysis of total SPQ-A scores found the score most predictive of conversion was a score of ≥ 51.50. This however, resulted in a reduction in

sensitivity from 0.88 to 0.65 and an increase in specificity from 0.54 to 0.78. The challenge for any test is that an increase in sensitivity will result in a reduction in specificity and vice versa. Haynes et al. (2006) suggest that ideally one would have as many cut-points as possible as the true likelihood ratio will differ according to each value of the test result. As the choice of cut-point is determined by the dataset within which it is used it is essential to conduct further studies to determine how well the findings can be replicated across studies.

Cannabis use before the onset of psychosis has been associated with a two-fold increased risk for psychosis (Weiser et al., 2003). Schizotypy has been suggested as a possible mediating factor between cannabis use and psychosis (Barkus et al, 2006). We tested whether such an association could be established in our cohort. Chi-square analysis found that cannabis use alone at baseline was not a significant predictor of psychosis at follow-up (p = 0.016). However when cannabis use at baseline and an SPQ-A score greater than or equal to 39 were entered into a regression analysis as interaction effects, conversion to psychosis could be significantly predicted. While this is an interesting and potentially important finding, it must be interpreted with some caution. We did not accurately record the amount of cannabis used at baseline or track cannabis use over the follow-up period. Without such detailed information, it is difficult to draw firm conclusions from this analysis. Nevertheless, it certainly merits further investigation.

The overall, social functioning of our cohort at baseline was low with the mean SOFAS score for referrals of 57.72 (SD 13.61). This indicates that help-seeking populations are already experiencing significant impairments in functioning. We sought to examine whether this level of impairment differed between those who had an ARMS and those who did not and whether this difference could distinguish at baseline between those who would subsequently develop a psychosis and those who would not. Severe deficits in social functioning have been found to precede psychosis onset (Hafner and an der Heiden, 1999) and Yung et al (2004) found that those with a GAF score of less than 51 present increased odds of developing a psychosis

within 6 months of the baseline assessment. In our cohort, social functioning was assessed by the SOFAS and was found to be lowest in those who were deemed UHR+ by the CAARMS (a mean score of 48.35), compared with those who were UHR- (a mean score of 66.89).

We found a statistically significant difference (p = 0.002) between the baseline SOFAS scores of those who converted and those who did not. The mean SOFAS scores at baseline of those who converted was 52.63 compared with 63.13 for those who did not. Those who converted also reported a statistically significant (p = 0.05) increased drop in functioning from their premorbid level (M = 17.75, SD 16.26, SE 3.64) when compared with those who did not convert (M = 9.75, SD 15.53, SE 1.38).

When the SOFAS decision rule was considered as a predictor of conversion in the absence of other instruments, 32 patients were classified as having an ARMS, of which 12 (37.5%) converted. The sensitivity of the SOFAS was 0.63 and the specificity was 0.76. This sensitivity was better than the CAARMS, which was 0.58. When the SOFAS decision rule is removed from the CAARMS the sensitivity of CAARMS increases to 0.89 but the specificity drops considerably to 0.41. This indicates that SOFAS plays an important role in differentiating between those who will convert and those who will not. Yung and Nelson (2011) introduced a measure of social functioning to the CAARMS decision rules for this expressed purpose as the CAARMS decision rules seek to prioritise specificity over sensitivity.

As discussed earlier the limitation of our study design was the absence of repeated assessments over the course of the follow-up period. Had we been able to track social functioning we would have been able to determine whether further deterioration occurred prior to psychosis onset. We are particularly interested to see whether those who met COGDIS and COPER criteria at baseline showed any further deterioration in functioning. If the model of psychosis development proposed by Schultze-Lutter et al (2010) were correct, we would expect to see a progressive functional decline the closer to the point of transition patients become. Rather interestingly those

deemed by the model to be furthest from conversion, the COPER criterion group had the highest mean SOFAS scores with a mean score of 61.85, COGDIS had lower scores with a mean of 56.50, with CAARMS UHR+ patients having the lowest mean score of 48.35. This suggests an insidious decline in functioning towards the point of conversion. Although, as not all people with low functioning convert even with positive results on the CAARMS we cannot rely solely on this factor. Nevertheless, given the earlier discussion around the overlap between Basic and Attenuated symptoms it would seem reasonable to suggest that a combination of Basic symptoms, attenuated symptoms, and functional decline may be the key to improved detection.

The conversion rates within our sample were somewhat higher than the most recent CAARMS studies (Yung et al., 2007), which report year on year declining rates of conversion. This decline in transition is hypothesised to be partly due to a reduction in symptom duration prior to receiving help and a possible 'dilution effect' (Yung et al, 2007) of more false positives being detected that were never at risk of developing a psychosis. The young people presenting to the LEAD clinic had been referred to the EIS because they were displaying symptoms indicative of a possible emerging psychosis. Therefore, the LEAD clinic sample was an enriched sample of those most likely to present a high risk of developing a psychosis. This raises an important question about whether conversions were predicted by the assessments used or whether they were simply a consequence of the sample enrichment process used.

Van Os and Delespaul (2005) assert that while enriched samples are the most commonly used approaches in early intervention literature, they often result in conversion prediction being wrongly attributed to the assessment measure, rather than to the sample enrichment strategy itself. To illustrate this they analysed the outcome of the Klosterkotter et al (2001) study which reports a 70% accuracy of prediction over a 9.6-year follow-up period. Of the 160 people who received a follow-up evaluation 79 (49%) developed a psychosis over the course of the follow-up period. Van Os and Delespaul (2005) argue that given the German University clinic's specialised interest in

early psychosis they attracted referrals of young people with a possible diagnosis of psychosis. This highly enriched sample already had a nearly 50% chance of developing a psychosis. The basic symptom assessment they suggest only modestly improved the predictive value from 50% to 70%.If we apply this thinking to our findings 19% of our conversions could have occurred because of the sample selection process. The use of the CAARMS improved the predictive value from 19% to 37% and the COGDIS criteria of SPI-A from 19% to 43%. Interestingly, the improvement in predictive value was 24%, similar to the findings of the Klosterkotter et al (2001) study. This suggests that in a sample that is highly enriched the basic symptom approach can improve the predictive value by between 20-24%.

The question of false-positives emerges when considering those who did not convert to psychosis over the course of the follow-up period. The potential false positive prediction rate of our study ranges from 57% to 63%. However, given that the follow-up period was only a mean of 30.44 months we do not know how many more patients will subsequently develop a psychosis over the course of their life. Psychosis prediction implies that symptoms follow a one-way linear course and that sub-threshold psychotic symptoms progress into psychotic symptoms. However, in a 1-year follow-up study of 72 at-risk patients Simon and Umbricht (2010) report that the probability of remission from an at-risk mental state was four times greater than the probability of conversion to psychosis. This indicates that the continuum of psychosis is more than one-dimensional. A quasi-dimensional model has been explored (Verdoux and van Os, 2002, Yung et al., 2009) in an attempt to explain the waxing and waning nature of psychotic-like symptoms. Van der Gaag et al. (2013) report that psychotic-like symptoms are not uncommon in the general population and one or more psychotic symptoms has been found to be present in 24.8% of the American population (Kendler et al., 1996). The Dutch population study NEMESIS (Hanssen et al., 2005), found the incidence of positive psychotic symptoms in the general population to be 100 times higher than the incidence of psychotic disorders such as schizophrenia. They conclude that it is far more likely that the outcome for most people experiencing positive psychotic symptoms will be discontinuity

rather than a clinical outcome. Therefore, the question remains regarding how effective tools such as CAARMS and SPI-A are in distinguishing normal variants of psychotic-like experiences from those who will have a clinical endpoint.

9.6 Clinical Implications

The meta-analysis and service evaluation both demonstrate that in help-seeking populations both the basic symptom and UHR approaches to detection can determine risk for psychosis. This offers EI services the further opportunity to reduce the duration of untreated psychosis by detecting psychosis onset at a much earlier stage of development. Increasingly, a two-stage model of early and late psychosis risk comprising both approaches has been proposed as a viable model for psychosis prediction (Fusar-Poli et al 2013, Schultze-Lutter et al 2010). The presence of both COGDIS and UHR criteria has been associated with the late prodromal phase and an increased risk of conversion (Ruhrmann et al, 2010). In our service evaluation, we found that when patients satisfy both the COGDIS and CAARMS criteria the likelihood ratio increases to 5.25 from 2.48 for CAARMS and 3.4 for COGDIS. This offers clinicians the opportunity of offering firstly clear feedback to patients about the degree of risk for psychosis their test result indicates and secondly enables decisions about the most cost efficient and effective service model for monitoring patients deemed to be at risk.

The current monitoring arrangements for patients deemed to be at-risk by the LEAD clinic assessment are determined by the outcome of the CAARMS assessment. We do not routinely offer care coordination to patients who only satisfy the COPER or COGDIS criterions; instead, we ensure that the referrer and the GP are aware of the risk of conversion. We based this protocol is on the findings of the Klosterkotter et al (2001) study, which found that conversion occurred after a mean of 4.3 years in women and 6.7 years in men. The findings of the service evaluation however, challenge this protocol as the mean time for conversion for the COGDIS criterion was 8.15 months and COGDIS was found to be the most sensitive and specific criterion. Logistic regression analyses also found that COGDIS and an SPQ-

A score greater than or equal to 39 were the only statistically significant predictors of psychosis. CAARMS did not remain within the model. The SPQ-A however, relies on the literacy skills of the service user, which does result in around 9% of service users being unable to complete the questionnaire so this would have some limitations as a prediction instrument. The SPQ_A also has low specificity (0.54) so would result in patients being offered follow-up who would not convert to psychosis. It could however, be used for symptom monitoring which will be further discussed in section 9.7.

The findings of both the meta-analysis and service evaluation suggest that both COGDIS and CAARMS are appropriate for use in the clinic. While the findings of the service evaluation indicate that COGDIS is superior to the CAARMS in detecting those who will convert to psychosis, the meta-analysis did not find a statistically significant difference between the UHR and Basic symptom approaches. Therefore, we would be cautious about moving to only using the COGDIS criterion in the clinic. It would seem sensible to use both approaches to detection in the clinic given that when both criteria are satisfied the likelihood ratio of conversion is increased from 2.48 from CAARMS and 3.4 for COGDIS to 5.25. We would not use the COPER criterion, as with a PPV of 0.12 and a likelihood ratio of 0.56, the prediction of conversion is little better than chance. By removing, the assessment questions required to determine the COPER criterion we would reduce the time taken to complete the SPI-A assessment by at least half. Only ten questions are required to assess COGDIS.

The results of the service evaluation indicate that it may be possible to develop a hierarchy of psychosis risk. This hierarchy of risk could be used to inform the post assessment follow-up. Three categories of risk present themselves as follows:

1) Very High Risk – CAARMS UHR and COGDIS criteria met
2) High Risk – either CAARMS UHR or COGDIS criteria met
3) Low risk – neither

In light of significant caseload pressures on teams, it has been suggested by the EIS that only those at very high risk of psychosis are offered case management. However, if this was implemented, only just over a half (52.94%, i.e. 9 out of 17) of converted people deemed to be at-risk of psychosis at baseline would have received case management. This could result in 47.06% of people experiencing a longer DUP as their conversion may not be quickly detected. The narrower the follow-up criteria becomes the fewer conversions would be detected in a timely manner. Therefore, we would suggest that those all those who present as very high and high risk receive case management from the EIS. Those presenting as low risk would be signposted to other appropriate services or to their GP.

The findings of the service evaluation do however, offer opportunities to reduce the length of the case managed follow-up period from the current 12-month duration. The mean time to conversion for people who met COGDIS criteria was 8.15 months, 6-months for CAARMS and 7.89 months for people who met both CAARMS and COGDIS criteria. For those meeting both COGDIS and CAARMS criteria 75% of conversions occurred within the first 6-months of follow-up. Similarly, 63.54% of CAARMS UHR positive conversions occurred in the first 6-months. Conversions in the COGDIS group occurred slightly later with only 26.7% of transitions occurring in the first 6 months. The current follow-up period is 12-months but we would suggest that this could be reduced to 6-months for those who meet CAARMS and both COGDIS and CAARMS criteria at baseline. We would suggest that those who meet COGDIS only criteria continue to receive 12-months case management as time to conversion for this group is longer.

The LEAD clinic has been operational for over 5 years and this is the first review of the accuracy of its predictions and overall efficiency. The first rather surprising finding was that just under a third (32.76%) of referrals to the clinic already satisfied the CAARMS psychosis threshold at baseline. This was unexpected, as all referrals to the clinic had previously been assessed by case managers using the PANSS assessment (Kay et al., 1987). The

Lancashire EIS was part of a large National study known as National EDEN (EDEN: Evaluating the Development and Impact of Early Intervention Services) and case managers had been assessed as satisfying a high level of concordance with PANSS assessments, so we did not expect such a high level of inaccurate tests. However, the Outreach and Support in South London (OASIS) service also received a high number of referrals (21%) who were psychotic at baseline assessment (Broome et al, 2005).

One of the possible explanations for such a high number of people meeting psychosis criteria at baseline could be that they were prodromal at the initial assessment by the EIS but converted while waiting for the LEAD clinic assessment. Initially, there was only one LEAD clinic per week serving the whole of Lancashire so waiting times reached 12 weeks in some areas at their peak. However, even when we opened two further clinics and reduced the waiting time to two weeks in some areas the trend continued. Broome et al (2005) found in their sample that that in most cases patients were in the early stages of psychosis and the severity of their symptoms was not immediately obvious. It could also be possible that a number of these patients present with more complex co-morbid disorders and case managers find them more difficult to assess. However, as we did not assess for co-morbidity in this evaluation, we cannot offer any firm conclusions regarding this.

A further explanation for the high number of people who satisfied the psychosis threshold of CAARMS could be an issue with the instrument itself. Yung et al. (2010) have recognised the potential limitations of the psychosis threshold cut-point within CAARMS. They describe this threshold as ‘arbitrary’ and suggest that it may not be useful diagnostically or prognostically. They suggest that for some people crossing this threshold may be a ‘trivial transition’ and have no implication for their long-term outcome yet some may never make this transition but manifest ‘the underlying schizophrenia substrate’. It would be interesting to conduct a follow-up analysis of those who were deemed psychotic at baseline, to determine their long-term outcome.

If all of the 57 people identified as psychotic at baseline were indeed experiencing a psychosis, the clinic is a worthwhile investment regardless of the subsequent 19 conversions that occurred. It is likely, that without the clinic those 57 people would have returned to the care of their GP and experienced a longer duration of untreated psychosis (DUP). We know from meta-analysis that longer DUP confers poorer outcomes (Marshall et al., 2005), so any delays introduced in the treatment of the young people accessing our service could have a detrimental impact on their overall outcome.

9.7 Opportunities for Further Research

One of the striking areas for further research is the developmental model proposed by the German Research Network (Schultze-Lutter et al, 2010), this model not unlike the CASIS model proposed by Cornblatt et al (2003) is assumed to begin with biological risk factors, 'non-specific mental problems' and functional decline, followed by Basic Symptoms, Attenuated Symptoms, BLIPS and eventually psychosis. We found evidence that seems to support this model. We found that 16 out of 17 patients identified, as at risk had basic symptoms, nine of which also had attenuated symptoms. We also found evidence of greater functional decline in those who converted and were psychotic at baseline. However, as we did not conduct any symptom or functioning assessments beyond our baseline assessment it is impossible to construct the actual pathway to psychosis for each patient. It would seem vital to test this model further to seek to better understand the pathway to psychosis. By understanding the pathway better and the points at which the person moves from one stage to another, we may be able to identify triggers for the symptom exacerbation. This could eventually lead to targeted intervention for prevention of the full-blown disorder.

Another possible opportunity for further research that seems to present itself is the SPQ-A. The results of the service evaluation seem to suggest that when used in help-seeking populations the SPQ-A is not simply a measure of a static state. The score appears to vary according to the symptom level of

the population within which it is used. For example, the mean scores of those who were psychotic were higher than the mean scores of those who were prodromal, whose scores were higher than those who were not at risk. Investigating, this prospectively in a cohort of at-risk patients could determine whether SPQ-A scores do indeed increase as symptoms progress. As mentioned previously, the SPQ-A as a self-report measure relies on the literacy levels of patients. However, it should be possible with the help of IT colleagues to develop a web based spoken version. This could enable easy completion of regular SPQ-A questionnaires regardless of literacy level. If indeed found to detect changes in attenuated symptom severity the SPQ-A could be used as a means of monitoring symptoms in those not offered care coordination. Patients could be given a unique password for a website that would record their SPQ-A scores for monitoring purposes.

Post-hoc analysis of the clinic data suggested an alternative model of assessment consisting of the SPQ-A with a cut off score ≥ 51.5, a SPI_A total score ≥ 16.5 and the new SOFAS decision rule (current functioning score ≤ 52.5 or a drop in functioning from pre-morbid level of ≥ 17.5). When all three criterions were satisfied, the likelihood ratio was 53. When both the SPQ-A or SPI-A total score were satisfied in addition to the SOFAS decision rule a good balance between sensitivity and specificity was achieved (sensitivity, 0.79, specificity, 0.83). However, it is likely that this model is only applicable to the dataset from which it was derived. We would want to conduct a replication study in the clinic to determine whether this model is generalizable beyond the findings of this current study.

Finally, an area for further investigation is the accuracy of psychosis assessments conducted by EIS services. The fact that a third were not detected by the initial assessment conducted by case managers raises questions are about the ability of case managers to accurately detect more subtle or perhaps complex first episode psychosis presentations. If such cases are deemed not psychotic by services without clinics available such as the LEAD clinic to conduct further assessment, it is likely that some patients may be experiencing a longer DUP than necessary.

9.8 Conclusion

Overall, the findings of the meta-analysis and the service evaluation demonstrate that both the Basic Symptom and UHR approaches are valid tools for psychosis prediction, in symptomatic help-seeking young people. There is emerging evidence from the review and our service evaluation to suggest that a combination of the two approaches may improve prediction. Our study also appears to suggest that the model of psychosis development proposed by the German Research Network (Schultze-Lutter et al) is broadly representative of the pathway to psychosis.

The service evaluation of the LEAD clinic was the first evaluation of the accuracy of our predictions. We did not expect to find that of a third of patients to be psychotic at baseline. We correctly predicted 17 out of the 19 patients who converted to psychosis, which represented a 26.56% transition rate in those who we found to be at risk at baseline. This means that in total over the course of the three-year evaluation period were able to reduce the DUP of 74 people (42.53% of referrals) referred to our clinic. This in itself underlines the importance of the LEAD clinic as an adjunct to the first-episode service.

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Appendices

Appendix 1: NRES Guidance

DIFFERENTIATING AUDIT, SERVICE EVALUATION AND RESEARCH

November 2006

The "Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees" recommended NRES should develop guidelines to aid researchers and committees in deciding what is appropriate or inappropriate for submission to RECs, and NRES (with the Health Departments and with advice from REC members) has prepared the guidelines in the form of the attached table.

RESEARCH	CLINICAL AUDIT	SERVICE EVALUATION
The attempt to derive generalisable new knowledge including studies that aim to generate hypotheses as well as studies that aim to test them.	Designed and conducted to produce information to inform delivery of best care.	Designed and conducted solely to define or judge current care.
Quantitative research – designed to test a hypothesis. Qualitative research – identifies/explores themes following established methodology.	Designed to answer the question: "Does this service reach a predetermined standard?"	Designed to answer the question: "What standard does this service achieve?"
Addresses clearly defined questions, aims and objectives.	Measures against a standard.	Measures current service without reference to a standard.
Quantitative research -may involve evaluating or comparing interventions, particularly new ones. Qualitative research – usually involves studying how interventions and relationships are experienced.	Involves an intervention in use ONLY. (The choice of treatment is that of the clinician and patient according to guidance, professional standards and/or patient preference.)	Involves an intervention in use ONLY. (The choice of treatment is that of the clinician and patient according to guidance, professional standards and/or patient preference.)
Usually involves collecting data that are additional to those for routine care but may include data collected routinely. May involve treatments, samples or investigations additional to routine care.	Usually involves analysis of existing data but may include administration of simple interview or questionnaire.	Usually involves analysis of existing data but may include administration of simple interview or questionnaire.
Quantitative research - study design may involve allocating patients to intervention groups. Qualitative research uses a clearly defined sampling framework underpinned by conceptual or theoretical justifications.	No allocation to intervention groups: the health care professional and patient have chosen intervention before clinical audit.	No allocation to intervention groups: the health care professional and patient have chosen intervention before service evaluation.
May involve randomisation	No randomisation	No randomisation
ALTHOUGH ANY OF THESE THREE MAY RAISE ETHICAL ISSUES, UNDER CURRENT GUIDANCE:-		
RESEARCH REQUIRES R.E.C. REVIEW	AUDIT DOES NOT REQUIRE R.E.C. REVIEW	SERVICE EVALUATION DOES NOT REQUIRE R.E.C. REVIEW

NRES ETHICS CONSULTATION E-GROUP Page 1 of 1

(National-Research-Ethics-Authority, 2006)

Appendix 2: Systematic Review Excluded studies

Author	Title	Year	Reason for Exclusion
Addington et al.	North American Prodrome Longitudinal Study: a collaborative multisite approach to prodromal schizophrenia research	2007b	Meta-analysis of modified individual patient data
Addington et al.	Clinical high risk for psychosis: The risk of false positive	2010	Meta-analysis of modified individual patient data
Addington et al.	Early detection of psychosis: Finding those at clinical high risk	2008	No follow-up
Addington et al.	Conversion in NAPLS: Those who do not convert to psychosis	2011a	Meta-analysis of modified individual patient data
Addington et al.	At clinical high risk for psychosis: outcome for non-converters	2011b	Meta-analysis of modified individual patient data
Bechdolf et al.	Self-experienced vulnerability, prodromic symptoms and coping strategies before schizophrenic and affective episodes	1998	In German
Bechdolf et al.	Early recognition and intervention for people at risk of schizophrenia.	2004	Intervention Study
Bechdolf et al.	Randomized controlled multicentre trial of cognitive behaviour therapy in the early initial prodromal state: Effects on social adjustment post treatment	2007	Intervention study
Borgmann-Winter et al.	Assessment of adolescents at risk for psychosis	2006	Review Article
Cannon et al.	Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America	2008b	Meta-analysis of modified individual patient data
Cotte et al.	Detection of early psychoses in children	1980	French
Demjaha et al.	Cognitive and negative symptom dimensions in the at	2010	Conference abstract –

Author	Title	Year	Reason for Exclusion
	risk mental state predict subsequent transition to psychosis		insufficient data
Hasan et al.	Early detection and treatment of schizophrenia	(2010)	In German
Heinimaa et al.	PROD-screen - A screen for prodromal symptoms of psychosis	2006	No follow-up
Kammermann et al.	Self-screen prodrome"--self-rating for the early detection of mental disorders and psychoses	2009	In German and no follow-up
Klosterkotter et al.	Is it possible to diagnose schizophrenia at the start of the initial prodromal phase prior to the first psychotic manifestation?	2000a	In German and data presented elsewhere
Klosterkotter et al.	Is the diagnosis of schizophrenic illness possible in the initial prodromal phase to the first psychotic manifestation?	2000b	In German and data presented elsewhere
Klosterkotter et al.	Is there a primary prevention of schizophrenic psychiasis?	2001b	In German and data presented elsewhere
Lencz et al.	Nonspecific and attenuated negative symptoms in patients at clinical high-risk for schizophrenia	2004	Baseline data, no follow-up
Liu et al.	Development of a brief self-report questionnaire for screening the at risk state of psychosis in Taiwan	2010	No follow-up data, conference abstract
Lin et al.	Long term follow-up of an ultra-high risk (Prodromal) group	2010	Conference Abstract not enough data Used data already included
Morrison et al.	Randomised controlled trial of early detection and cognitive therapy for preventing transition to psychosis in high-risk individuals. Study design and interim analysis of transition rate and psychological risk factors	2002	Intervention study

Author	Title	Year	Reason for Exclusion
Morrison et al.	Early detection and intervention evaluation for people at high-risk of psychosis-2 (EDIE-2): Trial rationale, design and baseline characteristics	2011	Intervention study
Muller et al.	The self-screen-prodrome as a short screening tool for pre-psychotic states	2010	No follow-up
Nelson et al.	Long term follow up of an ultra-high risk (prodromal) group	2010	Conference Abstract not enough data Used data already included
Nelson et al., 2011	Ultra high risk (UHR) for psychosis groups: Are there different levels of risk for transition to psychosis?	2011	Conference Abstract. Insufficient data. Cannot determine if sample already included in earlier papers.
Ord et al.	Screening for prodromal adolescents in an isolated high-risk population	2004	No follow-up & letter to the editor
Poustka et al.	Basic Symptoms, temperament and character in adolescent psychiatric disorders	2007	Retrospective study
Salokangas et al.	Vulnerability to and current risk of psychosis: Description, experiences and preliminary results of the detection of early psychosis or DEEP project	2004	Baseline data no follow-up
Seidman et al.	Neuropsychology of the prodrome to psychosis in the NAPLS consortium: Relationship to family history and conversion to psychosis	2010	Meta-analysis of modified individual patient data
Schafer et al.	Early detection of psychotic disorders	2007	RCT and in German
Schultze-Lutter et al.	Prevalence and burden of at-risk criteria of psychosis and help-seeking behaviour - A population survey - Prevalence	2010	Prevalence study no follow-up
Schultze-	Basic Symptoms and	2010	Retrospective

Author	Title	Year	Reason for Exclusion
Lutter et al.	ultrahigh risk criteria: Symptom development in the initial prodromal state		study
Schultze-Lutter et al.	Prevalence and burden of at-risk criteria of psychosis and help-seeking behaviour - A population survey	2011	Prevalence study
Shioiri et al.	Early prodromal symptoms and diagnoses before first psychotic episode in 219 in-patients with schizophrenia	2007	Retrospective Study
Schlosser et al	Redefining at-risk: Clinical and functional outcomes of putatively prodromal youth who do not develop psychosis	2011	Conference abstract. Insufficient data
Yung et al.	Psychotic-like experiences in a community sample of adolescents: implications for the continuum model of psychosis and prediction of schizophrenia	2009	No Follow-up
Winton-Brown-et al	The diagnostic significance of BLIPS (brief limited intermittent psychotic symptoms) in psychosis	2011	Single case study

Appendix 3 Medication Use Profile of the cohort

Case number	At Risk status	Medication	Included in follow-up cohort
2	Not at risk	Olanzepine 15mgs and Lithium 600mgs	Excluded
8	At-Risk	Olanzapine 15mgs	Excluded
12	At-Risk	Quetiapine 200mgs Depakote 1500	Excluded
31	At-Risk	Quetiapine 200mgs	Excluded
33	At-Risk	Olanzapine 5mgs	Excluded
46	At-Risk	Olanzapine 5mgs	Excluded
52	At-Risk	Quetiapine 175mg	Excluded
53	At-Risk	0.5mgs Risperidone	Included
55	Not At-Risk	Aripiprazole 15mgs	Excluded
56	At-Risk	Aripiprazole 15mgs	Excluded
109	At-Risk	Aripiprazole 5mg	Included
117	At-Risk	Quetiapine 100mg BD	Excluded
130	At-Risk	Quetiapine 300mg, Citalopram 20mg, Methadone 40ml	Excluded
135	At-Risk	Quetiapine 25mg TDS, 150mg nocte	Excluded
141	Not At-Risk	Olanzapine 2.5mg	Included
145	At-Risk	Olanzapine 2.5mg	Included
151	At-Risk	Quetiapine 400 BD	Excluded
159	At-Risk	Quetiapine 350 mg	Excluded