Investigating the psychological factors associated with distress in psychosis

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Abstract

This thesis investigated the psychological factors associated with distress in the early stages of psychosis. The first chapter is a systematic review and meta-analysis of the literature assessing the comorbidity rates of both depression and anxiety in first-episode psychosis (FEP). Prevalence rates were shown be similar between depression and anxiety for included studies, suggesting that both anxiety and depression should be targeted for intervention, together with the psychotic symptoms. The second chapter is a secondary analysis of clinical trial data investigating the relationship between distress, severity and frequency of attenuated psychotic symptoms in individuals meeting ultra-high risk criteria for psychosis (UHR), both cross-sectionally and over time. A confirmatory factor analysis (CFA) and latent growth curve (LGC) models were applied to assess the study aims. The impact of cognitive behavioural therapy (CBT) on distress reduction over time by symptom was also assessed which did not significantly reduce distress compared with monitoring. Overall distress reduced over time, particularly in the first three months after presentation, although this was dependent on the type of psychotic symptom. The final chapter provides a critical appraisal of the previous chapters and overall research process. In conclusion, this thesis recommends that distress should be used as an outcome in future clinical research and as a clinical indicator to guide professional involvement.

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.

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DEDICATION

This thesis is dedicated to Richard Shellam with all my love.

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I wish to thank all my supervisors for their help and support. Thank you to Dr Nick Shryane for increasing my statistical understanding. I am also very grateful to Prof Morrison for supporting the project throughout and providing excellent suggestions and advice.

Chapter 1

Comorbidity rates of depression and anxiety in first episode psychosis: a systematic review and meta-analysis

This chapter has been written in the format and style required for the journal *Schizophrenia Research*.

Word Count: *5935*

1.1 Abstract

Anxiety and depression symptoms are frequently experienced by individuals with psychosis, although prevalence rates have not been reviewed in first-episode psychosis (FEP). The aim of this systematic review was to focus on the prevalence rates for both anxiety and depression, comparing the rates within the same study population. A systematic review and meta-analysis was completed for all studies measuring both anxiety and depression in FEP at baseline. The search identified 6040 citations, of which n=10 met inclusion criteria. These reported 1265 patients (age 28.3±9.1, females: 39.9%) with diagnosed FEP. Studies which used diagnosis to define comorbidity count were included in separate meta-analyses for anxiety and depression, although the heterogeneity was high limiting interpretation of separate prevalence rates. A random-effects meta-analysis also compared the mean difference between anxiety and depression within the same studies. We show that anxiety and depression co-occur at a similar rate within FEP, although the exact rates are not reliable due to the heterogeneity between the small number of studies. Future research in FEP should consider routinely measuring anxiety and depression using continuous self-report measures of symptoms. Clinically we recommend that both anxiety and depression are equally targeted during psychological intervention in FEP, together with the psychotic symptoms.

Keywords: *Systematic review, meta-analysis, psychosis, first-episode psychosis, anxiety, depression, comorbidity, prevalence*

1.2 Introduction

Anxiety and depression symptoms are frequently experienced by individuals with psychosis. They are often experienced together and have been shown to be inter-related factors when assessed in schizophrenia (Kay, Fiszbein, & Opler, 1987; Kendall & Watson, 1989). It has also been hypothesised that anxiety and depression symptoms contribute to the development and maintenance of psychotic experiences (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001; Morrison, 2001), which also directly relates to the level of distress experienced and the content of psychotic symptoms (Hartley, Barrowclough, & Haddock, 2013). It has also been suggested that the presence of anxiety and depression symptoms could even predict and increase the risk of worsening symptoms or transition to first-episode psychosis (FEP) (Dominguez, Wichers, Lieb, Wittchen, & van Os, 2011). Indeed, psychotic symptoms are also reported by patients with anxiety and depression disorders (Saha, Scott, Varghese, & McGrath, 2012; Varghese et al., 2011), suggesting that negative affect is an important trans-diagnostic factor.

Severe psychosis is usually preceded by a prodromal period known as the at risk mental state or being at ultra-high risk for psychosis (UHR) (Yung et al., 1996a; Yung & McGorry, 1996b), where psychotic symptom severity and distress increases and functioning of the person deteriorates further, resulting in an increased risk of developing first episode psychosis (FEP) (McGorry, Yung, & Phillips, 2003; Yung et al., 2004; Yung et al., 2003a). The comorbidity of anxiety and depression rates within UHR have previously been reviewed, indicating higher levels of depression compared to anxiety (Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014). The comorbidity has also been reviewed within those with multi-episode psychosis

(Hartley et al., 2013). However, the rates of comorbidity within FEP has yet to be investigated and reviewed, although FEP has been shown to be associated with an increase in anxiety and depression in comparison to individuals with enduring psychosis (Emsley, Oosthuizen, Joubert, Roberts, & Stein, 1999).

Early studies focused on depression within schizophrenia. They identified prevalence rates ranging from 7-70% (Siris, 1991), leading to the development of a depression measure specifically for schizophrenia (Addington, Addington, & Maticka-Tyndale, 1993). Interestingly, the prevalence of depression assessed without anxiety was shown to be higher in individuals in the acute phase (Mulholland & Cooper, 2000) or first-episode psychosis (FEP), with 75% experiencing depression (Koreen et al., 1993). A more recent study focusing on depression comorbidity in FEP showed around 55% to have high rates of depressive symptoms (Dai et al., 2018), although how depressive symptoms are defined in psychosis markedly varies the overall prevalence rate (Siris & Bench, 2003). However, overall depression symptoms experienced in FEP have received somewhat limited investigation (Upthegrove, 2009) given that it has been shown to be a long-term risk factor, increasing the likelihood of a suicidal outcome in FEP (McGinty, Haque, & Upthegrove, 2018; Upthegrove et al., 2010).

While anxiety within schizophrenia has received much less focus than depression in early studies, there is a recognition more recently that high anxiety levels are associated with higher psychotic symptom severity and poorer outcomes (Braga, Reynolds, & Siris, 2013; Dernovšek & Šprah, 2009; Lysaker & Salyers, 2007). Prevalence rates are reported between 35-65% for anxiety in Schizophrenia (Braga et al., 2013; Buckley, Miller, Lehrer, & Castle, 2009; Kiran & Chaudhury, 2016; Pokos & Castle, 2006; Temmingh & Stein, 2015; Tibbo, Swainson, Chue, & LeMelledo,

2003), although there is limited research specifically looking at anxiety in FEP, overlap between psychosis and anxiety has been demonstrated in studies assessing genetic polymorphisms (Jones et al., 2016). This could suggest that psychosis is an anxiety disorder or anxiety is an important feature of the psychosis.

There are different comorbid anxiety and depression rates across the psychotic continuum. With the prodrome or 'at-risk' population (Yung et al., 2003b) showing a higher rate of depression (41%) than anxiety (15%) (Fusar-Poli et al., 2014). Historically the onset of anxiety and depression was suggested to indicate the initial psychosis prodrome (Häfner et al., 1999). Although anxiety and depression symptoms are often the primary concern to at-risk individuals rather than their attenuated psychotic symptoms (Fusar-Poli et al., 2013). Therefore, it is likely that FEP may have a different rate of comorbidity for anxiety and depression than 'at-risk' or long-term Schizophrenia.

This review aims to focus on the available first-episode psychosis (FEP) research investigating comorbidity prevalence rates for both anxiety and depression within the same study population. This will allow the comparison between these interrelated psychological phenomena to be reviewed for the first time in FEP.

1.3 Materials and methods

1.3.1 Study selection

Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009) were adhered to and the review was pre-registered with PROSPERO [CRD42019122431]. MEDLINE, EMBASE, PsycINFO and Thomson Reuters (Web of Science) were searched for

relevant papers published before 2018, with the last search run 09/2018. Search terms used: (Schizophrenia OR psychosis OR first*episode*Psychosis OR high*risk*psychosis OR at*risk*mental*state OR ultra*high*risk OR prodrom*) AND (Co*morbidity OR prevalence OR Depression OR Depressive Disorder OR low mood OR mood disorder OR Affective disorder OR Anxiety OR Anxiety disorder). A limiter of search terms present within the article title was applied. The reference lists of identified articles were also reviewed for additional studies.

1.3.2 Inclusion and exclusion criteria

A consensus amongst two authors (RW & AM) was established for the studies to be included or excluded. One author (RW) screened titles and abstracts, and then assessed the full texts of potentially eligible studies. Full texts were also consulted if eligibility was unclear from the title and abstract alone. A second reviewer (AM) validated studies if eligibility was uncertain and a 5% random sample of full texts were reviewed by an independent reviewer for eligibility and quality.

All studies had to include adolescents and/or adults who had experienced first-episode psychosis (FEP), in keeping with ICD codes F20- 29, F30.2, F31.2, F31.5 or F32.3. Data could be collected as part of a randomised control trial, cross-sectional or cohort study. Current symptoms or diagnosis of both depression and anxiety needed to be measured in the same FEP study using a validated measure (Table S1.1) at the same baseline time-point. All studies had to be full text journal articles published in English between1985-2018.

The exclusion criteria for studies were as follows:

1. Sample including individuals with chronic psychotic or personality disorders

2. Individuals with long-term diagnosis of Schizophrenia (greater than 24 months)
3. Aged below 12 years or over 50 years
4. Review articles
5. Qualitative or case studies

1.3.3 Data extraction

A standardised data extraction form was developed and piloted on a sample of included studies using excel (Microsoft Office 2016). Data was extracted by one author (RW) on the following domains: study identification (authors, year of publication, title), study characteristics (objectives of study, study design, sample size, follow-up time, start and end date, assessment method of depression and anxiety) population characteristics (gender, age, country) and reported outcome (outcomes considered, outcome measures, result, test statistic reported with 95% confidence interval, mean, standard deviation or standard error). If data were missing from any papers, or anxiety and depression was reported as a combined score the authors were contacted for a score breakdown. Any disagreements were resolved by reference to the papers together with the second author. A third party was not required to resolve any eligibility disagreements.

1.3.4 Quality assessment

One author (RW) completed the Downs & Black (1998) quality assessment tool for randomised and non-randomised studies in health care for all included studies. Any discrepancies were discussed, and consensus was agreed between the author and independent reviewer. It was hoped that the quality assessment would be used to inform sensitivity analysis and to help explain differences between the studies. The

Cochrane risk of bias tool was not used as the studies are not all randomised control trials.

1.3.5 Meta-Analysis

Comprehensive Meta-Analysis Software (CMA) was used to perform all meta-analysis. Depression and anxiety event rates were separately assessed and then compared. Effect sizes were either taken directly from each study or the mean effect size was calculated across groups. Odds ratios with 95% confidence intervals (CIs) were calculated using the CMA software separately for Depression and Anxiety. Standardised mean differences were used for the comparison between Depression and Anxiety. An effect size of <0.2 was considered a *small* effect, 0.5 a *moderate* effect and 0.8 a *large* effect (Riley, Higgins, & Deeks, 2011). Heterogeneity was assessed using the I^2 statistic, which represents the percentage of variance due to between-study factors rather than sampling error, $I^2 > 50$ % indicates large heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). Random effects models were used as inherent heterogeneity was anticipated due to the differences between the study populations.

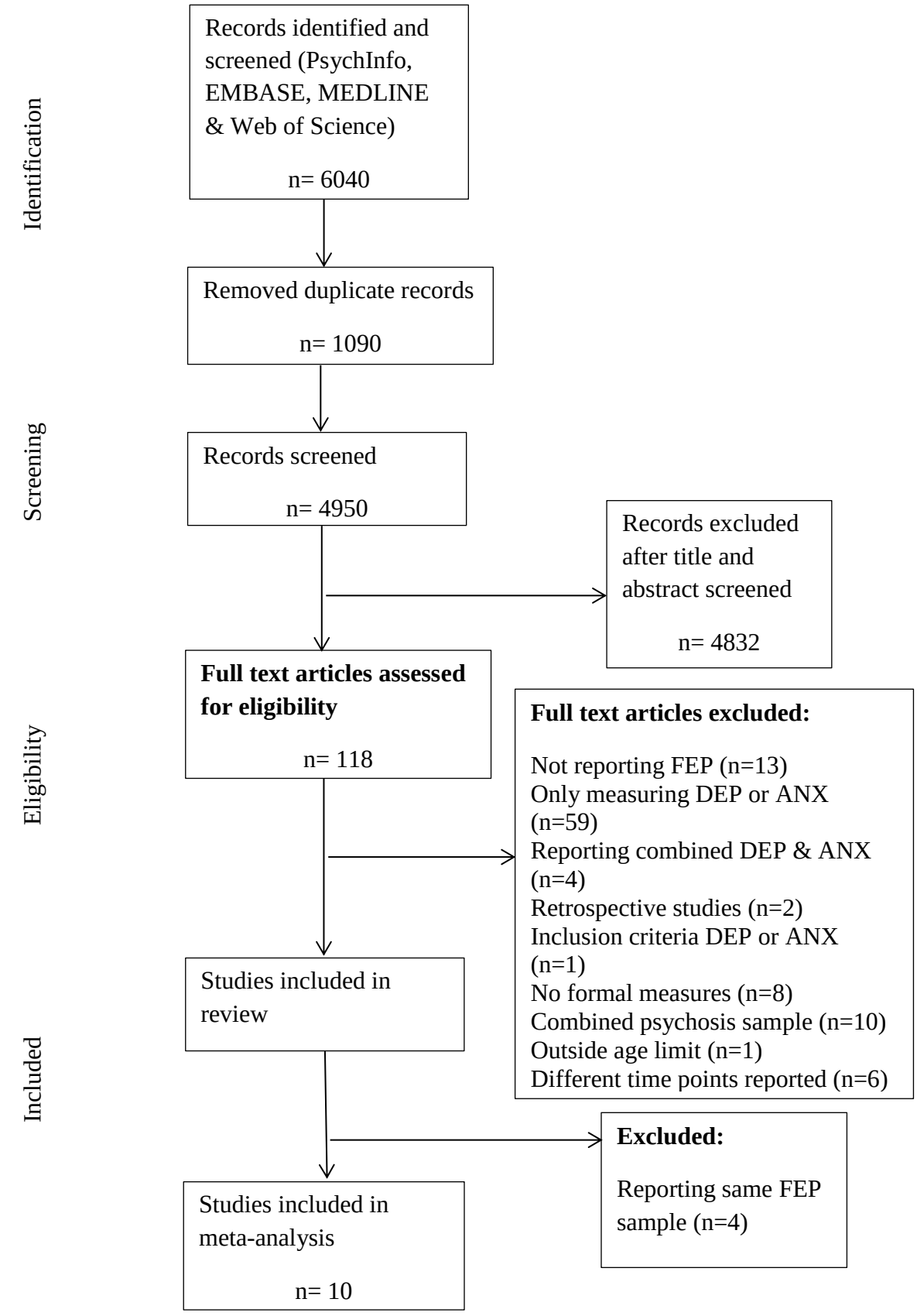

Figure 1. Study selection process PRISMA flow chart

1.4 **Results**

1.4.1 Study characteristics

The results of the searches are shown in Figure 1. Initial searches identified 6040 citations which were screened based on their title and abstract. Articles were selected for full-text review if they fulfilled inclusion criteria or were deemed relevant by the authors. Full texts were retrieved for 118 studies and were assessed for eligibility. After assessment 13 studies did not report FEP, 59 only measured either depression or anxiety not both symptoms, 4 studies only reported combined anxiety and depression scores (authors were contacted without success), 2 were retrospective studies, 1 study required depression or anxiety as inclusion criteria, 8 studies had no formal measures described, 10 studies had a combined psychosis sample, 1 study was not within the age limit and 6 studies had data reported at different time points. These studies were excluded, which resulted in 14 studies that fulfilled our inclusion criteria. However, 4 studies used the same participant data leaving 10 eligible studies included in the meta-analysis (Table 1). There was agreement amongst authors on included studies.

The 10 studies included 1265 participants, mean age 28.3±9.1, total females: 505 (39.9%), with PANSS or DSM-IV SCID diagnosed first episode psychosis. The range of diagnosis were Schizophrenia *n=414* (39.5%), Schizophreniform disorder *n=57* (5.4%), Schizoaffective disorder *n=34* (3.2%), delusional disorder *n=31*(3.0%), brief psychosis episode *n=50* (4.8%), bipolar *n=277* (26.4%), major depression with psychotic symptom *n=99* (9.4%) and Psychosis NOS *n=155* (14.8%). Three studies did not report the specific diagnosis types by participants and are therefore, not included within these percentages, although were included within

the meta-analysis (Malla et al., 2002; Michail & Birchwood, 2013; Oosthuizen, Emsley, Niehaus, Koen, & Chiliza, 2006). None of the studies reported the comorbidity by type of ICD-10 diagnosis, limiting our ability to analysis further. When studies reported the breakdown in anxiety disorders only the primary category of diagnosis was taken to avoid duplication (e.g where subjects have two anxiety disorder diagnoses). If this was not clear from the paper only the anxiety disorder cases were extracted.

1.4.2 Meta-analysis

Some studies did not assess or report event rates or diagnosis of anxiety and depression although did report the relationship between Anxiety and Depression. Significant event rates emerged for Anxiety (7 studies, n= 1016) and Depression (3 studies, n=653) within the included FEP studies. Anxiety had a 29% (range: 20-40%) comorbidity rate and Depression had a 23% (range: 14-34%) comorbidity rate, see Figure 2. However, the heterogeneity for these analyses was very high (Anxiety: I^2= 89.26% & Depression: I^2= 83.85%) suggesting that these results have low reliability.

There was a *small* non-significant standardised mean difference between Anxiety and depression within the same studies (10 studies, n= 1265), suggesting a similar level of comorbidity between Anxiety and Depression (Figure 3), with a trend towards increased Anxiety within FEP. Heterogeneity was moderate for this analysis (I^2= 62.9%).

The high heterogeneity could be due to multiple factors including; the age of the study, the different inclusion or exclusion criteria used or the variation in sample demographics (e.g age, gender, race, sociodemographic status).

1.4.3 Study quality and publication bias

There was a good inter-rater reliability between the author and independent reviewer for study eligibility and quality appraisal. No studies were excluded based on the quality of the method used, see supplementary for a quality assessment of included studies (Table S1.2-4). Due to the small number of included studies, further sensitivity analysis based on the quality assessment could not be completed. Therefore, the quality assessment was only used qualitatively to help explain differences between the studies. The only study to show greater levels of depression compared to anxiety within the same FEP group was the oldest study included in the review (Strakowski et al.,1995), this pre-dates much of the UHR literature (Yung, Yuen, Phillips, Francey, & McGorry, 2005) which could impact on the classification of FEP.

Table 1 FEP studies included in the systematic review and meta-analysis

Study	Country	Sample	Mean age (sd)	Female (%)	Anxiety measure	Anxiety diagnosis (n) or mean score (sd)	Depression measure	Depression diagnosis (n) or mean score (sd)	Depression & Anxiety rates OR (95% CI)
Malla et al (2002)	Canada	88	24.2 (±7.8)	18 (20%)	HAS: *Mild <17* *Moderate 18–24* *Severe 25–30*	Mean: 3.7 (4.6)	CDS Case = >6	1.5 (2.5)	1.13 (0.77, 1.65)
Ma et al (2018)	China	104	43.4 (±15.3)	57 (54.8%)	HAS: *Mild <17* *Moderate 18–24* *Severe 25–30*	Mean: 19.36 (13.85)	HAM-D: *Moderate 14-18* *Severe 19 – 22* *Very Severe >23*	21.56 (11.97)	1.03 (0.73, 1.46)
Romm et al (2012)	Norway	144	26.27 (±8.5)	52 (36.1%)	LSAS: Case = >60	Social anxiety disorder (n=68)	PANSS-D Mean = 1.9 (0.97)	13.14 (3.56)	1.14 (0.85, 1.54)
Oosthuizen et al (2006)	South Africa	57	28.2 (±8.6)	29 (50.8%)	PANNS-A: Mean=2.48(1.2)	7.05 (3.3)	CDS Case = >6	2.25 (3.15)	8.59 (2.79, 26.46)
Strakowski et al (1995)	USA	71	32.9 (±15.9)	32 (45%)	SCID DSM-III	Anxiety disorders (n=15)	SCID DSM-III	Major depression with psychosis features (n=14) Depressed affective subtype (n=5)	0.39 (1.64, 0.93)
Herniman et al (2018)	Australia	82	21.1 (±2.6)	28 (34.1%)	SCID DSM –IV	Anxiety disorders (n=30)	SCID DSM –IV	Depressive disorder (n=24) Major depressive disorder (n=12) Depressive disorder NOS (n=12)	1.93 (0.91, 4.13)
Salvatore et al (2009)	Italy & USA	500	31.7 (±13.7)	225 (45%)	SCID DSM –IV	Anxiety disorder (n=88)	SCID DSM –IV	Major depressive disorder (n=77)	1.22 (0.87, 1.72)

Table 1 Continued…

Study	Country	Sample	Mean age (sd)	Female (%)	Anxiety measure	Anxiety diagnosis (n) or mean score (sd)	Depression measure	Depression diagnosis (n) or mean score (sd)	Depression & Anxiety rates OR (95% CI)
Michail & Birchwood (2013)	UK	80	24.5 (±4.8)	27 (21.6%)	SIAS Case = >43	Social anxiety disorder (n=20)	CDS Case = >6	5.65 (5.0)	1.30 (0.87, 1.94)
Birchwood et al (2006)	UK	79	23.3 (±5.3)	18 (22.8%)	SIAS Case = >43	Social anxiety disorder (n=23)	CDS Case = >6	7.8 (4.8)	1.18 (0.79, 1.76)
Voges & Addington (2005)	Canada	60	27.45 (±8.3)	19 (31.7%)	SPAI Case = >60	69.57 (27.42)	CDS Case = >6	1.52 (2.27)	3.00 (1.12, 8.03)
Total		1265	28.3 (±9.1)	505 (39.9%)					

Note. OR; Odds Ratio, CI; confidence interval, CDS; Calgary Depression Scale, SCID; Structured Clinical Interview for DSM, PANSS-A/D; Positive and Negative Syndrome Scale – Anxiety/Depression, SIAS; Social Interaction Anxiety Scale, LSAS; Liebowitz Social Anxiety Scale, SPAI; Social Phobia and Anxiety Inventory, HAM-D, Hamilton Depression Scale, HAS; Hamilton Anxiety Scale.
DSM-IV: Generalised anxiety disorder, Panic, Agoraphobia, phobia, Obsessive compulsive disorder, Posttraumatic stress disorder, Acute stress disorder & Anxiety NOS
DSM-III: Generalised anxiety disorder, Panic, Agoraphobia, social phobia, Simple phobia & Atypical anxiety disorder

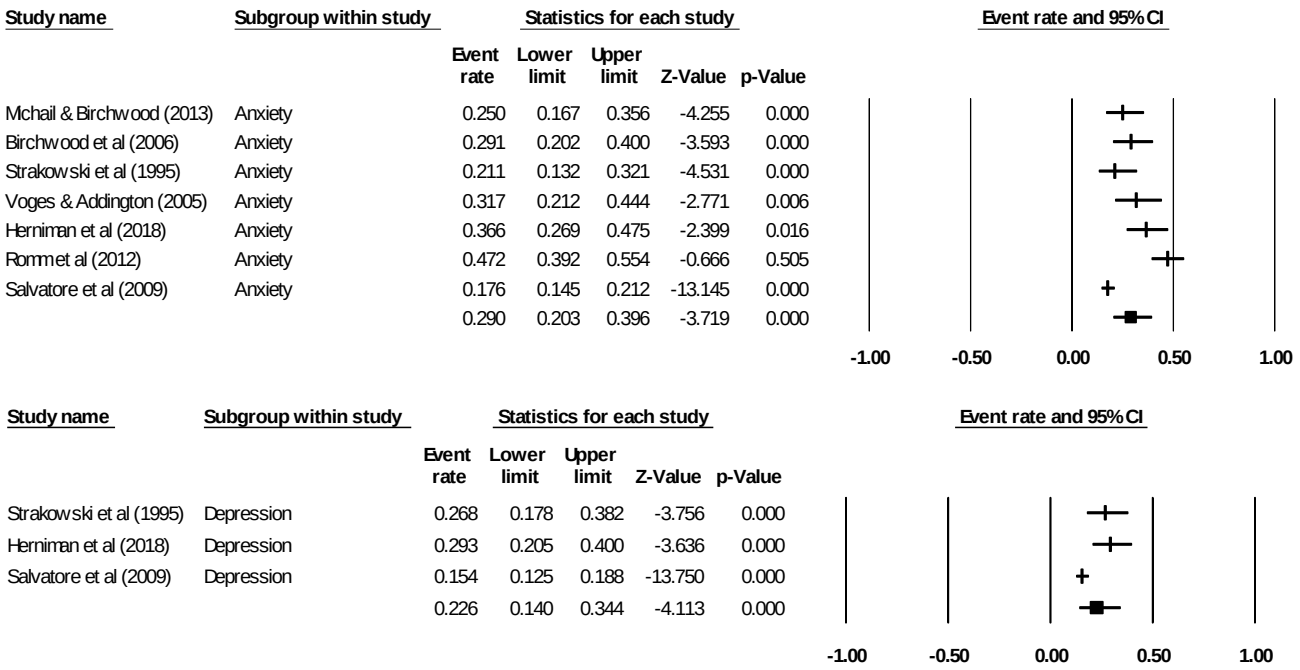

Figure 2. Comorbid diagnosis rates seperately for Anxiety and Depression in the included FEP studies. Note: The random effects analysis reported are for information purposes only and are not reliable estimates of prevelance.

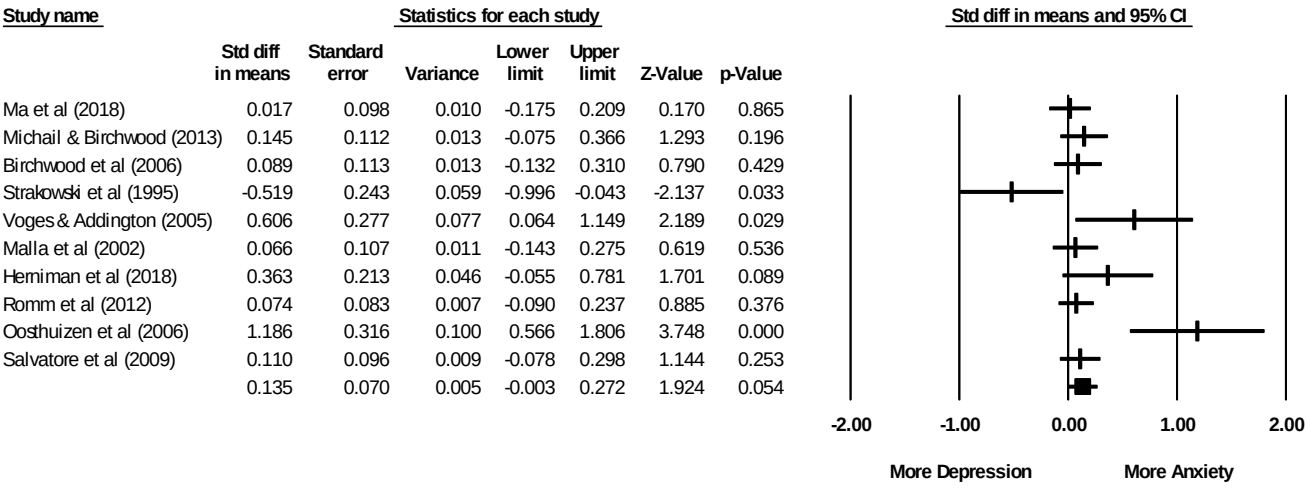

Figure 3. Standard mean difference for comorbid Depression and Anxiety in FEP studies. Random effects analysis are reported.

1.5 Discussion

A meta-analysis of available studies reporting both a measure of anxiety and depression, and a measure of the relationship between these comorbidities, suggests that anxiety and depression co-occur at a similar rate within first-episode psychosis (FEP). Comorbidity rates were 29% for anxiety and 23% for depression, although the reliability of these values should be cautioned due to the high study heterogeneity. We also found limited research assessing anxiety symptoms within FEP and the inclusion of both measures of anxiety and depression further reduced the number of eligible studies. The symptom relationship of both anxiety and depression within the same studies was assessed using standardised difference. We conclude that clinically distinguishing these factors may be difficult, although further research is required to investigate both anxiety and depression symptoms in FEP given the small numbers of heterogeneous studies.

A previous review in ultra-high risk for psychosis (UHR) showed higher rates of depression at 45% compared to 15% for anxiety (Fusar-Poli et al., 2014). Comparing these rates to the current FEP study, depression rates are lower (23%) and anxiety is higher (29%). However, the current review also finds comparative rates of depression and anxiety in FEP, unlike the previous UHR review, which showed much higher levels of depression compared with anxiety (Fusar-Poli et al., 2014). This suggests that over time or along the psychosis continuum levels of anxiety and depression change. The mechanistic reasons for this require further investigation and are likely to be multi-factorial.

A review assessing the prevalence rates for anxiety only in schizophrenia found rates ranging between 7-22% for all anxiety disorders defined by DSM, although high

heterogeneity across studies was reported similarly to the current study (Achim et al., 2011). Indeed a previous systematic review assessing psychosis concluded that there was a significant association with psychotic symptoms and distress, anxiety and depression, although they did not quantify this due to the variation in definition and measures across studies (Hartley et al., 2013). Similarly, while the current study quantified separate anxiety and depression comorbidities in FEP, due to the small number of eligible studies and large heterogeneity between studies the prevalence rates are unreliable.

Anxiety and depression are shown to be more prominent in first episode, when comparing to individuals with multiple episode schizophrenia (Emsley et al., 1999). However, the longstanding distinction between depression and psychotic symptoms (Kraepelin 1919) has been questioned more recently, with the increasing acceptance of convergence between depression and psychotic symptoms (Upthegrove, Marwaha, & Birchwood, 2017). The similar rates of anxiety and depression found in this review support their inter-relatedness as psychological phenomena and they appear to be of equal importance within psychosis.

Additionally, trans-diagnostic ideas within mental health are increasingly gaining credence. A general psychopathology dimension has been advocated across all mental disorders incorporating the dimensions/continuums; internalising difficulties to anxiety and depression, externalising to anti-social or substance abuse and thought disorder difficulties to symptoms of psychosis (Caspi et al., 2014). Caspi et al (2014) also include the general dimension of including the general propensity of the individual to develop psychopathology. Trans-diagnostic ideas have also been acknowledged within the UHR literature (McGorry, Hartmann, Spooner, & Nelson, 2018; McGorry & Nelson, 2016). Thus, comorbidity rates of anxiety and depression

in FEP are likely to be measuring the same underlying psychopathology. Indeed, recent fMRI analysis comparing FEP, alongside the anxiety disorder posttraumatic stress disorder (PTSD) and major depressive disorder show converging brain areas associated with the conditions (Gong et al., 2019), which arguably provides some biological support for a trans-diagnostic mechanism.

Anxiety has more recently been reviewed as a core aspect of schizophrenia, particularly panic and social anxiety symptoms (Pallanti, Cantisani, & Grassi, 2013). It has been suggested that the hierarchical organisation of earlier DSM editions which stipulated that Anxiety Disorders could not be diagnosed if there was an Axis-I (e.g psychosis) diagnosis led to anxiety in psychosis being under researched. However, more recent DSM editions are not restricted to one diagnosis. A relationship between anxiety symptoms and positive psychotic symptoms has been shown in schizophrenia, particularly between panic; with paranoia (Huppert & Smith, 2005) and voice hearing (Veras et al., 2017). Additionally a relationship has been shown between social anxiety and psychotic symptoms in schizophrenia (Lysaker & Salyers, 2007) and UHR (Cooper, Klugman, Heimberg, Anglin, & Ellman, 2016). The large cross-over of anxiety and Axis-I diagnosis has also led to the suggestion that anxiety and mood disorders should be along a dimension rather than categorical (Brown, Di Nardo, Lehman, & Campbell, 2001). Indeed, some researchers have concluded that regardless of diagnosis anxiety symptoms are strongly related to both depressive symptoms and personality (Karpov et al., 2016).

1.5.1 Strengths and limitations

Having a measure of anxiety and depression within the same study participants enabled us to reduce some of the heterogeneity. Additionally, all included studies

were from clinical samples not epidemiological meaning that the findings can be generalised to clinical practice.

However, there are some limitations with the current review, particularly the heterogeneity of studies which assessed anxiety in FEP. Some studies comprehensively assess all anxiety disorders included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and counted cases, while other studies have focused only on one type of anxiety disorder. This review only investigated the overall anxiety rate rather than focusing on the different anxiety diagnoses. This was due to studies not reporting the diagnostic breakdown or having individuals with two comorbidities as two case counts. Therefore, the multiple ways in which anxiety and depression are conceptualised limits our interpretation. We recommend that future research should routinely measure anxiety alongside depression in FEP using validated continuous symptom measures. However, only two different measures were used in included studies for depression in FEP the Calgary depression scale (CDS) (Addington et al., 1993) and various versions of the structured clinical interview for DSM (SCID) (First, 2015), somewhat reducing heterogeneity for depression.

In addition, applying the inclusion criteria to the results only identified 10 research studies for inclusion, a surprisingly small number given the recent research and clinical investment in the area of early intervention for psychosis (EI) services (Joseph & Birchwood, 2005). The reviewers noted that nearly all studies within UHR assessed both anxiety and depression within the same study, albeit often not reporting or knowing the rates when re-assessed at transition to FEP or worsening symptom severity. There is recognition in UHR that comorbid anxiety and depression can lead to a worse clinical outcome and poorer functioning (Lim et al.,

2015), although research does not appear to investigate the relationship with worsening psychotic symptom severity in FEP. Overall most studies are of adequate quality for the cross-sectional baseline focus of this review, although most studies had small sample sizes. Further sensitivity analysis based on quality was also not possible due to the small number of included studies. There is also a risk of publication bias with this review as grey literature was not assessed.

Major depression with psychotic features and psychosis with depression are categorised as two distinct but arguably overlapping diagnosis. The current review included both, with 9.4% of the sample having major depression with psychotic symptom. This could have increased the rate of comorbid depression. However, the rates of the current review are not reliable due to high heterogeneity, the inclusion of both diagnostic groups within the review could account for the high heterogeneity.

1.5.2 Implications for research and clinical practice

Based on the findings of this review clinically separating anxiety and depression symptoms should be cautioned within FEP due to the similar frequency of presentation. Future research should also consider longitudinal design to assess the degree of anxiety and depression symptoms across the psychosis continuum. We advocate using continuous measures of symptoms, rather than simply ordinal diagnosis criteria to help understand the relationship between strength and variability. In particular, patient reported or service user outcomes within psychosis are increasingly being used clinically and within clinical research (Reininghaus & Priebe, 2012) and some measures are also focusing more on psychological distress (Greenwood et al., 2010), which includes anxiety and depression symptomology.

Therefore, a self-report measure of both anxiety and depression rather than a clinical interview may be more valid for clinical and research use.

Cognitive behavioural therapy (CBT) is evidence-based and recommended for use in FEP, together with a recognition that reducing distress should be part of the psychological treatment offering (NICE, 2014). More recently trans-diagnostic CBT informed approaches have been suggested, including metacognitive therapy (MCT) which has been shown to have potential efficacy for treating psychosis in feasibility studies (Hutton, Morrison, Wardle, & Wells, 2014; Morrison et al., 2014). This review recommends the use of trans-diagnostic CBT informed strategies to focus both on anxiety and depression equally within FEP. Some other suggested strategies for anxiety and depression could include; relaxation techniques, behavioural activation, reduce safety seeking or avoidance behaviour, behavioural experiments, graded exposure and cognitive restructuring. Indeed, the successful treatment of depression has been suggested to reduce deliberate self-harm and suicidality in FEP (Challis, Nielssen, Harris, & Large, 2013).

A positive association has also been shown between the prevalence of sleep disorders and increased psychotic symptoms, anxiety and depression in early psychosis (Davies, Haddock, Yung, Mulligan, & Kyle, 2017; Reeve, Sheaves, & Freeman, 2019). Thus, psychological interventions should also target sleep as this may impact on anxiety and depression in FEP.

It has also been suggested that the negative affect or high levels of anxiety and depression could trigger help-seeking behaviour in those with early psychosis (Morrison et al., 2012), which could explain the high levels of negative affect seen in the UHR and FEP populations. Recent research in a help-seeking UHR population

has shown that the self-reported distress associated with psychotic symptoms is strongly correlated both cross-sectionally and longitudinally with the severity of psychotic symptoms (Chapter 2). This suggests that those who seek help are likely to see a reduction in distress over time, which also leads to a reduction in their psychosis severity. Thus, emotional disturbance or distress is intrinsically associated with increased severity of psychotic symptoms and measures of anxiety and depression should be used to further understand this relationship in FEP.

1.5.3 Conclusion

A meta-analysis of available studies reporting both a measure of anxiety and depression in FEP suggests that anxiety and depression co-occur at a similar rate within FEP. However, the number of eligible included studies was small with high heterogeneity. Future research should consider routinely measuring anxiety and depression using continuous measures of symptoms, rather than simply ordinal diagnosis criteria to improve our understanding of the relationship strength, variability and change over time. The relationship between psychotic symptom severity and increased levels of anxiety and depression is complex and requires further trans-diagnostic investigation focusing on the overall symptom distress rather than diagnosis comorbidity. Indeed, anxiety and depression symptoms could be an inherent part of FEP and developing symptoms may be *normal* given the negative impact of diagnosis and treatment experiences on the individual. We recommend that trans-diagnostic CBT is used clinically to focus on both anxiety and depression in FEP, together with the psychotic symptoms.

1.6 **References**

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1.7 **Supplementary**

Table S1.1 List of *a priori* defined validated measures

	Measure
FEP	
	Positive and Negative Syndrome Scale (PANSS) Structured Clinical Interview for DSM (SCID) Comprehensive Assessment of At-Risk Mental State (CAARMS)
Depression	
	Beck Depression Inventory (BDI-II) Centre of Epidemiology Studies Depression Scale (CES-D) Hamilton Anxiety Depression Scale (HADS) Major Depression Inventory (MDI)
Anxiety	
	Beck Anxiety Inventory (BAI) Generalized Anxiety Disorder (GAD-7) The Social Phobia and Anxiety Inventory (SPAI) Liebowitz Social Anxiety Scale (LSAS) Social Interaction Anxiety Scale (SIAS)
Depression & Anxiety	
	Mini-International Neuropsychiatric Interview (MINI) Patient Health Questionnaire (PHQ) – Depression or Anxiety Positive and Negative Syndrome Scale (PANSS) – Depression or Anxiety Composite International Diagnostic Interview (CIDI) Structured Clinical Interview for DSM (SCID)

Table S1.2. Study quality assessment Downs & Black (1998)

	Reporting									
	1. Aims/ hypothesis	2. Outcomes	3. Patient characteristics	4. Interventions	5. Principle confounders	6. Main findings	7. Random variability estimates	8. Adverse events	9. Patients lost to follow-up	10. Probability values reported
Malla et al (2002)	1	1	1	0	2	1	0	0	1	1
Ma et al (2018)	1	1	1	0	1	1	1	0	0	1
Romm et al (2012)	1	1	1	0	1	1	1	0	0	1
Oosthuizen et al (2006)	1	0	0	1	1	0	0	0	0	1
Strakowski et al (1995)	1	1	1	0	1	1	1	0	0	1
Herniman et al (2018)	1	1	1	0	1	1	1	0	0	1
Salvatore et al (2009)	1	1	1	0	1	1	1	0	1	1
Michail & Birchwood (2013)	1	1	1	0	1	1	1	0	0	0
Birchwood et al (2006)	1	1	1	0	0	1	1	0	1	0
Voges & Addington (2005)	1	1	0	0	0	1	1	0	0	0

Table S1. 3. Continued…

	External Validity			Internal Validity - Bias						
	11. Representative recruited sample	12. Representative participated sample	13. Facilities representative	14. Blind sample to intervention	15. Blind study staff	16. Data dredging	17. Different follow-up times	18. Appropriate statistical tests	19. Intervention compliance	20. Valid measures
Malla et al (2002)	1	1	1	0	0	1	0	1	0	1
Ma et al (2018)	1	1	1	0	0	0	0	1	0	1
Romm et al (2012)	1	0	1	0	0	1	0	1	0	1
Oosthuizen et al (2006)	0	0	0	0	0	1	0	1	0	1
Strakowski et al (1995)	1	0	0	0	1	1	0	1	0	1
Herniman et al (2018)	1	0	0	1	1	0	0	1	0	1
Salvatore et al (2009)	1	0	1	0	1	1	1	1	0	1
Michail & Birchwood (2013)	1	0	0	1	0	1	0	1	0	1
Birchwood et al (2006)	1	0	0	0	0	0	0	0	0	0
Voges & Addington (2005)	1	1	1	0	0	1	0	1	0	1

Table S1.4 Continued…

	Internal Validity – confounding (selective bias)						Power	
	21. Same patients recruited	22. Recruited at same time	23. Randomised intervention	24. Blinded to randomisation	25. Confounding effect adjusted	26. Considered patient loss	27. Sufficient power	Total
Malla et al (2002)	1	1	0	0	1	1	-	18
Ma et al (2018)	0	1	0	0	0	0	-	13
Romm et al (2012)	1	1	0	0	0	0	-	14
Oosthuizen et al (2006)	1	0	0	0	1	0	-	9
Strakowski et al (1995)	0	1	0	1	0	0	-	13
Herniman et al (2018)	0	0	0	1	1	0	-	14
Salvatore et al (2009)	1	1	0	0	0	0	-	18
Michail & Birchwood (2013)	1	1	0	0	0	0	-	13
Birchwood et al (2006)	0	0	0	0	0	0	-	8
Voges & Addington (2005)	0	1	0	0	0	0	-	11

Note: Total score = 27 (higher the score the higher the methodological quality of the study)

Chapter 2

Distress related to psychotic symptoms in individuals at high risk of psychosis

This chapter has been written in the format and style required for the journal *Schizophrenia Bulletin*.

Word Count: *4895*

2.1 Abstract

Objective

This study assessed the relationship between distress, severity and frequency of attenuated psychotic symptoms in individuals meeting Ultra High Risk (UHR) criteria, both cross-sectionally and over time. We also assessed distress in relationship to attenuated symptoms and whether cognitive behavioural therapy (CBT) reduced distress over time by symptom type.

Method

A secondary analysis of UHR trial data was conducted. Data were assessed focusing on the distress, severity and frequency of attenuated psychotic symptoms. At baseline a combined total of 592 UHR participants (mean age 19.9; males, 53.9%) were assessed using a confirmatory factor analysis (CFA) and change over time was assessed using latent growth curve (LGC) models.

Results

Distress associated with psychotic symptom was a separate psychological construct from severity and frequency. Distress was significantly associated with severity but not frequency. Longitudinal LGC models with 244 participants found distress, severity and frequency all reduced over six months, although the rate of distress reduction varied across symptom type. Non-bizarre ideas (NBI) were more distressing and had the fastest rate of distress reduction over time. Individuals with higher baseline distress had greater distress reduction over time, with higher initial distress causing severity change for some symptom types. A 3-month rapid distress reduction phase was observed. CBT was not significantly different from monitoring in its effect on distress.

Conclusion

UHR participants are distressed by their psychotic symptoms. Distress reduces over time, particularly in the first 3 months after presentation. We recommend that distress should be used as an outcome in future clinical research and as a clinical indicator to guide the length of professional involvement.

Keywords: *Psychosis, at-risk mental state, UHR, structural equation modelling, distress, CBT, Latent growth curves*

2.2 Introduction

Psychosis is a mental health problem that causes people to perceive or interpret things differently from those around them. This may involve hallucinations or delusions, causing changes in mood and behaviour, which often result in severe distress for the individual. However, psychosis is a descriptive term for a continuum of behaviours, ranging from relatively normal unusual experience through to schizophrenia, with each person experiencing a unique combination of symptoms and distress.

Severe psychosis is usually preceded by a prodromal period (Yung & McGorry, 1996) and extensive research over the last decade has established the concept of an at-risk mental state (ARMS) or being ultra-high risk for psychosis (UHR) (Yung et al., 1996). Using the UHR criteria allows us to prospectively identify individuals who are at an increased risk of developing first episode psychosis (Yung et al., 2004; Yung et al., 2003), where the psychotic symptoms severity increases and the level of distress and functioning of the person will deteriorate further. This includes a combination of both state and trait factors for psychosis including; a family history of psychosis, attenuated positive psychotic symptoms or a brief psychotic period.

The first validated and reliable semi-structured tool developed to assess and operationalise the UHR criteria, was the Comprehensive Assessment of At-Risk Mental States (CAARMS), which was designed to be administered regularly by health care professionals to help-seeking individuals (Yung, Yuen, Phillips, Francey, & McGorry, 2005). The CAARMS uses cut-off scores on the severity of the unusual experience and the frequency of occurrences to distinguish UHR, and first episode psychosis. Within the CAARMS there are four subscales or categories of unusual

experience; perceptual abnormalities (PA), Non-Bizarre Ideas (NBI), unusual thought content (UTC) and disorganised speech (DS). The intensity and frequency for each unusual experience within a subscale is subsequently rated, alongside a self-reported measure of distress (rated from 0 (no distress) to 100 (extremely distressing) associated with each experience. The CAARMS measure of Distress has not to our knowledge been extensively assessed. However, distress is the defining feature of all psychological problems (Chadwick, Birchwood, & Trower 1996) and the importance of distress within psychosis has been recognised both as a predictor of onset and relapse over time (Owens et al., 2005).

The UHR group also have high levels of comorbid depression and anxiety symptoms (Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014), which are associated with impaired social functioning and high levels of distress (Lim et al., 2015). Clinically UHR individuals often report greater concern for their anxiety or depression symptoms compared to their attenuated psychotic symptoms (Fusar-Poli et al., 2013), which may be linked to the level of distress associated with these symptoms. In first-episode psychosis (FEP), where symptom severity has increased beyond criteria for UHR a similar level of comorbid anxiety and depression have been also been shown (Chapter 1). Due to this overlap with other non-psychotic disorders and most of the UHR group not transitioning to psychosis (de Wit et al., 2014; Lin et al., 2015; Rutigliano et al., 2016), UHR has more recently been viewed as a trans-diagnostic or pluripotent risk, rather than simply a risk of transitioning or not to psychosis (McGorry, Hartmann, Spooner, & Nelson, 2018; McGorry & Nelson, 2016). Thus, the distress associated with psychotic symptoms reported by UHR individuals may be of more clinical importance to their overall treatment

outcome over time. However, the literature on the distress related to psychotic symptoms within the UHR population is small.

Power & Polari (2015) show perceptual abnormalities (PA) to be associated with increased self-reported distress compared with other the types of symptoms as measured on the CAARMS, although the level of distress was not found to be significantly associated with the rate of transition to psychosis. A similar study found non-bizarre ideas (NBI) to have the highest levels of associated distress, followed by PA, with higher reported distress associated with increased rates of transition at one year follow-up (Rekhi, Rapisarda, & Lee, 2017). Rapado-castro, Mcgorry, Yung, Calvo, & Nelson (2015) also found a significant association between increased levels of distress and transition to psychosis, although distress in this study was assessed from a clinician perspective rather than self-reported.

The cognitive model of psychosis hypothesises that appraisals and responses to unusual experiences are likely to develop and maintain psychotic experiences (Morrison, 2001). In accordance with this model, it has been shown that the type of appraisal of the psychotic experience directly predicts the level of distress experienced (Brett, Heriot-Maitland, McGuire, & Peters, 2014). A manualised cognitive behavioural therapy (CBT) treatment approach has been developed (French & Morrison, 2004) and trialled with the UHR group (Fusar-Poli et al., 2012; Morrison et al., 2012; Stafford, Jackson, Mayo-Wilson, Morrison, & Kendall, 2013).

However, in many randomised control trials (RCTs) of interventions in the UHR group, transition to psychosis has been the primary outcome (Fusar-Poli et al., 2012; Morrison et al., 2012; Stafford et al., 2013; Addington et al., 2011; McGorry et al., 2002; Morrison et al., 2004; Yung et al., 2011). While self-reported distress has been

assessed as a secondary outcome in some UHR RCTs focusing on CBT, the findings have been mixed and analysis limited to composite distress scores (Morrison et al., 2011; Stain et al., 2016). This study aims to further explore self-reported distress and its relationship to psychotic experiences and beliefs over time, as measured on the CAARMS.

2.2.1 Hypotheses

The following *a priori* cross-sectional hypotheses were developed. First, that Distress is a separate psychological construct, with discriminant validity from the Severity and Frequency of psychotic symptoms. Second, that severity and frequency will be positively associated with distress, with severity more strongly associated with distress than frequency.

Additional longitudinal *a priori* hypotheses were also developed. Specifically, that the rate of change in distress will be greater compared to the severity and frequency for all symptom types. It was also hypothesised that CBT for psychosis will lead to earlier and overall greater reductions in distress over time compared to treatment as usual (TAU). This hypothesis is based on the cognitive model of psychosis (Morrison, 2001), where appraisals and responses to unusual experiences have been shown to predict distress (Brett et al., 2014).

Given the differences in distress scores shown between the CAARMS subscales in previous research (Power et al., 2016; Rapado-castro et al., 2015; Rekhi et al., 2017), we predict that cross-sectional distress will be greater for NBI and PA compared to the other symptom subtypes. Longitudinally, we hypothesise that distress will have different rates of change between the types of symptom (UTC, NBI, PA & DS), with the subtypes with higher baseline scores of distress showing faster reductions in

distress over time. Finally, we also hypothesised that distress at the initial assessment would predict the rate of change in severity of symptoms over time by treatment and symptom type. Therefore, suggesting that distress may influence rates of severity over time.

2.3 Methods

2.3.1 Design and participants

The data were from two studies; 1) The Early Detection and Intervention Evaluation (EDIE 2) trial (Morrison et al., 2012) and 2) The NEURAPRO trial (McGorry et al., 2017). EDIE-2 evaluated the effect of Cognitive Behavioural Therapy (CBT) on the rate of transition to psychosis, whilst NEURAPRO assessed the efficacy of Omega-3 on reducing psychosis transition rates. Ethical approval was obtained for both studies, see McGorry et al (2017) and Morrison et al (2012) for further information. The comprehensive assessment of at risk mental state (CAARMS) (Yung et al., 2005; Yung et al., 2003) was used to assess entry criteria in both studies (see supplementary; Table S2.1) and all subjects were defined as being ultra-high risk (UHR). Data from both studies was used to assess our cross-sectional hypotheses.

To assess our longitudinal hypotheses only the EDIE-2 CAARMS data were used in the analysis due to the frequency of the assessment intervals. EDIE-2 administered individual Cognitive Behavioural Therapy (CBT) to those randomised to treatment, using an individualised formulation developed collaboratively with the client based on the cognitive model of psychosis (Morrison, 2001). For more details regarding the CBT treatment, see the treatment manual (French & Morrison, 2004). The longitudinal NEURAPRO data were not used as the treatment was pharmacological and could not be directly compared. EDIE 2 data were collected at 1-month intervals

for six months post-randomisation, seven time points in total (including baseline), for both CBT and treatment as usual (TAU).

2.3.2 Measure: Comprehensive assessment of at risk mental state (CAARMS)

The CAARMS uses the severity of the psychotic symptom and the frequency of occurrence as continuum indicators of UHR, attenuated psychosis or psychosis (Yung et al., 2005; Yung et al., 2003). Within the CAARMS there are four subscales of symptom type; Unusual Thought Content (UTC) (e.g. delusional mood, overvalued ideas and delusions), Non-Bizarre Ideas (NBI) (e.g suspiciousness, grandiose ideas), Perceptual Abnormalities (PA) (e.g visual or auditory hallucinations), and Disorganised Speech (DS) (e.g subjective and objective communication difficulties). The severity and frequency are assessed for each subscale (UTC, NBI, PA & DS) and rated by a trained interviewer (score 0-6, with 6 indicating higher levels). There is also a question within each subscale where participants were asked how distressing they found each symptom (scored 0-100%, with 100 being the most distress). These Distress raw scores were categorised into a 0 to 6 (categories: 0, 0≤20, 20≤40, 40≤60, 60≤80, 80≤100). If participants did not experience a symptom type then the associated frequency and distress are undefined (i.e. missing).

2.3.3 Statistical analysis

All statistical analysis was conducted using Stata 13© (StataCorp, 2013). Initially, the CAARMS scores were compared using a multivariate analysis of variance (MANOVA) by dataset to determine any significant difference between the EDIE-2 and NEURAPRO.

Using a structural equation modelling (SEM) framework, confirmatory factor analysis (CFA) models were used to evaluate the cross-sectional hypotheses. These models represent the observed scale items as error-prone measures of unobserved latent constructs.

A maximum likelihood estimator, robust to violations of mean and variance normality assumptions (MLMV) was used for all models. This estimator assumes that data were Missing At Random and therefore assumes the likelihood of a response being missing is predicted by the observed data (Little & Rubin, 1989). MLMV estimation has been shown to be an acceptable estimation method in cases where multivariate normality assumptions may be violated (Graham, 2009). A sensitivity analysis of the cross-sectional CFA models was also completed using ordinal logistic models.

2.3.3.1 Cross-sectional hypothesis testing

CFA was used to assess the dimensionality of the CAARMS by subscale (Severity, Frequency & Distress), to determine discriminant validity for the subscales at baseline. Using a nested modelling approach, Model 1 was a unifactorial model with one factor of overall experience, where the distress, frequency and severity items for all four symptom types loaded onto a single factor. Model 1 therefore assumed no discriminant validity, only a single dimension of psychosis *intensity*. Model 2 was a two-factor model with one factor for the Severity and Frequency items and one factor for the Distress items. Model 3 assumed full discriminant validity of the subscales, with three separate factors for Severity, Frequency and Distress. For all models the item residuals were allowed to correlate between symptom type within subscale.

2.3.3.2 **Longitudinal hypothesis testing**

Latent growth curve (LGC) models within a SEM framework were used (McArdle & Epstein, 1987). Growth curves were defined separately for the twelve combinations of symptom type (UTC, NBI, PA and DS) and subscale (Distress, Severity and Frequency). Each growth model had latent intercepts for the baseline measures and latent slopes representing the rate of change over the subsequent measures. Time was operationalised as months from treatment randomisation.

For each growth model we compared linear and quadratic slopes. The latent growth factors were allowed to inter-correlate freely. Because of computational limitations it was not feasible to fit models that simultaneously contained all three subscale outcomes; Distress, Severity and Frequency. Instead, each model estimated growth curves separately for either Distress and severity or Distress and Frequency, so that comparisons between subscales could be conducted. Due to the likely effect of occasion-specific influences, the residuals across subscales were allowed to correlate within timepoint. All models included the effect of treatment, by regressing the growth intercept and slope parameters on a dummy variable for CBT (vs. TAU). The effect of treatment on the growth intercepts was completed as a randomisation check, we did not expected a differences between the randomized treatment groups at baseline. For each symptom type the following models were fitted separately for Distress and Severity, or Distress and Frequency; Model 1 was a model of Distress and one of the other subscales (Severity or Frequency) with a linear slope. Model 2 added a quadratic slope. Model 3 added intercorrelated residuals across sub-scales within timepoint.

In the final models, we regressed the latent slopes of one sub-scale on the latent intercepts of another subscale to evaluate possible causal relationships among the

sub-scales of Distress and Severity. We compared nested models using Chi-squared test of difference. The comparative fit index (CFI) of > 0.9 (Bentler, 1990) and the root mean squared error of approximation (RMSEA) < 0.08 indicate an adequate model fit (Steiger, 1990) and were both used to determine model acceptability. See supplementary Table S2.2Table S2.3 for overview of models used to assess each hypothesis.

2.4 **Results**

2.4.1 Cross-sectional baseline analysis

The data were combined at the single baseline pre-randomisation time point (T1), with a total of *n=592* participants (319 males, 53.9%) with a mean age of 19.9 ± 4.5 years standard deviations (Table 2). The differences between scores on the CAARMS by dataset was first assessed using a MANOVA, which showed no significant difference between datasets at baseline for any of the scores *(F(12,176)=1.35, p=0.192).* On average, the subscale of NBI was associated with the highest distress scores (66.54%), followed by UTC (56.31%), PA (52.57%) and DS (34.88%), this pattern was the same across datasets. NBI was also associated with the highest Severity and Frequency scores.

Table 2. Demographic information and CAARMS mean scores at baseline (T1) by factor (Severity, Frequency and Distress) and symptom subscale (UTC, NBI, PA and DS)

			Dataset	
		All (n=592)	EDIE-2 (n=288)	NEURAPRO (N=304)
Age (years)				
	Mean (s.d)	19.9 (4.5)	20.7 (4.3)	19.1(4.5)
	Median	19	19	18
	Min-Max	13-39	14-34	13-39
Gender				
	Females (%)	273 (46.1)	108 (37.5)	165 (54.3)
	Males (%)	319 (53.9)	180 (62.5)	139 (45.7)
CAARMS *mean (s.d)*				
Severity (SEV) (0-6)				
	UTC severity	2.47(2.0)	2.52(1.9)	2.44(2.0)
	NBI severity	3.41(1.6)	3.49(1.5)	3.34(1.7)
	PA severity	3.16(1.6)	3.03(1.7)	3.29(1.5)
	DS severity	1.41(1.4)	1.46(1.5)	1.37(1.3)
Frequency (FREQ) (0-6)				
	UTC frequency	3.46(1.3)	3.57(1.3)	3.34(1.3)
	NBI frequency	3.86(1.1)	3.80(1.2)	3.85(1.1)
	PA frequency	3.13(1.3)	3.13(1.3)	3.17(1.2)
	DS frequency	3.46(1.2)	3.36(1.2)	3.56(1.2)
Distress (DIS) (0-100%)				
	UTC distress	56.31(32.0)	55.29(34.2)	57.38(29.6)
	NBI distress	66.54(26.7)	68.94(27.9)	64.05(25.2)
	PA distress	52.57(33.8)	53.57(34.7)	51.65(32.9)
	DS distress	34.88(30.4)	33.42(32.4)	36.34(28.3)

Note. A MANOVA showed no significant difference between datasets at baseline for any of the scores *(F(12,176)=1.35, p=0.192)*
See study protocol; NEURAPRO (McGorry et al., 2017) and EDIE-2 (Morrison et al., 2012)

The model fit indices of the CFA for each of the three different hypothesised factor models are shown in Table 3. Model 3 (three-factor) had the best overall fit, indicated by significant Chi-squared difference tests compared to models 1 and 2 (χ^2 =76.493(3), $p \leq 0.001$ and χ^2 =37.775 (2), $p \leq 0.001$, respectively). Model 3 also had the best fit statistics from all the Models tested (RMSEA=0.042 and a CFI= 0.924). This finding was reproduced when using ordinal logistical regression as part of a sensitivity analysis (see supplementary Table S2.4; Figure S2.1).

Table 3. Comparison of CFA models with fit indices for the CAARMS

Model	χ^2 (df)	Comparison	χ^2 (df) diff	RMSEA	CFI
1. One-factor model	156.257 (42), *p=0.001*	*n/a*	*n/a*	0.068	0.788
2. Two-factor model	117.539 (41), *p=0.001*	*Model 1 v. Model 2*	38.718 (1), *p≤0.001**	0.056	0.858
3. Three-factor model	79.764 (39), *p=0.001*	*Model 1 v. Model 3*	76.493(3), *p≤0.001**	0.042	0.924
		Model 2 v. Model 3	37.775 (2), *p≤0.001**		

Note. All statistics based on maximum likelihood robust estimation;
CFA, Confirmatory factor analysis;
CAARMS; Comprehensive assessment of at risk mental state
CFI, Confirmatory fit index;
RMSEA, Root-mean-squared residual;
n/a, not appilicable.
* Significant at p≤0.01

Model 3 is illustrated in Figure 4. All items had significant loadings onto their corresponding latent factor, with standardised loadings ranging from 0.19 to 0.66 (see supplementary Table S2.5). These are low to modest loadings, which together with the good goodness-of-fit model statistics suggest that some of the questionnaire items do not have a high reliability. Items with r<0.4 are usually considered not related to the other items (Osborne, Costello, & Kellow, 2008). NBI had the lowest loading onto Distress (r=0.39). However, the items for Frequency were all very low, except for UTC which had a very good loading (r=0.66), suggesting overall that Frequency may be a poorly measured construct on the CAARMS. PA and DS were both low loadings onto Severity. The resulting scale reliabilities were; Severity *ρ=0.43*, Frequency *ρ =0.49*, and Distress *ρ =0.51*.

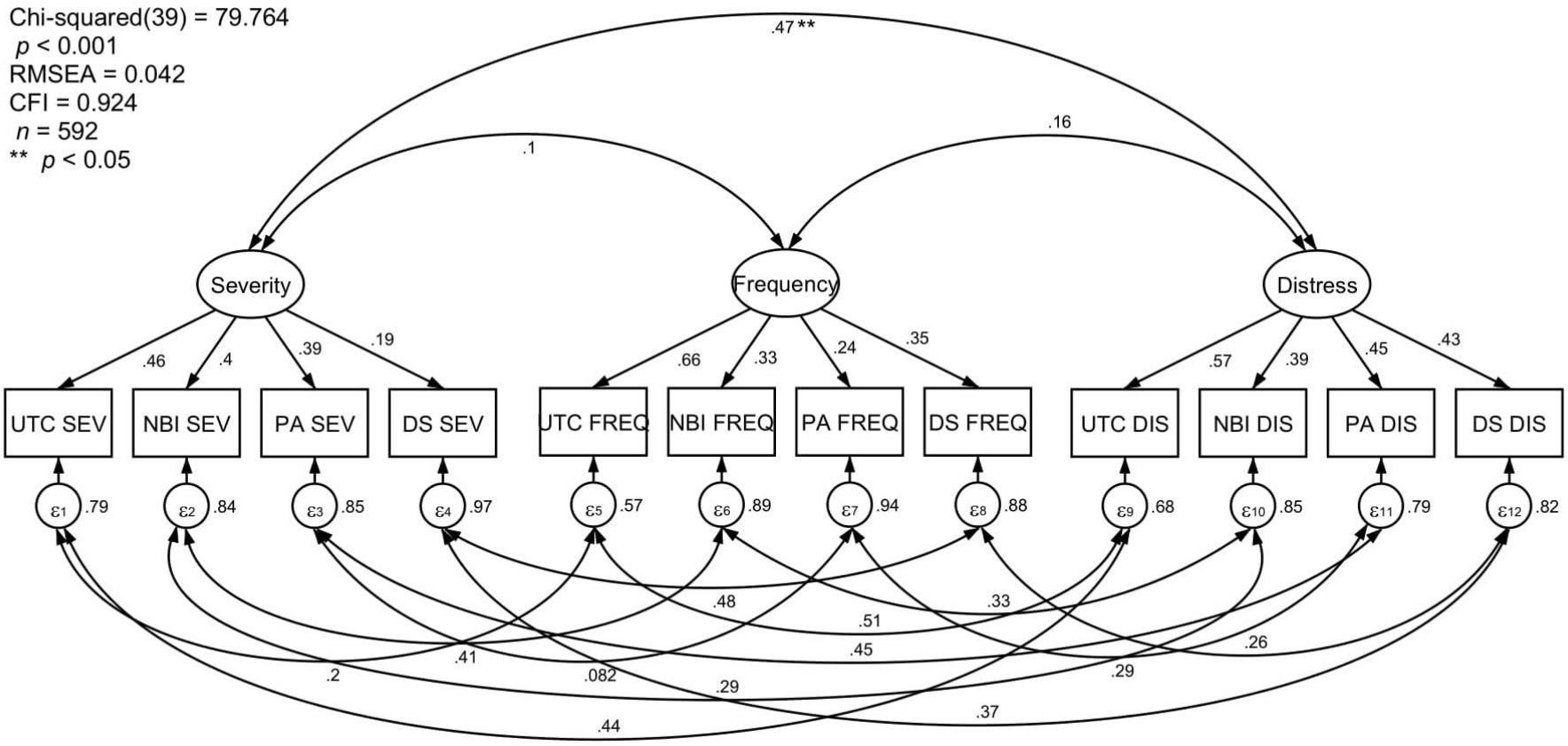

Figure 4. Model 3: Three-factor CFA of Severity, Frequency and Distress symptoms of psychosis at Baseline.

There was a significant correlation between the latent factors of Severity and Distress (*r=0.47, p=0.001),* indicating that the higher the severity score the higher the distress score. The other latent factors were not significantly correlated (Severity and Frequency, *r = 0.11, p=0.458;* Distress and Frequency, *r= 0.16, p=0.127*) Due to the three-factor model providing an improved goodness-of-fit and the factor correlations being <0.90 (Henseler, Ringle, & Sarstedt, 2014), discriminant validity was demonstrated between the factors of Severity, Frequency and Distress.

2.4.2 Longitudinal LGC analysis of EDIE data

Only the EDIE 2 data were analysed for the longitudinal hypotheses. Of the n=288 who completed the baseline time point (T1), 236 completed T2 (81.94%), 211 completed T3 (73.26%), 207 completed T4 (71.88%), 187 completed T5 (64.93%), 170 completed T6 (59.03%) and 196 completed T7 (68.06%) (supplementary Table S2.6).

For all symptom types the latent growth curve (LGC) Model 3 (Quadratic + residuals) had the best overall fit (Supplementary Table S2.7). The linear slope means were all negative and the quadratic were positive for all symptom types, resulting in the mean growth curves shown in Figure 5. Overall, non-bizarre ideas (NBI) were more distressing and had the fastest and largest rate of distress reduction over time, followed by unusual thought content (UTC), perceptual abnormalities (PA) and disorganised speech (DS). The parameter estimates for the Distress predicted by treatment are shown in Table 4 and demonstrate no significant effect of treatment on the longitudinal development (intercept, linear slope or quadratic slope) of distress in any symptom type (supplementary: Table S2.8; Figure S2.2). This

suggests that CBT does not differentially influence the rate of change in distress between symptom types, see Supplementary Figure S2.3.

Table 4. Distress parameter estimation from final models for each symptom type.

Symptom type	Mean Intercept	Linear slope	Quadratic slope
Unusual Thought Content (UTC)			
TAU	2.71 (0.15)	-0.60 (0.09)	0.07 (0.01)
CBT	-0.20 (0.19)	-0.041 (0.12)	0.012 (0.02)
Treatment effect	*z= -1.04, p=0.297*	*z= -0.34, p=0.731*	*z= 0.59, p=0.555*
Non-Bizarre Ideas (NBI)			
TAU	3.49 (0.13)	-0.76 (0.08)	0.08 (0.01)
CBT	0.07 (0.17)	0.024 (0.11)	-0.002 (0.02)
Treatment effect	*z= 0.38, p=0.703*	*z= 0.21, p=0.834*	*z= -0.13, p=0.896*
Perceptual Abnormalities (PA)			
TAU	2.75 (0.14)	-0.59 (0.09)	0.07 (0.01)
CBT	-0.32 (0.20)	-0.00 (0.12)	0.01 (0.02)
Treatment effect	*z= -1.64, p=0.102*	*z= -0.02, p=0.985*	*z= 0.39, p=0.695*
Disorganised Speech (DS)			
TAU	1.63 (0.14)	-0.18 (0.08)	0.021 (0.01)
CBT	0.15 (0.18)	-0.03(0.10)	-0.003 (0.02)
Treatment effect	*z= 0.82, p=0.410*	*z= -0.32, p=0.753*	*z= -0.20, p=0.843*

Note. All statistics based on maximum likelihood robust estimation; effects labelled TAU are the actual latent growth factors parameter estimates, and effects labelled CBT are the differences in latent growth parameters estimates between treatments.
TAU: Treatment as usual *(constant=0).*
Treatment effect is when Treatment =1(CBT).
Coef. (Standard error)
* Significant at $p \leq 0.05$, when treatment effects are zero in the population

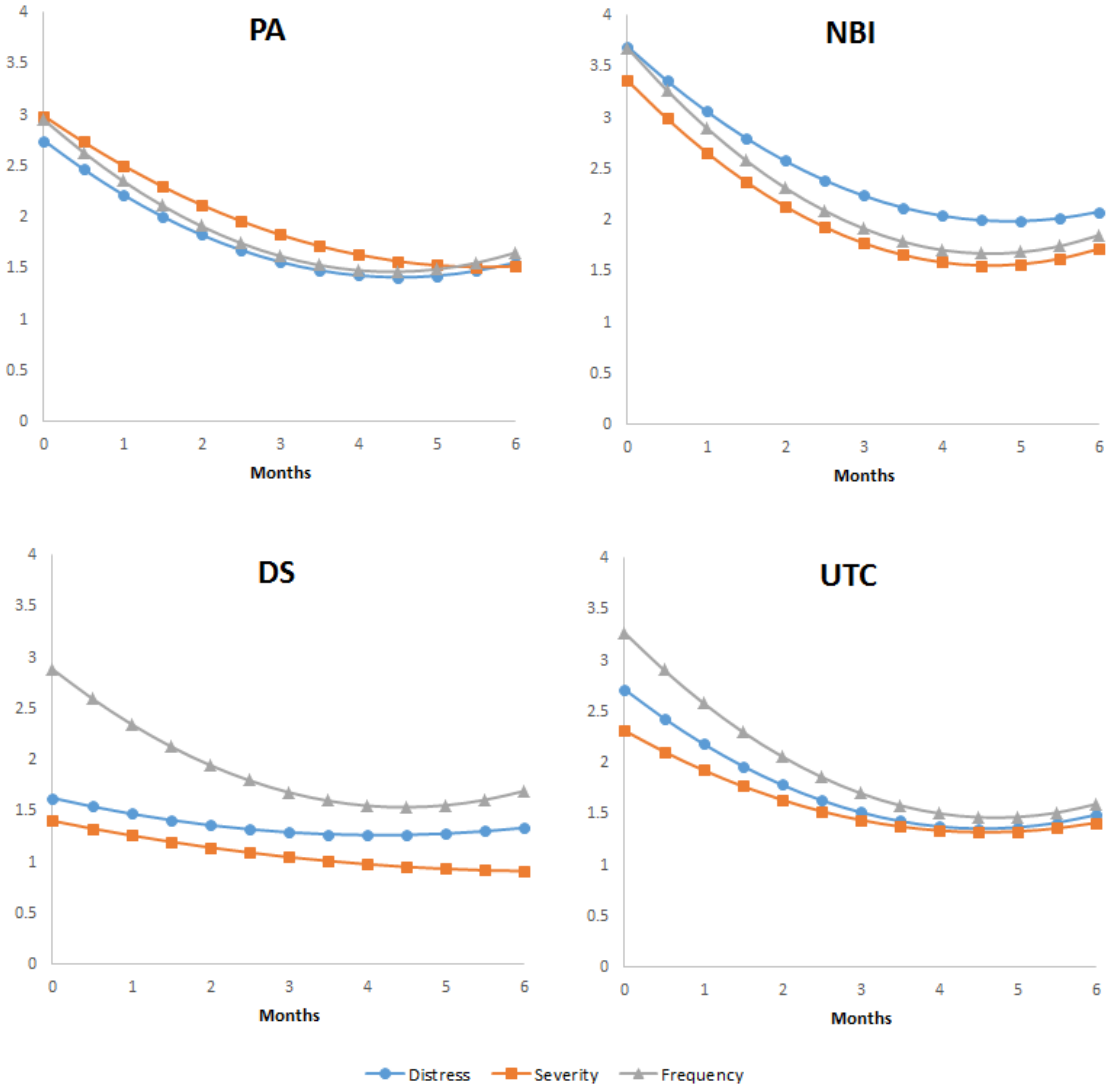

Figure 5. The rate of change of Distress, Severity and Frequency by symptom type when Treatment=0 (TAU).

A significant negative covariance was found between the Distress intercept and slope within UTC (r= -0.095, SE:0.034, z=-2.75, p=0.006), PA (r= -0.165, SE:0.043, z=-3.85, p<0.001) and DS (r= -0.121, SE:0.025, z= -4.78, p<0.001), indicating higher initial distress was associated with a greater reduction in distress over time. NBI (r= -0.011, SE: 0.027, z= -0.41, P=0.685) did not show a significant covariance between growth intercept and slope.

A series of Wald Chi-squared tests were used to evaluate the equality of growth slopes (linear + quadratic) of Distress compared to Severity and Frequency, which showed no significant difference for any of the symptom types (supplementary Table S2.9).

A final series of cross-lagged models for each symptom type, showed a significant effect of baseline Distress on the rate of Severity change over time for UTC (Linear: z= 5.88, SE:0.11, p<0.001 and Quadratic slope: z= 6.10, SE:0.16, p<0.001) and NBI (Linear: z= 3.41, SE:0.09, p=0.001 and Quadratic slope: z= -3.90, SE:0.01, p<0.001). For UTC and NBI, higher Distress at baseline resulted in a slower and more protracted reduction in Severity change over time (Figure 6). However, the effect of baseline Severity on rate of Distress change was not as large or significant for UTC and NBI respectively. Therefore, suggesting some causal plausibility for initial baseline Distress causing reduced rates of Severity change over time for UTC and NBI symptoms. For PA and DS no significant cross-lagged relationship emerged with baseline distress, although PA showed initial baseline severity significantly predicted distress rate of change (Linear: z=-3.17, SE:0.07, p=0.002 and Quadratic slope: z=-2.34, SE:0.01, p=0.019), suggesting that severity of symptom causes distress change over time for PA symptoms. See Figure 6 for the path model of each symptom type. While each type of psychotic symptom appears to have a different causal relationship with distress, no significant effects of CBT were found (supplementary Table S2.10).

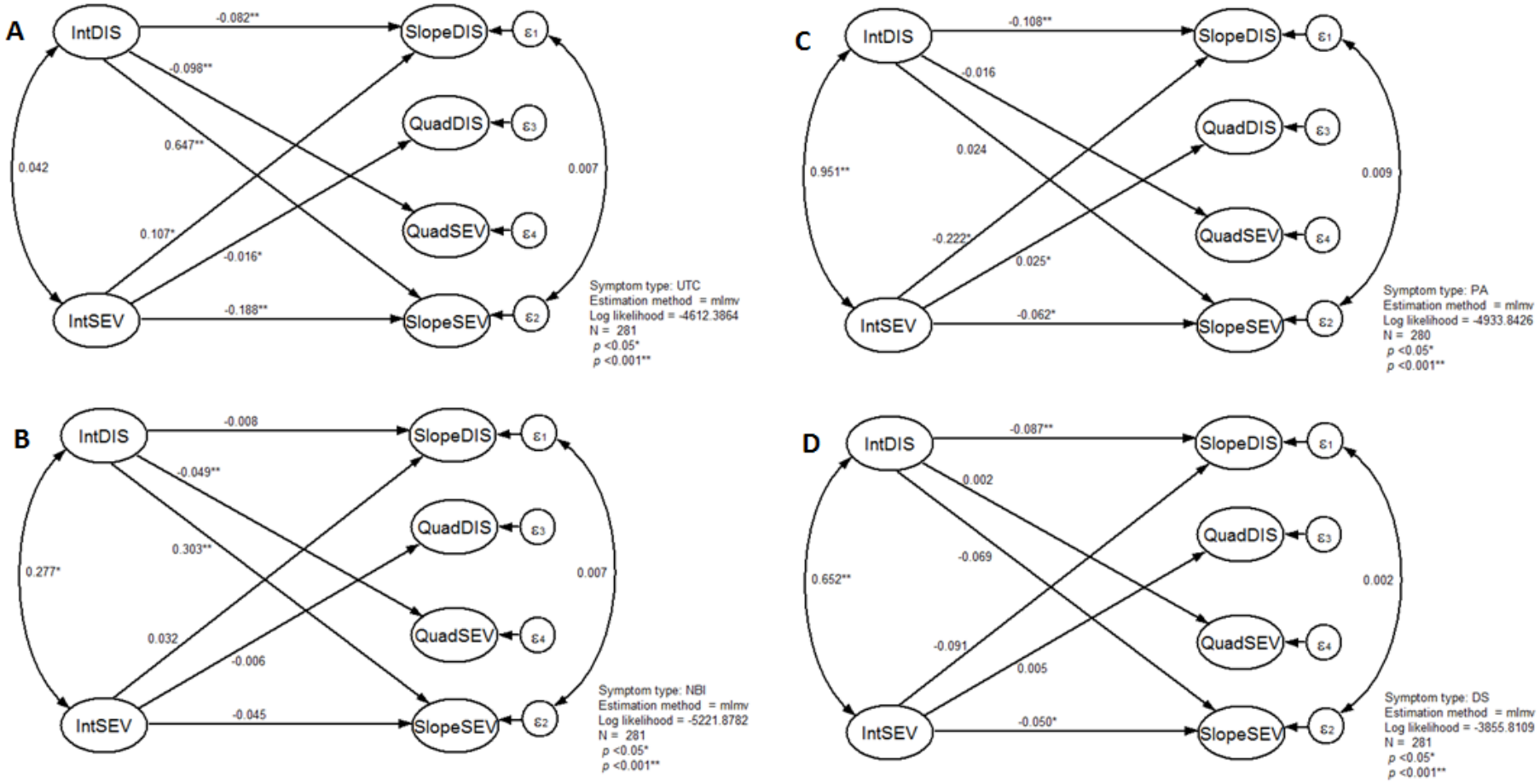

Figure 6. Estimated models for cross-lagged LGC relating Distress and Severity for each symptom subscale; A) UTC, B) NBI, C) PA & D) DS

2.5 Discussion

Distress associated with psychotic symptoms was shown to be a separate psychological construct from the severity and frequency of symptoms in individuals at ultra-high risk (UHR) of psychosis. Symptom severity and distress are also shown to be significantly correlated at baseline. However, symptom frequency was not shown to be associated with either severity or distress. Longitudinally, distress, severity and frequency of psychotic symptoms all reduced over time, although the rate of distress change varied for symptom type. Overall, non-bizarre ideas (NBI) were more distressing and had the fastest and largest rate of distress reduction over time, followed by unusual thought content (UTC), perceptual abnormalities (PA) and disorganised speech (DS). The effect of CBT on distress over time was not significantly different from that of TAU for any of the symptom types. However, distress did reduce over time on average across subjects. Individuals with higher distress at initial assessment also had a higher distress reduction over time, with a three month rapid distress reduction phase observed. We also found evidence to support high initial distress causing symptom severity to change over time for UTC and NBI.

To our knowledge this was the first study to show discriminant validity between distress, severity and frequency of symptoms. The ultra-high risk (UHR) criteria is based on the severity and frequency of symptoms (Yung et al., 2004; Yung et al., 2003) as assessed on measures like the CAARMS (Yung et al., 2005). However, we show that the distress associated with symptoms was also associated with the symptom severity. Indeed, we additionally show that symptom severity change over time was also strongly predicted by the initial baseline distress score for some types

of symptom, notably UTC and NBI. Recently, McGorry and colleagues (2016, 2018) have highlighted the importance of distress as a trans-diagnostic factor within the UHR population, which the current study supports.

Based on the cross-sectional CFA only the severity of symptoms was strongly associated with distress, whereas the frequency was not, concordant with our hypothesis. This was likely to have been due to some individuals being highly distressed by low frequency symptoms and others experiencing low distress with high frequency symptoms (Yung et al., 2004; Yung et al., 2003). Interestingly, no significant association was shown in the cross-sectional data between severity and frequency of symptom. This requires further investigation and suggests that quantifying the symptom in terms of the severity and frequency, albeit important within the traditional UHR criteria, may not be as clinically useful or robust as the associated distress within the population.

Some of the item factor loadings for severity and most for frequency were low (Osborne et al., 2008), suggesting that these items may not be reliably measuring the UHR criteria or additional factors should be explored. However, three out of four items for distress had satisfactory loadings, suggesting greater similarity across symptom type compared to severity or frequency. This was supported by our finding that the distress scale had the highest overall reliability compared to severity or frequency. Nevertheless, the low factor loadings and, therefore, weak reliability could account for the lack of treatment effect of CBT.

The different symptom types showed different baseline cross-sectional distress, with NBI having the highest associated distress, followed by UTC, PA and lastly DS. This was a robust finding across multiple datasets. NBI has previously been

associated with the highest reported distress levels, alongside increased transition to psychosis rates at one year follow-up (Rekhi et al., 2017). This was arguably not surprising given that suspiciousness or persecutory ideas are included within the NBI CAARMS subscale. These symptoms are associated with negative appraisals that have been clinically observed to be more closely linked with distress. However, the initial level of NBI distress was not associated with subsequent rates of distress reduction. This suggests that NBI contains a heterogeneous population where some highly distressed people have a slow rate of change, while others with a low baseline distress make quicker change. This could be due to grandiosity also being within the NBI subscale, which anecdotally has been associated with less distress. This idea was supported by our finding of low factor loading of NBI onto distress in the CFA.

The finding that CBT does not affect distress reduction over time in UHR was not novel with the EDIE dataset and possible reasons for this have been extensively reviewed elsewhere, although unlike the previous trial (Morrison et al., 2012), we assessed the CAARMS distress within each symptom type rather than as a composite distress measure across all positive symptoms. However, we do not show more distress reduction over a six month time period with CBT separately for any of the symptom types. This was perhaps surprising given that an individual's appraisal of their symptoms has been shown to influence the level of distress (Brett et al., 2014; Mawson, Cohen, & Berry, 2010), consistent with the cognitive model of psychosis (Morrison, 2001).

However, effect sizes for CBT for psychosis have thus far been small for the improvement of positive symptoms (i.e. symptom severity) (Jauhar et al., 2014), although recently it has been suggested that by focusing on particular symptoms

(Lincoln & Peters, 2019), such as distressing voices using CBT (Thomas et al., 2014) the effect sizes could be improved and distress targeted and reduced (Hayward, Edgecumbe, Jones, Berry, & Strauss, 2018). The findings from this study also support symptom specific treatment approaches, as we show that distress may cause the change in severity of symptom for UTC and NBI, although severity of PA appears to lead to change in distress over time. This suggests specific theoretical treatment models may be required for the different symptom types.

Overall, distress reduced over time across treatment groups for all symptom types. It could be that the regular empathic monitoring could have been both normalising and therapeutic, reducing distress over time. Indeed, having somebody to talk to, even during the monitoring sessions, was identified as a positive experience by EDIE trial participants (Byrne & Morrison, 2014). Additionally, being part of a clinical trial may have prevented people from feeling lost within the health system, allowing them to gain help and support.

2.5.3 Clinical implications

Patient reported outcomes within psychosis, such as the CAARMS distress measure used in the current study, are increasingly being used clinically and within clinical research (Greenwood et al., 2010; Reininghaus & Priebe, 2012). This has coincided with the greater emphasis on personal recovery and the patient reported outcomes fit well within a recovery conceptual framework (Leamy, Bird, Le Boutillier, Williams, & Slade, 2011). Within psychosis there has been a focus on improving outcome measures for service users which take more consideration of distress, including psychosis-specific distress (Greenwood et al., 2010). With the clinical and research focus in UHR increasingly moving from identifying worsening symptom severity or

rates of transition to first-episode (FEP) to improving the overall level of distress and quality of life trans-diagnostically (McGorry et al., 2018; McGorry & Nelson, 2016), we show that the already used CAARMS measure of distress can add clinical and research information.

However, we recommend that future clinical research trials and clinicians working therapeutically evaluating pre- and post- therapy outcomes should consider measuring distress alongside traditional symptom severity. While severity of symptom and the level of distress are correlated, distress offers a more collaborative and client-centred approach, which clearly shows a reduction over time. Additionally, with more trials assessing distress, future meta-analyses could also assess distress across similar interventions for UHR.

Higher distress at initial assessment was associated with a higher rate of distress reduction over time in UHR patients. Clinically, this suggests that patients who are distressed should be given sufficient opportunity to engage with mental health professionals. Conversely, intervening when attenuated symptoms are not associated with distress may not be justified. Although, we do not show evidence to support a CBT intervention by symptom type for distress reduction. Regular (once a month) supportive listening and assessment which was empathic, understanding and normalising, together with access to crisis care and signposting, during the monitoring appointments with a healthcare professional seemed sufficient to reduce distress over time for all symptom types.

The causal relationship between distress and symptom severity change over time was dependent on the symptom type. This could explain the low effect sizes typically reported for generalised CBT approaches in psychosis. Future trials should consider

developing psychological treatment focusing on specific symptoms. However, we recommend that primarily clinicians should focus on reducing distress, particularly for UTC and NBI symptoms, as this has been shown to reduce the symptom severity over time. We also show that the first few initial assessment sessions will be the most efficacious at reducing distress over time and clinicians should be aware of their importance.

2.5.1 Limitations and implications for future research

There are some limitations which should be considered. The CFA assumed homogeneity across symptom type, which could account for the low reliability, although the overall model fit statistics were good, separate models for each symptom could evaluate this further. In addition to this, only having one observed measure of distress may have limited measurement of the latent variables. Separate measures for depression and anxiety were collected as part of the original EDIE data collection, although they were not considered within the current study analysis which was a potential limitation. Future research should include other validated measures of distress, such as depression and anxiety measures.

The longitudinal growth models also assumed that data were missing at random, while reasons for missing data were investigated, it was possible that the drop-out of participants or missing data may not be random. Therefore, alternative models which assume the data are not missing at random (Enders, 2011) could be applied in future. The growth models also assumed homogenous, normally distributed latent variables for subscales and growth. Growth mixture models, which allow for non-homogenous, non-normal growth, could be used instead. Finally, the reductions in scores could represent a regression to the mean, a ubiquitous problem in studies

designed around selection of participants with high scores and subsequent reassessment on the same factors.

2.5.2 Conclusion

People at ultra-high risk (UHR) of psychosis are distressed by their psychotic symptoms. Distress was associated with the severity of symptom type but not with its frequency. After engagement in a clinical service, distress reduces over time, particularly in the first 3 months. Non-bizarre ideas (NBI), including persecutory ideas, are the most distressing symptom type, followed by perceptual abnormalities (PA), unusual thought content (UTC) and disorganised speech (DS). Distress may also cause the severity of symptom to change over time for UTC and NBI, suggesting that symptom specific psychological treatment approaches are required. We recommend that distress associated with attenuated psychotic symptoms should be assessed as an outcome measure in future UHR research and clinical practice. Our findings also suggest that distress could be used as a clinical indicator to guide the length of professional involvement.

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2.7 Supplementary

Table S2.1 Comparing the combined studies according to study protocol

	EDIE 2	NEURAPRO
Setting	Multi-site UK study involving; • Manchester • Birmingham/ Worcestershire • Glasgow • Cambridgeshire • Norfolk	Multi-site study involving; • Australia (Melbourne, Sydney) • Netherlands (Amsterdam) • Germany (Jena) • Switzerland (Basel, Zurich) • Austria (Vienna) • Denmark (Copenhagen) • Singapore • Hong Kong (Pok Fu Lam).
Sample	• N=288 • Help-seeking • Age 14 - 35	• N=304 • Help-seeking • Age 13 - 40
Inclusion	CAARMS criteria (+ GAF): 1. BLIPS 2. Attenuated symptoms 3. State-plus-trait	CAARMS criteria (+ SOFAS) 1. BLIPS 2. Attenuated symptoms 3. State-plus-trait
Exclusion	• Current or previous antipsychotic medication for more than 2 days • Moderate to severe learning disability • organic impairment • Insufficient fluency in English (for standardized measures)	• Past history of a treated or untreated psychotic episode of one week's duration or longer • Organic brain disease • Abnormal coagulation profile parameters or thyroid function test results >10% above or below the limits of the normal range. • Any physical illness with psychotropic effect, if not stabilized • Current treatment with any mood stabiliser, or recreational use of ketamine. • Past neuroleptic exposure • Diagnosis of a serious developmental disorder, e.g. Asperger's syndrome • Premorbid IQ < 70 and a documented history of developmental delay or intellectual disability • Current aggressive/ dangerous behaviour • Current suicidality/self harm • Current pregnancy • Current attenuated due to acute intoxication • > than 4 weeks of regular omega-3 supplementation
Trial design	Randomized single-blind controlled, trial; randomized after 2nd baseline	Randomized placebo controlled trial; randomised at entry

Note. See study protocol; NEURAPRO (McGorry et al., 2017) and EDIE-2 (Morrison et al., 2011)

Table S2.2 Cross-sectional hypothesis and corresponding model specifications

Hypotheses	Model type	Model comparisons	All or separately by symptom type
Cross-sectional			
1) Distress has discriminant validity from Severity and Frequency	Confirmatory Factor Analysis (CFA)	Compare model fit statistics and χ^2 between: 1) One-factor model 2) Two-factor model 3) Three-factor model If three-factor model has significantly improved model fit accept hypothesis 1.	Across all symptom types
2) Severity and Frequency are positively associated with distress, with severity more strongly associated	Confirmatory Factor Analysis (CFA)	Final CFA model latent variable (Distress, Severity and Frequency) correlations	Across all symptom types
3) Distress will be greater for NBI and PA compared to the other symptom subtypes	Mean scores	Highest mean score at baseline	Separately by symptom type

Table S2.3 Longitudinal hypothesis and corresponding Latent Growth Curve (LGC) model specifications

Hypotheses	Model comparisons
1) Distress rate of change will be greater compared to the severity and frequency for all symptom types	Part 1: Compare model fit statistics and χ^2 between: 1) Model with Linear slope 2) Model with Quadratic slope 3) Model with Quadratic slope + correlated residuals Which model has the best overall fit. Part 2: Assess slope for rate of change and compare slopes between Distress, Severity and Frequency using Wald χ^2 tests. If slopes are statistically different accept hypothesis.
2) CBT for psychosis will lead to earlier and overall greater reductions in distress over time compared to TAU	Final LGC model including treatment as a covariate on the intercept, linear or quadratic slope. If CBT significantly effected the slope of Distress change over time accept hypothesis.
3) Distress will have different rates of change between the types of symptom	Final LGC model including treatment as a covariate on the intercept, linear or quadratic slope. Compare slopes of distress across different symptom types using Wald χ^2 tests. If the slopes are statistically different accept hypothesis.
4) Higher baseline Distress scores will show faster reductions over time.	Final LGC model including treatment as a covariate on the intercept, linear or quadratic slope. Assess the covariance between the intercept and slope for distress If there is a significant covariance accept hypothesis.
5) Distress at the initial assessment would predict rates of severity change over time.	Final LGC model including treatment as a covariate on the intercept, linear or quadratic slope. Also including baseline Distress (Distress Intercept) as a covariate on Severity slope and baseline Severity (Severity Intercept) as a covariate on Distress slope. If there is a significant effect of Distress intercept on severity slope accept hypothesis

Note: Each analysis was completed separately for each symptom type.

Table S2.4 Comparison of CFA models for the CAARMS

Model	AIC	BIC	Comparison	Difference
4. One-factor model	18639.96	18986.25	*n/a*	*n/a*
5. Two-factor model	18621.7	18972.38	*Model 1 v. Model 2*	AIC: 18.26 ↓ BIC: 13.87 ↓
6. Three-factor model*	18593.09	18952.54	*Model 1 v. Model 3*	AIC: 46.87 ↓ BIC: 33.71 ↓
			Model 2 v. Model 3	AIC: 28.61 ↓ BIC: 19.84 ↓

Note. All statistics based on ordinal logistic regression. Reduced AIC/BIC values between models indicates improved model fit; * Indicates model with the best comparative fit
CFA, Confirmatory factor analysis;
CAARMS; Comprehensive assessment of at risk mental state
AIC, Akaike's information criterion
BIC, Bayesian information criterion
n/a, not applicable

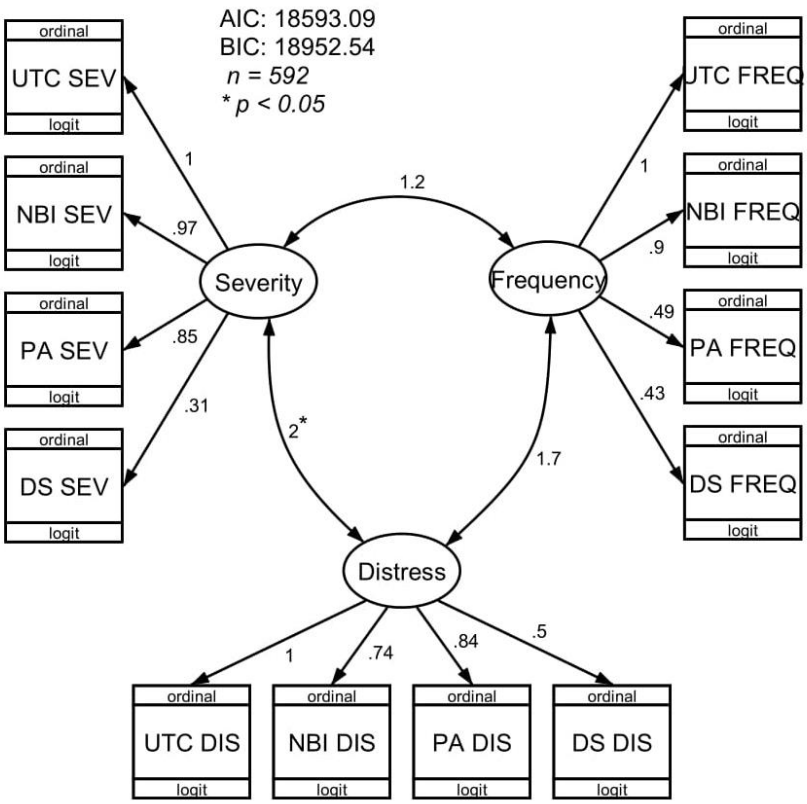

Figure S2.1 Three-factor CFA using ordinal logistic regression *(unstandardised);* AIC, Akaike's information criterion; BIC, Bayesian information criterion.

Table S2.5 Final Model standardised and unstandardised parameters with the CAARMS

Parameters	Unstandardised estimate	Standardised estimate
Factor loadings		
Severity (SEV)		
UTC severity	1.00 (fixed)	0.46 (0.09)*
NBI severity	0.72 (0.26)*	0.41 (0.08)*
PA severity	0.69 (0.21)*	0.39 (0.07)*
DS severity	0.28 (0.10)*	0.19 (0.08)*
Frequency (FREQ)		
UTC frequency	1.00 (fixed)	0.66 (0.11)*
NBI frequency	0.45 (0.16)*	0.33 (0.07)*
PA frequency	0.35 (0.13)*	0.24 (0.07)*
DS frequency	0.52 (0.19)*	0.35 (0.08)*
Distress (DIS)		
UTC distress	1.00 (fixed)	0.57 (0.08)*
NBI distress	0.55 (0.14)*	0.39 (0.07)*
PA distress	0.85 (0.21)*	0.45 (0.07)*
DS distress	0.72 (0.16)*	0.43 (0.07)*
Variances		
UTC severity	3.13 (0.37)	0.79 (0.09)
NBI severity	2.24 (0.21)	0.84 (0.06)
PA severity	2.24 (0.18)	0.85 (0.05)
DS severity	1.83 (0.12)	0.97 (0.03)
UTC frequency	0.99 (0.27)	0.57 (0.15)
NBI frequency	1.24 (0.10)	0.89 (0.05)
PA frequency	1.48 (0.10)	0.94 (0.03)
DS frequency	1.48 (0.18)	0.88 (0.06)
UTC distress	2.08 (0.31)	0.68 (0.09)
NBI distress	1.63 (0.14)	0.85 (0.05)
PA distress	2.76 (0.29)	0.79 (0.06)
DS distress	2.35 (0.27)	0.82 (0.06)
SEV	0.83 (0.35)	1.00 (fixed)
FREQ	0.75 (0.27)	1.00 (fixed)
DIS	0.99 (0.29)	1.00 (fixed)
Factor covariances/ correlation		
SEV - FREQ	0.08 (0.12)	0.10 (0.14)
FREQ - DIS	0.14 (0.11)	0.16 (0.11)
DIS - SEV	0.42 (0.14)*	0.47 (0.10)*

Note. CAARMS, Comprehensive assessment of at risk mental state.
Coef(SE)
* $p \leq 0.05$.

Table S2.6 Missing values for EDIE-2

	Baseline T1	1-Month T2	2-Months T3	3-Months T4	4-Months T5	5-Months T6	6-Months T7
Missing							
CBT	0	24	36	44	53	59	47
TAU	0	28	41	37	48	59	45
Total	0	52	77	81	101	118	92
Included							
CBT	144	120	108	100	91	85	97
TAU	144	116	103	107	96	85	99
Total	288	236	211	207	187	170	196
Cumulative (%)							
CBT	100	83.33	75.00	69.44	63.19	59.03	67.36
TAU	100	80.56	71.53	74.31	66.67	59.03	68.75
Total	100	81.94	73.26	71.88	64.93	59.03	68.06

Table S2.7 Comparison of LGC models with fit indices for each symptom type (UTC, NBI, PA and DS) for Distress with Severity and Frequency, including covariate of Treatment.

Model	χ^2 (df)	Comparison	χ^2 (df) diff	RMSEA	CFI
Unusual Thought Content (UTC)					
Distress & Severity					
1. Linear slope	465.78(114), p<0.001	*n/a*	*n/a*	0.105	0.705
2. Quadratic slope	401.523(110), p<0.001	*Model 1 v. Model 2*	64.26(3), p<0.001*	0.097	0.755
3. Quadratic slope + residuals	296.98(103), p<0.001	*Model 1 v. Model 3*	168.80(11), p<0.001*	0.082	0.837
		Model 2 v. Model 3	104.54(7), p<0.001*		
Distress & Frequency					
1. Linear slope	640.642(114), p<0.001	*n/a*	*n/a*	0.127	0.493
2. Quadratic slope	516.07(110), p<0.001	*Model 1 v. Model 2*	124.57(3), p<0.001*	0.114	0.609
3. Quadratic slope + residuals	288.50 (103), p<0.001	*Model 1 v. Model 3*	352.14(11), p<0.001*	0.079	0.821
		Model 2 v. Model 3	227.57(7), p<0.001*		
Non-Bizarre Ideas (NBI)					
Distress & Severity					
1. Linear slope	461.99(114), p<0.001	*n/a*	*n/a*	0.104	0.652
2. Quadratic slope	373.77(110), p<0.001	*Model 1 v. Model 2*	88.22(3), p<0.001*	0.092	0.736
3. Quadratic slope + residuals		*Model 1 v. Model 3*			
		Model 2 v. Model 3			
Distress & Frequency					
1. Linear slope	884.04(114), p<0.001	*n/a*	*n/a*	0.154	0.424
2. Quadratic slope	729.68(110), p<0.001	*Model 1 v. Model 2*	15436(3), P<0.001*	0.140	0.536
3. Quadratic slope + residuals	245.07(103), p<0.001	*Model 1 v. Model 3*	638.97(11), p<0.001*	0.069	0.894
		Model 2 v. Model 3	484.61(7), p<0.001*		

Table S2.7 Continued…

Model	χ^2 (df)	Comparison	χ^2 (df) diff	RMSEA	CFI
Perceptual Abnormalities (PA)					
Distress & Severity					
1. Linear slope	438.37(114), p<0.001	*n/a*	*n/a*	0.101	0.669
2. Quadratic slope	381.77(110), p<0.001	*Model 1 v. Model 2*	56.6(3), p<0.001*	0.094	0.723
3. Quadratic slope + residuals	249.08(103), p<0.001	*Model 1 v. Model 3*	189.29(11), p<0.001*	0.071	0.851
		Model 2 v. Model 3	132.69(7), p<0.001*		
Distress & Frequency					
1. Linear slope	516.46 (114)	*n/a*	*n/a*	0.111	0.528
2. Quadratic slope	381.78 (110)	*Model 1 v. Model 2*	134.68(3), P<0.001*	0.093	0.681
3. Quadratic slope + residuals	202.975 (103)	*Model 1 v. Model 3*	313.485(11), p<0.001*	0.058	0.883
		Model 2 v. Model 3	178.805(7), p<0.001*		
Disorganised Speech (DS)					
Distress & Severity					
1. Linear slope	279.491 (114)	*n/a*	*n/a*	0.072	0.855
2. Quadratic slope	273.450 (110)	*Model 1 v. Model 2*	6.041(3), p=0.110	0.073	0.857
3. Quadratic slope + residuals	218.914 (103)	*Model 1 v. Model 3*	60.577(11), p<0.001*	0.063	0.899
		Model 2 v. Model 3	54.536(7), p<0.001*		
Distress & Frequency					
1. Linear slope	516.456 (114)	*n/a*	*n/a*	0.111	0.528
2. Quadratic slope	488.097 (110)	*Model 1 v. Model 2*	28.359(3), p<0.001*	0.109	0.531
3. Quadratic slope + residuals	402.466 (103)	*Model 1 v. Model 3*	113.99(11), p<0.001*	0.101	0.629
		Model 2 v. Model 3	85.631(7), p<0.001*		

Note. All statistics based on maximum likelihood robust estimation;
LGC, Latent growth curve;
UTC, Unusual thought content;
CFI, Confirmatory fit index;
RMSEA, Root-mean-squared residual;
n/a, not appilicable.
* Significant at $p \leq 0.05$

Table S2.8 Parameter comparison for rates of Distress change between the symptom types for CBT.

Parameter comparison	Wald χ^2 (df)
UTC = NBI	0.98(1), *p=0.3211*
UTC = PA	0.06(1), *p=0.8065*
UTC = DS	0.62(1), *p=0.4301*
NBI = PA	0.01(1), *p=0.9399*
NBI = DS	0.49(1), *p=0.4842*
PA = DS	0.53(1), *p=0.4649*

* Significant at $p \leq 0.05$

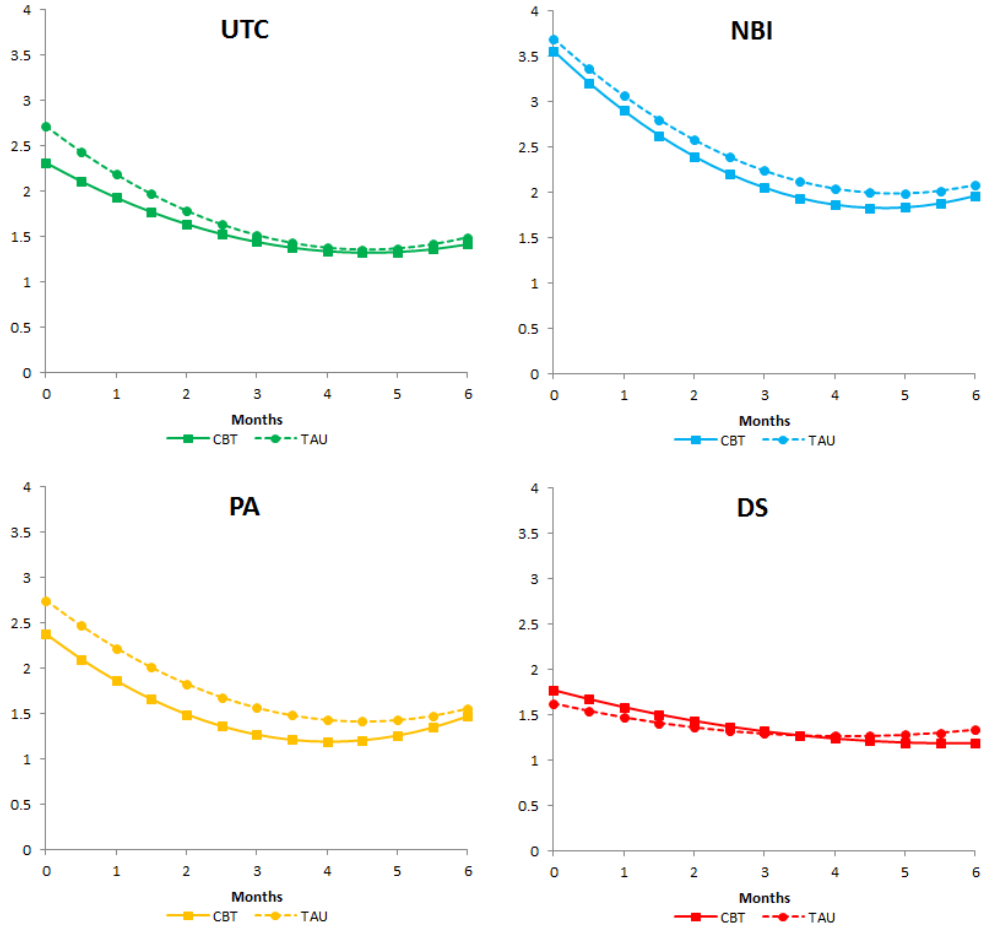

Figure S2.2 The rate of change over time for Distress by treatment condition for each symptom type.

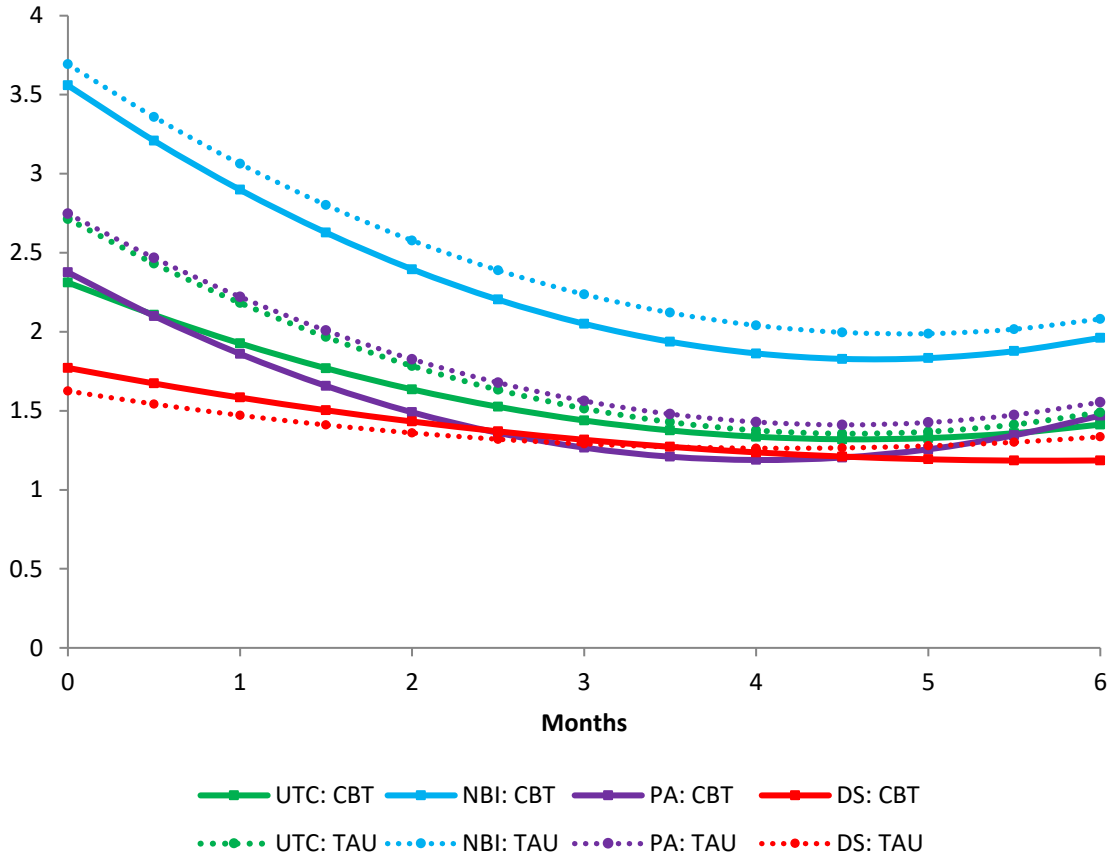

Figure S2.3 The Distress rate of change by symptom type (UTC, NBI, PA and DS) for CBT and TAU.

Table S2.9. Parameter comparison for rates of change between distress and severity and frequency for each symptom type (UTC, NBI, PA and DS) by CBT treatment.

Parameter comparison	Wald χ^2 (df)
Unusual Thought Content (UTC)	
Severity = Distress	0.75(1), *p=0.385*
Frequency = Distress	2.25(1), *p=0.134*
Non-Bizarre Ideas (NBI)	
Severity = Distress	0.64(1), *p=0.4247*
Frequency = Distress	0.44(1), *p=0.507*
Perceptual Abnormalities (PA)	
Severity = Distress	0.12(1), *p=0.7278*
Frequency = Distress	3.23(1), *p=0.0725*
Disorganised Speech (DS)	
Severity = Distress	0.12(1), *p=0.7307*
Frequency = Distress	0.85(1), *p=0.3555*

* Significant at $p \leq 0.05$

Table S2.10 Parameter estimation from cross-lagged models for each symptom type.

Symptom type	Mean Intercept	Linear slope	Quadratic slope
Unusual Thought Content (UTC)			
Severity			
Constant	2.29 (0.15)	-2.22 (0.34)	3.19 (0.05)
CBT	0.18 (0.21)	-0.06 (0.17)	0.00 (0.03)
Distress Intercept	-	0.65 (0.11)	-0.10(0.16)
Distress baseline effect	-	*z= 5.88, p<0.001**	*z= -6.10, p<0.001**
Treatment effect	*z= 0.83, p=0.405*	*z= -0.36, p=0.721*	*z= 0.02, p=0.982*
Distress			
Constant	2.76 (0.14)	-0.83(0.15)	0.10(0.02)
CBT	-0.17 (0.18)	-0.08 (0.12)	0.02 (0.02)
Severity Intercept	-	0.12(0.46)	-0.02 (0.01)
Severity baseline effect	-	*z= 2.30, p=0.021**	*z= -2.10, p=0.035**
Treatment effect	*z= -0.95, p=0.365*	*z= -0.65, p=0.514*	*z= 0.87, p=0.382*
Non Bizarre Ideas (NBI)			
Severity			
Constant	3.36 (0.12)	-1.85 (0.33)	0.26 (0.05)
CBT	0.05 (0.18)	0.11 (0.13)	-0.02 (0.02)
Distress Intercept	-	0.30 (0.09)	-0.05 (0.01)
Distress baseline effect	-	*z= 3.41, p=0.001**	*z= -3.90, p<0.001**
Treatment effect	*z= 0.31, p=0.759*	*z= 0.81, p=0.420*	*z= -1.15, p=0.0.249*
Distress			
Constant	3.48 (0.12)	-0.85(0.26)	0.10 (0.04)
CBT	0.08 (0.17)	0.01 (0.11)	-0.00 (0.02)
Severity Intercept	-	0.03(0.07)	-0.00 (0.01)
Severity baseline effect	-	*z= 0.45, p=0.650*	*z= -0.48, p=0.629*
Treatment effect	*z= 0.47, p=0.642*	*z= 0.10, p=0.919*	*z= -0.02, p=0.986*
Perceptual Abnormalities (PA)			
Severity			
Constant	2.98 (0.14)	-0.60 (0.22)	0.09 (0.03)
CBT	-0.20 (0.19)	-0.04 (0.12)	-0.00 (0.02)
Distress Intercept	-	0.02 (0.08)	-0.02 (0.01)
Distress baseline effect	-	*z= 0.31, p=0.754*	*z= -1.40, p=0.161*
Treatment effect	*z= -1.05, p=0.292*	*z= -0.32, p=0.752*	*z= -0.05, p=0.958*
Distress			
Constant	2.70 (0.15)	0.14 (0.24)	-0.02 (0.04)
CBT	-0.33 (0.20)	-0.04 (0.11)	0.01 (0.02)
Severity Intercept	-	-0.22 (0.07)	0.03 (0.01)
Severity baseline effect	-	*z= -3.17, p=0.002**	*z= 2.34, p=0.019**
Treatment effect	*z= -1.64, p=0.102*	*z= -0.33, p=0.742*	*z= 0.60, p=0.545*
Disorganised Speech (DS)			
Severity			
Constant	1.40 (0.12)	-0.04 (0.10)	0.01 (0.02)
CBT	0.08 (0.16)	0.01 (0.08)	-0.00 (0.01)
Distress Intercept	-	-0.07 (0.05)	0.00 (0.01)
Distress baseline effect	-	*z= -1.28, p=0.201*	*z= 0.29, p=0.769*
Treatment effect	*z= 0.47, p=0.637*	*z= 0.14, p=0.889*	*z= -0.11, p=0.916*
Distress			
Constant	1.60 (0.14)	-0.03 (0.14)	0.11 (0.02)
CBT	0.15 (0.18)	-0.03 (0.10)	-0.00 (0.02)
Severity Intercept	-	-0.09 (0.06)	0.01 (0.01)
Severity baseline effect	-	*z= -0.21, p=0.837*	*z= 0.63, p=0.529*
Treatment effect	*z= 0.85, p=0.393*	*z= -0.29, p=0.771*	*z= -0.19, p=0.850*

Note. All statistics based on maximum likelihood robust estimation; effects labelled Constant are the actual latent growth factors parameter estimates, and effects labelled CBT and Distress Intercept are the differences in latent growth parameters estimates with CBT and controlling for distress intercept.
Coef. (Standard error) * Significant at p≤0.05, when treatment effects are zero in the population

Chapter 3

A critical appraisal of the thesis

This chapter is not for journal publication.

Word Count: *5272*

3.1 Abstract

This Chapter is a critical appraisal of the research conducted as part of this thesis. It will include critical comment on the development, implementation and interpretation of both the systematic review and empirical study. As part of this appraisal the strengths and limitations of both Chapters will be discussed, alongside further personal reflection and exploration of important issues which arose during the overall research process.

3.2 Chapter one: Systematic literature review

3.2.1 Question selection

Deciding on the question for the systematic review focusing on anxiety and depression was firstly due to the concept of psychological distress, which has a large association with symptoms of depression and anxiety (Veit & Ware, 1983). Research has shown that individuals with an at-risk mental state have high levels of 'distress' and that this is also associated with symptoms of anxiety and depression (Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014). Anxiety and depression are inter-related concepts (Kendall & Watson, 1989), therefore examining them collectively was important to determine the overall symptomology and co-occurrence.

Clinically, working within Early Intervention (EI) services anxiety and depression symptoms are often a significant factor influencing the level of distress in individuals with psychotic symptoms. Therefore, the question felt clinically relevant. However, there were also other important considerations when deciding on a question:

1) That there were enough existing empirical articles to ensure a meaningful and generalisable result.
2) There were no other reviews completed within the area, with the same question focused on first-episode psychosis (FEP).

Initially, rates of anxiety and depression diagnostic cases or symptom level of those at ultra-high risk of psychosis (UHR) were going to be compared to FEP. However, there was only a single study which had looked at both at-risk and FEP based on eligibility criteria. This would make it impossible to answer the question meaningfully (Higgins & Green, 2008).

A recent review had also addressed rates of anxiety and depression within the UHR population (Fusar-Poli et al., 2014), as such it was decided that there was a gap within the literature looking at FEP and a systematic review would provide an overview of the rates of both anxiety and depression within the current FEP literature. A systematic review would help determine areas for future research by synthesising the existing evidence-base and identifying any gaps in knowledge or large heterogeneity between studies. Importantly, by identifying how prevalent symptoms of anxiety and depression are in FEP it could indicate a possible future focus for psychological intervention.

A preliminary search of the literature found an adequate number of empirical articles with; 1) a diagnosis of FEP and 2) measuring anxiety and depression. By synthesising research findings, it was felt that it could help clinicians recognise the frequency by which depression and anxiety co-occur within FEP. Thus, potentially increasing clinicians' awareness of the importance of these symptoms as a treatment focus. However, the trainee was surprised that within most FEP articles Depression or Anxiety symptoms were not considered. This suggests that their potential importance in the overall distress of the patient may not be recognised, either in research or clinically.

One recent meta-analysis completed for comorbid anxiety and depression in UHR concluded that often patients are more distressed by their anxiety and depression rather than the psychotic symptom (Fusar-Poli et al., 2014). Therefore, it is surprising that this would also not extend to those with FEP, which is simply a worsening of the severity and/or frequency of psychotic experiences from UHR. However, the review aimed to address this by exploring, reviewing and meta-synthesising the existing evidence of anxiety and depression in FEP.

3.2.2 Search terms

Developing the search terms firstly required developing a list of key words, including; 'first-episode psychosis', 'depression', 'anxiety' and 'comorbidity'. After this a list of synonyms were developed, this was completed in consultation with the main supervisor who is an expert within the field of psychosis. All synonyms were included and added to the Medical Subject Headings (MeSH) terms. Previous terms used in similar reviews (Fusar-Poli et al., 2014; Hartley, Barrowclough, & Haddock, 2013) were also added, with key references then used to cross-check search terms. Truncation was then applied to all terms to allow for alternative spelling (US/UK), plurals, presence of hyphens and noun or adjective form of all search terms. However, a pilot search was completed which identified too many unrelated references, therefore an additional limiter was applied to only include search terms in title rather than topic. After successfully checking that the key references were identified by title, the final search produced a manageable number of articles to review.

3.2.3 Inclusion and exclusion criteria

In the systematic review only articles from peer-reviewed research journals were included and so-called 'grey literature' or unpublished research was excluded. In recent years there has been a greater awareness of publication bias in research, where studies with a significant finding are published over non-significant findings. For meta-analysis, it has been suggested that excluding grey literature can inflate the effect sizes, providing less precise estimates, due to the over representation of studies with a significant finding (Conn, Valentine, Cooper, & Rantz, 2003; Hopewell, McDonald, Clarke, & Egger, 2007). As such, researchers have advocated

for grey literature to be included in reviews, although this is not without its complications (Mahood, Van Eerd, & Irvin, 2014). For example, searching conference abstracts as part of the review process is problematic due to the limited number of abstracts on electronic systems (Conn et al., 2003). Additionally, it is not always practical given the time and resources required to exhaustively review all grey literature. Therefore, grey literature was not included within the review, although it is recognised as a possible confounder to the reliability of the review. The review also only included English language articles, whilst potentially limiting the comprehensiveness of the overall review, the time or resources were not available to translate.

3.2.4 Contacting authors

After retrieving articles, there were several studies which appeared to collect the relevant data but either did not report or analysis it appropriately. Some studies had a combined sample of psychosis but did not report the separate results for FEP (n=13), while several studies also reported a combined depression and anxiety score (e.g PANSS combined anxiety/depression factor) (n=4). It was noted that some of these articles were from the same researchers and were the same data sample. Therefore, the authors of potentially relevant articles were contacted, which is suggested to improve the quality of the review and uses a systematic process (Mullan et al., 2009). However, of the authors contacted (n=12) the majority did not reply and those that did (n=2) no longer had access to the data. The rate of author response was disappointingly low, although the data were considered, and every attempt was made to access data in the ethos of systematic review.

3.2.5 Meta-analysis

It was decided that the rate of anxiety and depression, and the relationship between them would be best analysed using a meta-analysis. This is controversial given the relatively small number of studies included (n=10), thus heterogeneity measures were important considerations when assessing the reliability of the results. The I^2 statistic was used to assess heterogeneity, which represents the percentage of variance due to between-study factors rather than sampling error, with $I^2 > 50$ % indicating large heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). While, high heterogeneity was found, it was deemed to be important to report the rates of cases (anxiety and depression), whilst cautioning their reliability. Some researchers advocate additional measures such as the Q statistic being used to assess heterogeneity, although I^2 is easier to interpret and has been shown to be a better measure of the estimate effect magnitude in meta-analysis (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006).

A further step not completed in the meta-analysis due to time limitations, was meta-regression of the various factors which could result in increased heterogeneity. By controlling for these factors, the heterogeneity could be better explained, increasing the reliability of the results. These factors could include age, gender, type of FEP diagnosis or country of data origin. However, some of these factors were not always explicitly reported in articles, particularly the type of FEP diagnosis. Therefore, it would require further time and efforts to contact all authors. Additionally, given the small number of studies (n=10), there were inadequate degrees of freedom to allow additional parameters to be added to the regression model. Therefore, the trainee decided not to complete a comprehensive meta-regression.

3.2.6 Quality appraisal

An important part of the systematic review process is to access the methodological quality of articles included (Khan, Kunz, Kleijnen, & Antes, 2003). While there is no clear quality assessment tool recommended, a validated and reliable measure should be used if possible (Sanderson, Tatt, & Higgins, 2007). One such tool is the Downs and Black checklist for measuring quality, which can be used for intervention and non-intervention studies (Downs & Black, 1998). This tool was chosen in the systematic review due to the validity and use in many previous reviews.

However, as all quality assessment tools can have biases and poor inter-rater reliability (Higgins et al., 2011), a second independent rater co-rated a sample for quality appraisal (n=1), where a 'good' inter-rater reliability was found (k= 0.79). The discrepancies between raters were around making quality assessment based on whether the study was an RCT or cohort design. These disagreements were resolved following a shared understanding being developed. Thus, improving the reliability of the quality appraisal.

However, no studies were excluded based on methodological quality and it was not used extensively in review discussions. The checklist for measuring quality, uses 0-2 for each question (Downs & Black, 1998), which would have been useful if it formed part of the meta-regression. An improvement to the meta-analysis design could have utilised meta-regression for study quality, with the aim of explaining possible heterogeneity, although a larger sample of studies would be required as previously discussed above.

3.2.7 Clinical implications and future research

The systematic review highlights how frequent depression and anxiety 'casesness' (e.g diagnoses) can be made within FEP. It suggests that there is a large cross-over of symptomology between FEP, anxiety and depressive symptoms. Therefore, clinicians should focus treatment towards the most distressing symptom, often anxiety or depression. Importantly the review also shows that rates were similar between depression and anxiety in FEP and should therefore be equally considered.

However, the use of diagnosis rather than amount of a depression or anxiety symptom is a potential psychological criticism of the review, with the reliance on binary (diagnosis or not) measures in accordance with diagnostic manuals such as the DSM or ICD-10 (American Psychiatric Association., 2013; World Health Organisation, 1992). Nevertheless, most included articles used diagnosis 'caseness' as a measure of anxiety and depression, reflecting research methodology. Future research should investigate depression and anxiety using self-reported continuous measures to improve our understanding of the relationship strength and the variability of symptoms. Using self-reported continuous measures would allow for better integration with psychological formulations, improve collaboration between service user and therapist and provide a more sensitive post-intervention assessment. This is also more aligned with recovery focused mental health approaches (Leamy, Bird, Le Boutillier, Williams, & Slade, 2011).

Cognitive behavioural therapy (CBT) is evidence-based and recommended for use in FEP, together with a recognition that reducing distress should be part of the psychological treatment offering (NICE, 2014). Interestingly, much of the research looking at CBT within FEP relies on meta-analysis where the primary outcome is change in psychotic symptoms severity and frequency. Based on the findings of the

review trans-diagnostic CBT informed strategies should be used to focus both on anxiety and depression equally within FEP. Additionally, measures of anxiety and depression should be used to assess future FEP intervention trial outcomes, alongside measures of psychotic symptoms.

It has also been suggested that the negative affect or high levels of anxiety and depression could trigger help-seeking behaviour in those with early psychosis (Morrison et al., 2012), which could explain the high levels of negative affect seen in FEP populations. This is supported by the findings of Chapter 2 that emotional distress is intrinsically associated with increased severity of psychotic symptoms. Therefore, measures of anxiety and depression should be used to further understand this relationship in FEP.

3.3 Chapter two: empirical paper

Chapter 2 assessed the relationship between distress, severity and frequency of attenuated psychotic symptoms in individuals meeting Ultra High Risk (UHR) for psychosis criteria, both cross-sectionally and longitudinally. It also assessed whether cognitive behavioural therapy (CBT) reduced distress over time by symptom type. Data were combined from two clinical trials to asses cross-sectional hypothesis using confirmatory factor analysis (CFA). A sample with longitudinal data were then used to determine longitudinal latent growth curves (LGC) using a structural equation modelling (SEM) framework to assess the change over time. This secondary data analysis to our knowledge was one of the first to formally assess the distress associated with psychotic symptoms in UHR population over time.

3.3.1 Gaining usable data

During the pre-study design stage, three datasets were understood to be available to the trainee. These included; 1) The Early Detection and Intervention Evaluation (EDIE 2) clinical trial (Morrison et al., 2012), 2) The NEURAPRO clinical trial (McGorry et al., 2017) and 3) The Personal Assessment and Crisis Evaluation (PACE-400) study (Nelson et al., 2013). There were at least 2 time points across all data, including longitudinal data for two of the studies across six months. Initially gaining access to the previously published datasets was not envisaged to be a potential problem, with both supervisors having ownership over the data and all additional consent required from any co-investigators or collaborators thought to be easily granted.

However, gaining some of the data caused unforeseen delays and the trainee was not able to have all data requested due to denial of one of the previous collaborators.

This limited the longitudinal analysis to one dataset, although large enough to answer the hypothesis, the longitudinal findings are unfortunately not cross-validated across dataset as first hoped.

Nevertheless, all three datasets could have been used for the cross-sectional analysis (n=860), although the PACE -400 data set had several problems. Namely, this cohort had originally been assessed prior to the distress item being added to the comprehensive assessment of at-risk mental state (CAARMS) questionnaire, which meant that when distress was recorded at timepoint 2 the patients were likely to be at a different point in their recovery. While the data required considerable time to reformat and 'clean', the trainee decided not to include the PACE-400 data within the analysis. This was also due to the very different covariance structure compared with the other datasets which were almost identical in nature. This is likely due to the different time points used to compare distress. As such, the more recently acquired data were used as this would likely best represent the current clinical population. On reflection the amount of time taken to understand, re-format, 'clean' and merge the data prior to analysis was underestimated by the trainee.

3.3.2 Secondary data analysis

Secondary analysis of existing data has several advantages namely, the saving of costs, both monetary and patient/participant and researcher time. The scale of the sample used within the empirical study could not have been acquired during the timeframe of clinical training. Therefore, the hypotheses examined could not have been adequately assessed without the use of secondary data, particularly the longitudinal hypotheses. More recently with the improvement of online storage for 'big data', it has improved the ability to combine datasets, as the current study did. It

has also meant that researchers are now often encouraged to share data publicly, with many different types of anonymised datasets now freely available online. Although there are potential ethical problems with secondary data analysis (Tripathy, 2013), all were mitigated by the trainee only being given fully anonymised data and where written consent was required from other research collaborators or the wider research team, this was applied for via the formal channels.

3.3.3 Choosing the hypothesis

As the data were already acquired it was important for the hypothesis to be defined *a priori,* given the potential for data mining and lack of interpretability. A formal hypotheses plan with the corresponding statistical analyses to assess each hypothesis was developed before any modelling started. The hypotheses were primarily developed during the trainee's clinical placement working in an Early Detection and Intervention team (EDIT), where the trainee noticed that distress was not discussed about as much as the severity and frequency of symptoms within the service. While the comprehensive assessment of at risk mental state (CAARMS) questionnaire did measure distress, it did not contribute to clinical management. By comparing distress with the constructs already used to assess UHR or FEP (severity and frequency), this could align distress with severity and frequency.

The trainee had used CBT during clinical placement based on the manualised approach developed as part of a previous clinical trial (French & Morrison, 2004). The trainee also assessed patients with the CAARMS before and after CBT treatment, finding distress had often reduced for many individuals. All hypotheses around CBT were developed from clinical experience and following discussion with supervisors.

3.3.4 Deciding on statistical methodology

After discussion with supervisors it was agreed that more complex statistical analyses were required to answer the hypotheses. The first part of the analyses focused on conducting a confirmatory factor analysis (CFA), which is an important first step within the SEM framework. A CFA allows multiple measures or observed variables to have their own unique variance (Brown, 2014). The latent variables represent the shared variance of the observed or measured variables and assumes that a latent variable explains all responses. The latent factors specified in the current thesis were Severity, Frequency and Distress, based on the hypothesis.

To assess the longitudinal hypotheses, it was decided that Latent Growth Curves (LGC) within the SEM framework would be the most appropriate statistical methodology. The traditional approach of evaluating change over time based on the comparison between measures before and after intervention (i.e two time points) may be inadequate when assessing longitudinal change (Willett & Sayer, 1994). Additionally, the change may not be a linear straight line and the use of LGC allows for different trajectories over time, such as quadratic slopes.

LGC modelling would enable the identification of the trajectory over time and allow us to predict who has the more negative or positive trajectory, rather than simply predicting an individuals score on a measure or question (Acock, 2013; Duncan, Duncan, & Strycker, 2013). In the most basic example of a linear growth curve, the intercept is where the curve begins or where it crosses the x-axis and the slope is the rate of change (increase or decrease) for each unit change over time. However, in LGC the intercept and slope are considered as latent variables that required SEM identification. While linear LGC consider the change to be based on a straight line, it was hypothesised that the change in distress over time was likely to be faster

initially. This would represent a quadratic curve in the model, thus increasing the model complexity. A measure at each timepoint is represented with latent error terms, allowing for variation between individuals. The more time points in the data the more rigorous the test, with added degrees of freedom and information, a strength of this study was having seven timepoints (including baseline).

A basic growth curve could have been fitted using mixed modelling rather than within a SEM framework, although mixed models would use listwise deletion where items that are missing are excluded from the analysis. Instead, to include all available data the estimator used assumed data were missing at random, which is only available within a SEM framework. Additionally, LGC within SEM has the advantage of giving model fit statistics to enable comparison between different model specifications. These model fit statistics enabled the assessment of whether the linear or quadratic slope was the best fit to the observed data, or whether growth reductions were rapid or more protracted over time. Thus, allowing hypothesis testing based on the chi-squared test of log likelihood.

Additionally, to assess the plausibility of Distress causing Severity of symptom change over time, the intercept of Distress was regressed onto the slope of Severity and vice versa. This would identify for every unit increase of baseline Distress (intercept) what effect this had on the rate of change in severity. If the unit increase with Distress is larger compared with the unit increase with Severity this indicates that distress may cause change in Severity over time. Using LGC to investigate causality allowed us to estimate the effect of the initial level (baseline) on the rate of change (Duncan, Duncan, & Strycker, 2013; Willett & Sayer, 1994).

3.3.5 Other statistical methodological decisions

The trainee decided not to use modification indices as part of the modelling process and instead focused on models stipulated by the hypotheses plan. The modification indices suggest alterations to the model based on the data which could improve the overall model fit. While data driven approaches are commonly used in research, it was felt that focusing on hypothesis testing would be theoretically underpinned, thus aiding interpretation.

The decision was also made to run smaller LGC models with less parameters. Two models were run for each symptom type with Severity and Frequency analysed separately. This was instead of one model including Distress, Severity and Frequency. This was to aid interpretation and to reduce the time taken to run the models. The smaller models were adequately able to answer the hypotheses, which all related to Distress, rather than the relationship between Severity and Frequency.

3.3.6 Comprehensive assessment of at risk mental state (CAARMS)

The results of the CFA highlighted that the CAARMS has some low factor loadings onto the Severity and Frequency latent variables, which are used as clinical indicators for defining transition to FEP. Future research may be required to assess the reliability of the CAARMS in the current format. The type of symptom appears to be very important in determining the Distress, Severity and Frequency, with large variation between symptom type. However, how these symptoms are grouped for extracting information about Distress may be problematic. In particular, the NBI symptom type contains some of the most distressing beliefs (e.g paranoia), although also contains grandiosity, which has been associated with narcissistic defence which may not be distressing for the individual.

The CFA was not completed as a traditional questionnaire measurement model, instead it aimed to assess whether the data were best explained as a one, two or three factor structure. However, the results of the CFA do allow interpretation of the CAARMS reliability, which was not high. Future research should measure multiple measures of distress, alongside the CAARMS to further assess this important psychological construct.

3.3.7 Clinical implication and future research

The main clinical implications of Chapter 2 suggest a greater focus on the psychological distress associated with psychotic symptoms. This could potentially be facilitated clinically with the use of patient reported outcomes (Greenwood et al., 2010; Reininghaus & Priebe, 2012), both as part of the diagnostic process and to guide the length of treatment. In addition to the primary clinical implications discussed in Chapter 2, it is also suggested that distress could be considered when there is uncertainty over which service a patient requires; primary care, early detection and intervention (EDIT) or early intervention (EI) for first-episode psychosis, a decision currently based on the CAARMS or PANNS severity/ frequency scores. Based on our findings it is suggested by the trainee that greater focus is given to the patients self-reported distress when making this clinical service decision, alongside other important care needs including social functioning and level of risk, which is likely to require additional care management provided in EI. Clinicians should consider which service has the capacity to offer regular, empathic listening over a longer period of time to reduce distress at initial assessment.

It is interesting that researchers are beginning to move away from focusing on 'transition rate' for FEP (McGorry et al., 2018; McGorry & Nelson, 2016), these are

arbitrarily defined and based on clinician training to score a measure based on the severity of the symptoms. This presents a degree of measurement error, relying on the ability of the rater scoring and ultimately variable inter-rater reliability. The current findings show a very close relationship with distress experienced and the subsequent severity of symptoms, even a potentially causal relationship for some types of symptom (NBI and UTC). Therefore, if you could ask the patient how distressed they were by their symptoms and this provided adequate information for diagnostic or service decisions, arguably self-reported distress should and could be used for this. Distress is also more useful in guiding psychological treatment and evaluating outcomes compared with the severity of the symptom. Indeed, distress appears to be a trans-diagnostic process, although the type of symptom does appear to impact on distress.

A further limitation not discussed in Chapter 2 was that individuals could have scored for each of the different symptom types. For example, clinically it is not unusual for UHR individuals to have both delusions and hallucinations, which would score highly on both the UTC and PA subscales. The possible duplication or cross-correlated scores across subscales was not considered in the analysis and the relationship between subscales not investigated. Instead each subscale was assessed in isolation. However, some patients were likely to be highly distressed on multiple subscales. Future research could assess the change on distress across subscales in individuals who score highly on multiple symptom types.

Higher patient distress at initial assessment was associated with a higher rate of distress reduction over time in UHR patients.. Higher initial distress also caused severity to reduce at a slower rate for UTC and NBI. Clinically, this suggests that patients who are very distressed should be given a longer opportunity to engage with

mental health professionals As such, for UTC and NBI focusing on reducing distress at first would be important. Strategies for this could involve, normalising and validating thoughts, feeling, experiences and behaviours. Focus on building rapport with the person, address any inter-personal dynamics within the therapy as they arise and suggest coping skills or distress tolerance techniques to help them manage their high level of distress. As the first three sessions or contacts with health care professionals appeared to show the greatest rate of distress reduction, every attempt should be made to address high distress during this early period.

The causal relationship between distress and symptom severity change over time is dependent on the symptom type. This could explain the low effect sizes typically reported for generalised CBT approaches in psychosis. In Chapter 2 it is suggested that future clinical trials should consider developing psychological treatment focusing on specific psychosis symptoms. The NHS guidelines recommend CBT for psychosis, including UHR (NICE, 2014), although the specifics of what aspect of CBT reduces distress for each symptom type has not been adequately investigated. Future research should identify which type of treatment approach works for the type of psychotic symptom, as this will be important for recovery and distress reduction. It may well also improve the effectiveness of CBT for psychosis.

3.4 **Personal reflections**

The opportunity to conduct clinically relevant research within the area of mental health was one of the main reasons the trainee entered clinical training. Having worked in research and completed a PhD prior to beginning training the trainee was eager to find academic advisers who shared an interest in sleep, mental health and advanced statistics. On reflection the trainee was used to working with some degree of research independence prior to clinical training, with freedom and flexibility to define research questions within the trainees preferred area. Therefore, attempts were made to tailor the topic and project title to fit with the trainee's research interests.

The trainee started on their first adult clinical placement in an Early Detection and Intervention team (EDIT) and Early Intervention (EI) for Psychosis service, where they met Professor Alison Yung, at that time EDIT service lead. After discussions with Prof Yung she agreed to supervise a project using longitudinal clinical trial data of the at-risk or ultra-high risk (UHR) population. The trainee during clinical placement was trained and frequently used the comprehensive assessment of at-risk mental state (CAARMS) questionnaire. It was during this period that questions around distress associated with psychotic symptoms became of interest. On reflection, the trainee's clinical experience of working within this service had a large impact on the research question, design and theoretical interpretations of the results.

The trainee, together with Prof Yung approached Professor Anthony Morrison to advise on the project, and to provide additional clinical trial data. It was agreed that combined secondary analysis on previously published clinical trials would be advantageous for providing a large enough sample to test the hypothesis. During the initial stage of the project Prof Morrison became the main supervisor and for the

advanced statistical analysis supervision was sought from a biosciences statistician, Dr Nick Shyrane with expertise in longitudinal modelling approaches. Working closely with different professionals as part of the supervisory team was enjoyable and the trainee learnt a great deal, both about advanced structural equation modelling and psychosis research.

Initially the trainee was aware of their own limited competencies, particularly within the area of LGC modelling and had no prior experience of applying these approaches. This was a large and daunting prospect at the start of the research project. The data were expansive, and formatting required knowledge of software coding. However, the trainee was able to draw on previous experience using other scripted software languages, which helped inform the trainee's ability with STATA. A proactive self-directed approach was used throughout, the trainee would write scripts and then attempt to fix problems unaided.

Every attempt was made to understand using internet tutorials, journal articles and books, prior to seeking expert advice. However, when required Dr Shyrane would offer an excellent explanation, with recommendations for additional reading. This approach proved successful and following worked examples from recommended text books was helpful to understand the analysis and STATA functions and code. Additionally, as part of the thesis the trainee also completed a meta-analysis for the first time. This was a stimulating self-directed exercise and has improved the trainee's understanding and ability to critically appraise other systematic reviews and meta-analyses in the future.

During the final year of the research project the trainee has been on clinical placement within a paediatric Neuropsychology service completing cognitive testing

with patients. These cognitive tests are usually developed and validated using CFA. Additionally, most child developmental research requires longitudinal analysis. Therefore, having an improved knowledge of SEM and LGC modelling has informed the trainee's clinical understanding within a different field.

The trainee is also hoping to submit a future clinical academic grant application which will incorporate the statistical methods learnt during this research project. The trainee hopes to maintain their research interests going forward, by building on the skills developed during the training process. Additionally, the trainee hopes to encourage, help and support others with their research in the future. Research activity which shapes the clinical offering of NHS services is important and psychologists have a duty to contribute, which is in line with the ethos of evidence-based clinical practice

In conclusion, conducting research and developing additional skills and knowledge throughout the process has been an enjoyable experience. The process reaffirmed the importance of taking responsibility and ownership for skill development, together with the importance of working alongside experienced research colleagues. It is hoped that the implications of the findings are incorporated and disseminated into clinical practice.

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