SLEEP DISTURBANCES AND RISK FOR PSYCHOSIS

By Latoya Clarke

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DECLARATION

This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been composed by myself and has not been submitted in any previous application for any degree.

Signed… [redacted] …… Date…11/08/21……

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ABSTRACT

There is increasing evidence showing an association between sleep disturbances and Psychotic Experiences (PE) in clinical and non-clinical groups. However, important research questions remain relating to (i) which specific sleep disturbances are associated with PE cross-sectionally and longitudinally (ii) the prospective relationship between sleep problems in childhood and PE in adulthood and (iii) how sleep disturbances are associated with PE and other key outcomes in at risk for psychosis groups.

Chapter 3 of this thesis presents a systematic review examining the cross-sectional and longitudinal relationship between sleep disturbances and PE across at risk for psychosis groups. Chapter 4 investigates the prospective association between childhood and adolescent sleep disturbances and PE in adulthood. Chapter 5 examines sleep disturbances and associated PE, functioning and Quality of Life (QoL) in an Australian and UK help seeking sample. The findings are integrated in Chapter 6 through the outline of an interventional study to be carried forward as part of the next steps.

Findings from Chapter 3 show that self-reported and objectively assessed sleep disturbances are associated with PE. However there is a dearth of evidence examining the relationship between sleep disturbances and QoL, and limited longitudinal research in this area. In Chapter 4, difficulties initiating and maintaining sleep, in addition to parasomnias during childhood and adolescence are found to be associated with the occurrence and persistence of PE at 24 years old. Chapter 5 reports a significant association between daytime sleepiness, chronotype and positive psychotic symptoms, functioning and QoL across a 12 month period.

This thesis presents compelling evidence to suggest that the relationship between sleep disturbances and PE is maintained over time and populations. Furthermore, there is some specificity in relation to which types of sleep problems relate to increased PE and therefore increased risk for psychosis. Chapter 6 presents the findings from a patient and public involvement study which explores methodological considerations for future studies seeking to understand the potential causal pathways underlying these co-occuring experiences across the psychosis continuum.

LIST OF ABBREVIATIONS

ALSPAC	Avon Longitudinal Study of Parents and Children
ARMS	At Risk Mental State
CAARMS	Comprehensive Assessment of the At Risk Mental State
CBT	Cognitive Behavioural Therapy
CHR	Clinical High Risk
DSM	The Diagnostic and Statistical Manual of Mental disorders
EEG	Electroencephalography
ESS	Epworth Sleepiness Scale
FEP	First Episode Psychosis
GAD	Generalised Anxiety Disorder
GFS	Global Functioning Scale
HPA	Hypothalamic-Pituitary-Adrenal system
ICD	International Classification of Disease
K-10	Kessler Psychological Distress Scale
NREM	Non-Rapid Eye Movement
OR	Odds Ratio
PE	Psychotic Experiences
PLE	Psychotic Like Experiences
PLIKSi	The psychosis-like symptoms semi-structured interview (PLIKSi
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSG	Polysomnography
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
QIDS	Quick Inventory of Depressive Symptomatology
QME	Questionnaire of Morningness and Eveningness
QoL	Quality of Life
RCT	Ultra High Risk
REM	Rapid Eye Movement
SCID	The Structured Clinical Interview for DSM Disorders
SIPS	Structured Interview for Prodromal Symptoms
SWS	Slow Wave Sleep
TST	Total Sleep Time
UHR	World Health Organisation
WASO	Wake After Sleep Onset
WHO	World Health Organisation

Chapter 1. **INTRODUCTION**

1.1 **PSYCHOSIS**

Psychosis is an umbrella term used to describe a set of serious and often chronic psychological symptoms associated with a distorted perception of reality and/or a lack of insight (Gaebel and Zielasek, 2015, Waters et al., 2018, Arciniegas, 2015). Although there is no formal definition for psychosis in classification systems such as The Diagnostic and Statistical Manual of Mental disorders (DSM-5) and International Classification of Disease (ICD-10) (Gaebel and Zielasek, 2015) factor analysis studies divide symptoms into 4 or 5 dimensions; positive, negative, depressive, manic symptoms and disorganisation (van Os et al., 1999, Potuzak et al., 2012, van der Gaag et al., 2006, Liddle, 1987, van Veelen and Sommer, 2014).

Positive symptoms are a cluster of symptoms that include hallucinations and delusions (Morrison, 2001). Hallucinations are defined as perceptual phenomenon (auditory, visual, tactile and olfactory) not attributable to external stimuli (e.g., hearing voices) (Morrison, 2001, Dudley et al., 2016). Delusions are characterised by firmly held beliefs or ideas that are unwavering even when evidence to suggest otherwise is presented, and are often accompanied by distress and preoccupation (e.g., the belief of being a religious figure sent to save the world) (Dudley et al., 2016).

Negative symptoms are a subgroup of psychosis that include two domains; namely reduced motivation and pleasure plus diminished emotional expression (Strauss et al., 2021, Liemburg et al., 2013). These symptoms are primarily focused on impairments to typical emotions and behaviours and consequently can be challenging to define and vary across populations (Strauss et al., 2021).

Psychotic symptoms are reported across several serious and enduring affective and non-affective psychiatric disorders including schizophrenia, schizoaffective disorder, personality disorder, bipolar disorder and major depression (Thomas, 2001, van Veelen and Sommer, 2014). Symptoms of psychosis are also seen across general medical conditions including Alzheimer's disease, lupus, HIV/AIDS, malaria and Parkinson's disease (Stephane et al., 2014).

Research has estimated lifetime prevalence rates of psychotic disorders to be between 3.06% - 3.48% (Perälä et al., 2007), with differences in the assessment of psychotic symptoms contributing to variations in reported rates across studies (Moreno-Küstner et al., 2018). Psychosis places significant burden on individuals, service providers and society (Bebbington et al., 2004, Goldner et al., 2002, Jacobs et al., 2020). For instance, the World Health Organisation (WHO) suggested that the 'burden and human suffering' caused by psychosis is only surpassed by dementia and quadriplegia, when evaluated at a family level (Bebbington, 2014). Furthermore, those diagnosed with psychosis tend to experience poorer outcomes including obesity, cardiovascular problems, higher rates of suicide and mortality compared to general population samples (Barrett et al., 2010, Foley and Morley, 2011, McGrath et al., 2008, Bebbington, 2014).

Higher incidence rates of psychosis have been reported in men compared to women (pooled incidence rate ratio=1.54, CI=1.37-1.72), in urban compared to rural areas (pooled incidence rate ratio= 1.64, CI=1.38–1.95) and in lower socioeconomic areas (pooled incidence rate ratio= 3.09, CI=2.74-3.49) (Castillejos et al., 2018). There are considerable efforts within research and clinical practice to understand psychosis and its manifestations to reduce the suffering associated with this illness. Importantly, identifying and treating psychosis early, as is the focus in First Episode Psychosis (FEP) patients experiencing their first episode of frank psychosis, is central to many early intervention services seeking to improve patient outcomes (Lester et al., 2011).

1.1.2 Psychosis Aetiology

Several plausible theories and concepts involving biogenetic, psychosocial and neurodevelopmental factors have been proposed to explain the causes and maintenance of psychosis (Strauss et al., 1974, Broome et al., 2005, Jarvis, 2007, Holtzman et al., 2013, Longden and Read, 2016). A social framework proposed by Shah et al. (2011) propositions that the interaction between four factors contribute to the expression of psychosis. These factors are (i) individual factors, (ii) ecological factors, (iii) individual factors and ecological factors and (iv) time. Firstly, individual factors include social influences that may exacerbate underlying genetic or biological predispositions to psychosis. For instance, personal exposures to substances (e.g., cannabis) and social adversities (e.g., bullying or childhood trauma) may increase the

risk of psychotic illness, with a dose response relationship reported between increasing severity and frequency of personal exposures and risk of psychosis. Secondly, ecological factors are concerned with population or environmental risk factors such as urbanicity, migration status and social cohesion. These factors would explain why individuals with the same social risk factors may experience diverse outcomes if the ecological factors differ. The interactions between individual and ecological risk factors are dynamic, and can increase or decrease the risk of the other. For example the risks posed by childhood trauma may be mitigated by social cohesion and support, thereby reducing the risk of psychosis. When this is layered with the final factor, which is time, adequate exposure and interaction between the individual and/or ecological risk factor, particularly during critical developmental periods (e.g., adolescence) may result in the expression of psychosis. The multifaceted interaction between these risk factors is challenging to study, primarily due to challenges in measuring the contribution, timing and factors that may be responsible for psychosis across individuals (Shah et al., 2011).

Alternatively, a socio-developmental cognitive model proposed by Howes and Murray (2014) is a hybrid model that integrates two well evidenced concepts of psychosis; namely the neurodevelopmental hypothesis (Holtzman et al., 2013) and the cognitive model (Howes and Murray, 2014). It suggests that genetic predisposition, early hazards to the brain and childhood adversity result in a vulnerability to developing schizophrenia through sensitisation of the dopamine system. Against this background of genetic and developmental vulnerability, cognitive schemas develop through social adversity/psychosocial stress. These schemas influence the individual's interpretation of themselves, the world and others, with a tendency towards paranoid interpretations. Further stress causes abnormal dopamine release and misinterpreted cognitive biases, resulting in increased levels of stress and the hardwiring of psychotic beliefs. This theory provides a broad robust explanation for the development of psychosis which accounts for biological, developmental, social and cognitive processes (Howes and Murray, 2014).

Alternatively, Lunsford-Avery and A. Mittal (2013) postulate a neurodevelopmental diathesis stress model which suggests that the interaction between genetic and early

environmental factors provide fertile ground for vulnerability for schizophrenia. When these early vulnerabilities interact with neuromaturational, endocrine and psychosocial stressors during the adolescent period they create the perfect storm for an over-sensitised Hypothalamic-Pituitary-Adrenal (HPA) system and functional and structural brain changes (e.g., atypical synaptic pruning and white matter growth). The consequences of impaired stress response are instrumental in driving attenuated psychotic symptoms through the interaction between cortisol and dopamine. Whilst neurodevelopmental models provide robust explanation for factors implicated in the emergence of psychotic symptoms, questions have been raised surrounding their ability to explain the timing of illness onset and differences between those experiencing subthreshold and clinically diagnosable psychotic illness (Broome et al., 2005).

1.2 **THE PSYCHOSIS CONTINUUM**

The conceptualisation of psychosis as a dimensional rather than a categorical phenomenon is accepted amongst many clinicians and researchers today (Chapman et al., 2020). Whilst the clinical threshold for psychotic and affective disorders are defined in diagnostic criteria, psychotic symptoms are seen to varying degrees in non-clinical groups (Chapman et al., 2020). Positive and negative symptoms are therefore not exclusive to clinical populations (Linscott and van Os, 2013, Cougnard et al., 2007).

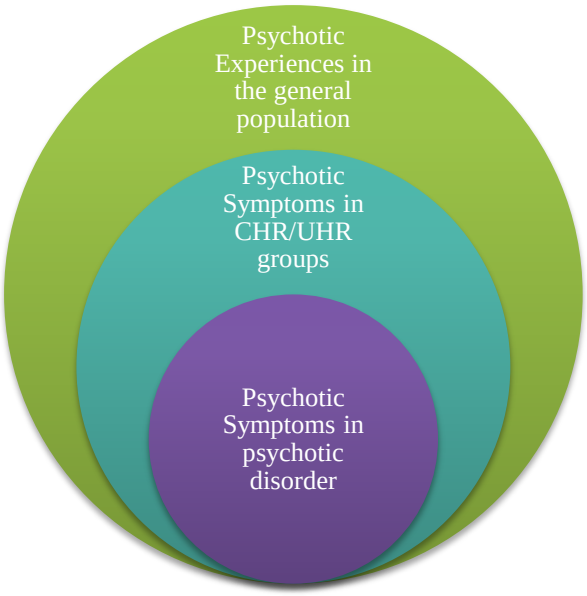
The Psychosis Continuum suggests that some individuals will have no experience of Psychotic Experiences (PE), a larger number will experience subclinical PE that are transient and not associated with distress (Van Os et al., 2009). Further along the continuum are the Clinical High Risk/ Ultra High Risk group who have more severe psychotic symptoms that put them at increased imminent risk for developing psychotic disorders (Chapman et al., 2020). They may experience PE at a higher severity and frequency compared to the previous group with accompanied distress, reduction in functioning and cognitive impairment (Chapman et al., 2020). At the furthest end of the continuum are those diagnosed with psychotic disorder such as Schizophrenia (Chapman et al., 2020). Those diagnosed with psychotic illness are differentiated from the CHR/UHR group based on the conviction or belief in the PE but also the increased frequency and severity of the psychotic symptoms (Chapman

et al., 2020, Van Os et al., 2009). Importantly, it is understood that some individuals may move along the continuum throughout their lifetime and subclinical PE's often emerge prior to clinical psychotic illness (Chapman et al., 2020).

1.2.2 Psychotic Experiences

Research has reported that most PE occur in non-clinical groups, with significantly fewer people experiencing clinical threshold symptoms (Nelson et al., 2012a) (see Figure 1). The quality of these experiences in non-clinical compared to clinical groups is significantly lower in their frequency, intensity and accompanied distress. Furthermore, the timing of these experiences have been shown to occur more often in adolescence, between the ages of 13 -24 years and peaking at approximately 18 years old (Sullivan et al., 2020). Such PE's then reduce with age, suggesting that they may be part of normal developmental trajectory (Nelson et al., 2012a, Laurens et al., 2012, Nelson et al., 2012b). For instance, in a sample of 1438 adolescents, almost half (43%) reported Psychotic Like Experience (PLE) (Fonseca-Pedrero et al., 2011). Such common experiences have been shown to spontaneously resolve without need for care or treatment (Unterrassner et al., 2017). However, a smaller number of adolescents will experience multiple, persistent PE which may increase risk for later disorders (Fonseca-Pedrero et al., 2011). This is exemplified by research reporting a 5-16 fold increase in psychotic disorder amongst adolescents who reported persistent PE (Poulton et al., 2000). Furthermore, in a systematic review and meta-analysis of cohort studies, the presence of PE as the exposure variable carried a 3.5 times higher risk of developing a psychotic disorder, compared to the absence of PE (Kaymaz et al., 2012). This review included a 3-24 year follow up assessment period, and reported that severity and persistence of baseline PE moderated the relationship in a dose response fashion (Kaymaz et al., 2012). The severity of PE has also been shown to be related to risk of non-psychotic disorder in other research studies (Bourgin et al., 2020, Yung et al., 2006, Zhang et al., 2019a). It is therefore unsurprising that there is a large body of evidence examining PE in non-clinical groups, with particular attention to those experiencing persistent and severe PE (Van Os et al., 2009).

FIGURE 1. THE DISTRIBUTION OF PSYCHOTIC EXPERIENCES ACROSS POPULATIONS



Various methodologies have been adopted when measuring PE in general population samples including interviews and questionnaires; producing differences in reported severity and frequency of experiences (Lee et al., 2016). This may reflect the unstable nature of PE over time; the lack of universal definition for what constitutes a PE; or the absence of a 'gold' standard' measure to enable consistent assessment across studies (Lee et al., 2016). Therefore, ongoing research into PE in general population samples is invaluable in aiding understanding surrounding the nature and implications of PE (Lee et al., 2016). Researchers have suggested that there is a need for longitudinal assessment to add to our understanding of severity and persistence across time and qualitative interviews which tease out the various qualities of the PE (Lee et al., 2016).

1.2.3 Psychotic Symptoms

Research has reported that a large amount of the disability associated with psychotic disorders is accrued early in the illness and impacts on the amount of recovery that an individual makes (Birchwood et al., 1998, McGorry et al., 2003, Schultze-Lutter et al., 2006). This knowledge has led to a focus in reducing the time from the onset of the first frank psychotic symptom to the initiation of treatment (also referred to as the duration of untreated psychosis) to improve patient prognosis and reducing

treatment resistance (Birchwood et al., 1998, Marshall et al., 2005, Perkins et al., 2005, Addington et al., 2004, Gottesman and Erlenmeyer-Kimling, 2001, McGLASHAN, 2005, Warner, 2005). Providing timely and appropriate interventions relies heavily on being able to prospectively identify those at highest risk of developing psychosis accurately (Yung et al., 2003). This is particularly challenging as PE are prevalent in the general population and are not necessarily an indicator of impending psychotic illness on their own.

Extensive research has been conducted over the past two decades to prospectively identify individuals at a higher risk of developing a psychotic disorder compared to another person in the general population (Sykes et al., 2020). Traditional studies adopted a 'genetic high risk model' to understanding the development of symptoms through following children with a family history of psychotic illness over time (Cannon and Mednick, 1993, Erlenmeyer-Kimling et al., 1995, Niemi et al., 2003). However, most individuals that develop a psychotic illness do not have an immediate family member with the disorder, consequently this method failed to identify a large of majority patients that do go onto develop psychosis (McGorry, Yung and Phillips, 2003). The *At Risk Mental State* is a risk paradigm which uses genetic and clinical risk factors to 'close in' on at high risk individuals (Bell, 1992, Thompson et al., 2015). This paradigm has been operationalised using the 'Ultra High Risk' (UHR) criteria and has been more successful in prospectively identifying those at high risk of transitioning to psychosis, with fewer false positives and shorter follow ups than genetic high risk models (McGorry, Yung and Phillips, 2003). Those deemed to be in the Ultra-High Risk phase are identified based on their symptoms and static factors (e.g., screened at an age when the incidence of the illness is at its highest between 16-35 years old) (Phillips et al., 2005). Studies suggest that individuals that meet this criteria are 200-400 times more likely to develop psychosis than an average person in the general population (Nelson, Thompson and Yung, 2012). A similar construct known as the 'Clinical High Risk' criteria has also been developed, by the Hillside Recognition Prevention Program in New York, to detect the developmental course of schizophrenia (Cornblatt et al., 2002). Unlike the UHR criteria, this strategy targets first episode schizophrenia rather than first episode psychosis (Phillips et al., 2005, Fusar-Poli et al., 2013). Another commonly used criteria

adopted to prospectively identify risk of psychosis is the Basic Symptoms approach (Ebel et al., 1989). The Basic Symptoms approach is complimentary to the UHR criteria but seeks to detect symptoms which may present before the Attenuated Psychotic Symptoms (APS) measured by the UHR criteria (Meng et al., 2009). This criteria fits with retrospective research which reports that prior to frank psychosis, there are three prodromal stages (i) non-specific mood and anxiety symptoms; (ii) an early prodromal phase dominated by negative symptoms (lasting for approximately 5 years); and (iii) a late prodromal phase involving subclinical psychotic symptoms (with an average duration of 1.1 years) (Cascio et al., 2016). The Basic Symptom concept is concerned with the early prodromal symptoms which include subtle subjective experiences that may not be observable to others but may increase in severity and frequency throughout psychotic illness (Cascio et al., 2016, Schultze-Lutter et al., 2007). Disturbances in thoughts, motivation, sensory perception, stress response and motor actions are recognised by the individual and may result in compensatory behaviours (such as withdrawal from social situations)(Schultze-Lutter, 2009). Importantly, these basic symptoms are concerned with experiences beyond positive and negative symptoms, they represent subtle changes in mental state that may precede frank psychosis, and relapse in those with a diagnosis of schizophrenia (Schultze-Lutter, 2009).

According to literature in this area, individuals experiencing basic symptoms represent the earlier stages of the psychosis prodrome, whilst youth meeting the UHR criteria are closer to transition and subsequently represent the later stages of the prodrome (Simon et al., 2012, Fusar-Poli et al., 2016a, Daneault and Stip, 2013). It is important to distinguish between these stages of the prodrome as research has shown that these two ARMS groups have clinical and neurobiological differences (Simon et al., 2012). In this thesis, the term ARMS is used in the systematic review and meta-analysis (see chapter 3) to describe findings gathered from several studies assessing risk for psychosis using a variety of instruments and capturing quite broadly the psychosis trajectory. Conversely, the term UHR is used in the transitions study (see chapter 5) to refer to participants meeting the UHR criteria following assessment using the Comprehensive Assessment of At Risk Mental States (CAARMS) instrument.

A meta-analysis quantitatively examining 2,502 Clinical High Risk outcomes reported transition rates to be 18% after 6 months, 22% after 1 year, 29% after 2 years and 36% after 3 year follow up in high risk patients (Fusar-Poli et al., 2012). A similar pattern of transition has been reported more recently in the North American Prodrome Longitudinal sample, with one third of participants transitioning within one year of psychotic symptom onset, one third 1-2 years after symptom onset and the final third of participants over two years later (Powers et al., 2020). Furthermore, whilst transition rates have been reported to be at their highest within the first two years, longitudinal research has reported transition rates of 34.9% across 10 years, suggesting that the risk extends beyond the two year window (Nelson et al., 2013). Other studies have reported diluted transition rates, with researchers suggesting that this may be a consequence of increased public awareness and self-referrals to effective early intervention services producing a larger number of false positives (Guloksuz et al., 2020). To reduce the number of false positives identified by the UHR criteria and to improve the predictive accuracy of prospective tools there is a continued need to examine predictive variables and vulnerability markers closely (Nelson, Thompson and Yung, 2012). This is particularly crucial as a large number of patients do not transition to psychosis but experience poor outcomes including continued attenuated psychotic symptoms and non-psychotic disorder (such as anxiety and substance use disorders) (Lin et al., 2015).

Whilst approximately one third of UHR youth transition to psychosis over the medium to long term, research suggests that around two thirds experience a range of other adverse outcomes including significant and long lasting impaired social and occupational functioning and reduced Quality Of Life (QoL) (Ong et al., 2020, Hofstetter et al., 2005b, Ritsner et al., 2004, Afonso et al., 2011). At a patient level the costs of such impairments can be grave, with individuals struggling to maintain core aspects of everyday life including critical relationships with friends and family, in addition to difficulties retaining employment which bring not only financial gains but psychological benefits (Robustelli et al., 2017, Lee et al., 2017, Hodgekins et al., 2015). Therefore, it is unsurprising that functioning and quality of life are viewed by clinicians and patients as important outcomes with far reaching consequences.

1.3 **RISK FACTORS FOR PSYCHOSIS**

In the context of the psychosis continuum, understanding how and why one person experiencing psychotic symptoms may go on to develop psychotic disorder but another will experience transient PE's key to early intervention and prevention of serious psychotic illness (Trotta et al., 2015, Collip et al., 2013, Wigman et al., 2011, DeVylder et al., 2015). Risk factors for both PE and psychotic illness have been examined, with findings suggesting that PE and psychotic illness share similar demographic (e.g., ethnicity, migration status, socioeconomic status) and clinical risk factors (e.g., trauma, substance misuse) which provides further support for the concept of a psychosis continuum (Linscott and van Os, 2013, Bourgin et al., 2020, Scott et al., 2008). This has catalysed a wealth of research examining PE in non-clinical groups who are often easier to access and engage, enabling new insights into psychotic phenomena which can be translated into clinical groups (Freeman, 2006).

1.4 **SLEEP DISTURBANCES AS A RISK FACTOR**

Sleep is an important biological need that is commonly disrupted in individuals experiencing psychosis compared to non-clinical populations (Rowland and Wickwire, 2018, Kaskie et al., 2017b, Freeman et al., 2015). Research has shown that disturbances to sleep occur early in the course of psychotic illness, often pre-diagnosis, and persist throughout the course of the disorder (Yung and McGorry, 1996a, Cohrs, 2008). Although prevalence rates are difficult to determine, one study reported that 21-100% of individuals experience difficulties with their sleep in the early stages of psychosis, whilst another study reported 77-100% of sleep disturbances occurring before the first episode of psychosis (Tan and Ang, 2001, Yung and McGorry, 1996b). Both the widespread nature of sleep disturbances and the early presence of sleep problems in psychosis, including pre-diagnosis, suggests that they are not necessarily a consequence of disease chronicity or medication status (Keshavan et al., 2011, Yung and McGorry, 1996b). Instead, sleep disruptions may be an indicator, or in some cases a marker, of impending deteriorations to mental health and possibly transition to psychosis (Zanini et al., 2013, Poulin et al., 2008).

Understanding the function of sleep is a critical first step in contextualising it as a potential risk factor for PE and psychotic illness. Sleep is a universal process defined by changes in consciousness, brain waves, muscle tone and response to external

stimuli (Horne, 1988). It has been shown to be vital for physical and psychological wellbeing including energy conservation, restoration of the body, brain thermoregulation, cognitive and emotional processing and for immune system functioning (Cappuccio et al., 2010, Siegel, 2003, Horne, 1988, Walker, 2017). Although sleeping behaviours vary significantly worldwide, sleep wake patterns are largely determined by synchrony between external cues (e.g., 24 hour light dark cycles) and the internal body clock (e.g., circadian rhythm)(Cappuccio et al., 2010). The two-process model postulates that sleep regulation is dependent upon the interaction between two processes; Process S and Process C (Borbély, 1982, Borbély et al., 2016). Process S represents the sleep wake cycle, with sleep debt accruing during wakefulness and reducing during sleep. This is coordinated with the environment, or Process C, also referred to as the circadian pacemaker which detects environmental cues for day and night. The signatures for Process S can be measured by electroencephalography (EEG) as Slow Wave Activity (SWA) during non-Rapid Eye Movement sleep and increasing theta activity during wakefulness (Borbély, 1982, Borbély et al., 2016). Conversely, biological markers of process C are core body temperature and melatonin levels (Borbély, 1982, Borbély et al., 2016).

There are two different types of sleep: Rapid Eye Movement sleep and Non-Rapid Eye Movement sleep; which is further divided into 3 further stages N1, N2, N3 (Zanini et al., 2013). When entering sleep it is typical to begin in non-Rapid Eye Movement sleep (N1) (which is a light sleep marking the transition from wakefulness to falling asleep), then into N2 (which is marked by regular breathing and heart rate and a reduction in body temperature), next N3 (also called slow wave sleep) and then Rapid Eye Movement sleep (REM) (whereby brain activity resembles wakefulness, with vivid dreams occurring during this stage) (Zanini et al., 2013, Siegel, 2003). The total cycle repeats every 90-110 minutes on average in healthy sleepers, with longer periods of REM sleep in the later stages of the night (Zanini et al., 2013). Across the lifespan, the structure of sleep changes drastically, for instance, in infancy REM sleep constitutes around half of all sleep (Garbarino, 2020). However, in primary school aged children the amount of REM sleep falls to approximately 20% and slow wave sleep increases (Garbarino, 2020). The shift into adolescence also brings about structural changes to sleep, such as reductions in slow

wave activity (Garbarino, 2020). In addition to structural changes to sleep across the life span, dynamic changes to the rhythm, quantity and quality of sleep also take place between infancy and adulthood. For instance adolescence is marked by delays in the timing of sleep (with later bedtimes and wake up times), reduced sleep time, increased daytime sleepiness and irregular sleep patterns (Sadeh et al., 2009). Such alterations have been linked to complex biological and psychosocial changes that occur during this sensitive developmental period which can have negative consequences including disruptions to cognitive processes, mood, social and behavioural difficulties (Sadeh et al., 2009, Carskadon, 2011).

In research and clinical practice, sleep is assessed and quantified using a range of validated self-report and objective assessments (Sadeh, 2015). The gold standard measurement of sleep disorders is Polysomnography (PSG) (Kushida et al., 2001, Davies et al., 2017). PSG records physiological processes during sleep including brain activity, eye movement, muscle activity, breathing and heart rate through electrodes and sensors placed across the head (in line with the International 10-20 system) and body in addition to video recording to monitor body position (Marino et al., 2013, Jafari and Mohsenin, 2010).The evaluation of sleep through electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), electrocardiogram and pulse oximetry produces output that can be used to aid in the diagnosis of sleep disorders (Marino et al., 2013, Jafari and Mohsenin, 2010). Standardised manuals (such as the American Academy of Sleep Medicine version 2.4) can then be used to assess sleep stages and respiratory events to build a picture of the parameters of an individual's sleep (Jafari and Mohsenin, 2010). Alternatively, actigraphy can be used as an objective sleep assessment tool (Kushida et al., 2001). Compared to PSG it is a cost-effective and less obtrusive method, as it is a computerised device typically worn on the wrist or ankle and has a large memory enabling recording for up to several weeks (Marino et al., 2013). Whilst it is a proxy measurement tool due to the direct measurement of movement (through accelerometers) rather than sleep, the users rest and activity levels can be monitored to build a picture of sleep wake patterns (Kushida et al., 2001, Sadeh, 2015). Computer algorithms are then used to analyse rhythm patterns and sleep parameters including total sleep time (TST), number of awakenings and sleep efficiency

(Ancoli-Israel et al., 2003). The reliability and validity actigraphy compared to PSG, has been debated over the past two decades (Ancoli-Israel et al., 2003, Scott et al., 2020, Conley et al., 2019). However, it is widely agreed that for the purposes of diagnosis of sleep disorders, polysomnography is superior due to its sensitivity, accuracy and the multimodal channels enabling monitoring of several physiological processes simultaneously compared to actigraphy (Kushida et al., 2001).

Sleep diaries and questionnaires (e.g., the Pittsburgh Sleep Quality Index) are alternative methods for assessing sleep quality and quantity across clinical and non-clinical groups (Sadeh, 2015). Validated and widely used questionnaires are often condition (e.g., measuring symptoms of insomnia) or dimension specific (e.g., assessing daytime sleepiness) or capture generic sleep disturbances through a range of questions (Ji and Liu, 2016). Sleep questionnaires are often low in participant burden, are suitable for repeated assessment and are complimentary to objective assessments (Ji and Liu, 2016). For instance, it is not possible to assess perception of sleep objectively as this is a subjective experience, consequently questionnaires play a unique role in understanding an individual perspective of sleep (Mollayeva et al., 2016, Devine et al., 2005)

TABLE 1. DEFINITION OF SLEEP TERMS

Sleep terms	Definition
Sleep Latency	The amount of time it takes to transition from wakefulness into a state of sleep or NREM stage 1 sleep.
Sleep Efficiency	The amount of time spent asleep compared to the total time spent trying to fall asleep; also calculated as the ratio of total sleep time (TST) to time spent in bed (TIB).
Sleep Duration	The length of time spent asleep.
Wake After Sleep Onset (WASO)	Time spent awake after defined sleep onset. Can indicate fragmented sleep.
Insomnia	A sleep disorder characterised by difficulties falling and/or staying asleep.
Rapid Eye Movement (REM)	A state of sleep usually occurring during a normal sleep cycle characterised by raised activity in the forebrain and midbrain neuronal regions, in addition to reduced muscle tone. Dreaming and rapid eye movements typically take place during this state of sleep.
Non Rapid Eye Movement (NREM)	A state of sleep (also called non-REM or slow wave sleep) usually occurring during a typical sleep cycle characterised by delta waves and reduced levels of physiological activity.
Circadian Rhythms	Internal biological rhythms that that coordinate behavioural and physical activity with the environment during a twenty four hour period. The circadian rhythm regulates the sleep wake cycle.
Parasomnias	Sleep disorders characterised by abnormal behaviours during any stage of sleep such as sleep walking, sleep related eating.
Actigraph	A non-intrusive device worn to monitor and record movement/activity levels and

	light exposure. The data can be used in conjunction with a sleep diary to understand rest/activity cycles. Actigraph's are usually worn on the wrist or ankle over a period of a week or more.
Polysomnography	A gold standard test which records sleep cycles and bodily functions (including eye movement, breathing rhythms, heart rate, respiratory data, muscle activity) during sleep.
Sleep spindle	Electrical brain activity measuring 7 to 14 Hz lasting for 1 to 2 seconds typically observed in sleep stage 2.
Sleep stage	There are three distinct stages on sleep which humans cycle between during a sleep period. Stage 1 is NREM sleep is recognised on EEG by low voltage, missed frequency waves with small eye movements. Stage 2 is the second stage of NREM sleep characterised by sleep spindles and K-complexes. Stage 3 is NREM sleep identified by high voltage, slow wave activity tonic muscles and no eye movements.

Sleep disturbances as a risk factor for psychosis, PE and poor outcomes

The implications of reduced or impaired sleep have been documented in research involving patients diagnosed with psychotic illness whereby behavioural, neurological, cognitive and psychological difficulties have been recorded and linked to sleep disturbances (Sharafkhaneh et al., 2005, Sheaves et al., 2015b, Blanchard et al., 2020b, Waters et al., 2013, Chiu et al., 2016, Kaskie et al., 2017a, Barrett et al., 2020). In one study, 80% of patients (n=60) diagnosed with non-affective psychosis reported experiencing multiple sleep disorders including insomnia (see Table 1) or nightmares (Reeve et al., 2019). These sleep disorders correlated with more severe positive psychotic symptoms (including hallucinations and paranoia), cognitive disorganisation, mood regulation difficulties and a lower quality of life (Reeve et al., 2019).

There have been two key reviews bringing together the evidence on sleep problems in early psychosis. The most recent is a qualitative review synthesizing 21 studies (Davies et al., 2017). Self-reported and objective (sleep architecture and spindles) sleep abnormalities in UHR and First Episode Psychosis (FEP) groups were explored, revealing that sleep disturbances are associated with symptomatology, neurocognitive deficiencies, help seeking behaviour and suicidality (Davies et al., 2017). However, a lack of causal evidence was found for poor sleep causing increased symptoms and the reviewers called for further robust longitudinal data measuring sleep objectively and subjectively to understand the role of sleep in the early stages of psychosis.

The second qualitative review in this area by Zanini et al. (2013) suggests that disrupted sleep is not a consequence of chronic psychosis but confirms that they can be seen in the early stages of the illness (Zanini et al., 2013). This review identifies that abnormal sleep parameters, homeostasis and misaligned circadian rhythm in early psychosis may have a neurobiological basis (Zanini et al., 2013). Similar to the review by Davies et al. (2017) and Zanini et al. (2013) qualitatively explore sleep in early psychosis as well as in the latter stages, discussing the presence of sleep disturbances prior to the onset of frank psychosis and the importance of these disturbances in relation to outcomes. Whilst these reviews have advanced what is known about the relationship between sleep and early psychotic illness, there have been a number of new studies in the area since 2017, consequently an update on the literature is currently needed. Furthermore, there is a lack of meta-analytical evidence to enhance understanding through the statistical significance of pooled results; consequently this is an important research area for future research.

The incidence of psychotic experiences often peaks during adolescence to early adulthood (McGrath et al., 2016) and sleep disturbances frequently co-occur with psychotic-like experiences during this time (Taylor et al., 2015). Importantly, the transition from childhood to adulthood is a sensitive developmental period as biological, psychological and social risk factors can result in the emergence of mental health difficulties (Paus et al., 2008). As young people enter into adulthood, common developmental experiences such as sleep problems and psychotic experiences can be a signal of underlying difficulties that may be responsive to intervention (Freeman et al., 2015). Previous research exploring data from the Avon Longitudinal Study of Parents and Children (ALSPAC) reported that children, aged 2.5 and 9 years old, experiencing frequent nightmares were more likely to report PLE at age 12 (Fisher et al., 2013b). Similarly, nightmares at 12 years old were shown to be associated with an increased risk of persistent psychotic-like symptoms at aged 18 (Thompson et al., 2015). Such findings suggest that nightmares during childhood may represent an important and clinically significant indicator for risk of psychotic experiences in adolescence. However, little is known about whether childhood and adolescent sleep disturbances contribute to PE that persist beyond 18 years old.

Disturbed sleep has also been shown to be associated with poor quality of life and functioning in clinical and non-clinical samples (Ruhrmann et al., 2008, Fusar-Poli et al., 2015, Hofstetter et al., 2005a, Ritsner et al., 2004, Afonso et al., 2011, Anderson and Bradley, 2013). Such outcomes are especially important in UHR youth they are often reported prior to diagnosis, are persistent and linked to transition to psychosis (Rapado-Castro et al., 2015, Velthorst et al., 2013, Robustelli et al., 2017). Furthermore, functional deficits are recognised as important for UHR youth who transition to psychosis and those who do not; as they correlate with neurocognitive impairments, negative symptoms and disorganised behaviour (Cotter et al., 2014, Lin et al., 2011). However, little is known about the specific sleep disturbances associated with QoL and functional outcomes in UHR youth, although both may present as a risk factor for poorer long-term clinical outcomes (Fusar-Poli et al., 2017, Alderman et al., 2015).

1.5 **GAPS IN THE LITERATURE**

Despite the recent increase in research on sleep disturbances and PE in clinical and non-clinical groups there are still several research questions in this area that are yet to be answered. These include:

1. What does the cumulative evidence to date tell us about the cross-sectional and longitudinal association between sleep disturbances and positive psychotic symptoms, functioning and QoL in youth at risk for psychosis?
2. Are early childhood and adolescent sleep disturbances associated with persistent psychotic experiences beyond 18 years old?
3. Can we develop further understanding, and replicate previously reported relationships, surrounding which specific sleep disturbances are associated with positive psychotic symptoms, functioning and QoL in UHR longitudinally?

Therefore, chapter three of this thesis will present a systematic review and meta-analysis examining the evidence to date on sleep disturbances in UHR youth. Chapter four will examine the prospective association between childhood and adolescent sleep and psychotic experiences in adulthood. In Chapter five there will be a replication study examining the longitudinal associations between sleep

difficulties (quantity, quality, chronotype and daytime sleepiness) and subsequent psychotic symptoms, functioning and QoL in an Australian and UK sample of UHR and non-UHR help seeking youth. Informed by the findings from chapter 3-5, Chapter 6 will outline the plans for a future trial investigating sleep disturbances in UHR youth. Finally, chapter 7 includes a discussion of the findings from this thesis, limitations and priorities for future clinical and research practice.

Chapter 2. **AIMS AND OBJECTIVES**

2.1 **OVERVIEW**

This thesis seeks to explore the nuanced relationship between sleep disturbances and psychotic symptoms across time and populations. As outlined in chapter 1, research has reported an association between sleep disturbances and subsequent psychotic symptoms across clinical and non-clinical groups. However, there are gaps in the literature concerning the timing, specificity and persistence of sleep disturbances which relate to psychotic experiences in early adulthood. Furthermore, the role of negative affect as a mediating factor in the longitudinal relationship is an area that requires replication.

In addition to examining the prospective association between sleep disturbances and PE, this thesis aims to investigate two further important outcomes reported in Ultra High Risk (UHR) samples experiencing subclinical psychotic symptoms; namely functioning and Quality of Life (QoL). It is well reported that less than one third of UHR youth endorsing psychotic experiences transition to psychosis. More widely reported are impairments to functioning and QoL. There is little evidence concerning the relationship between sleep disturbances and functioning or quality of life as a key outcome. Therefore, this thesis will advance existing knowledge surrounding the potential role of sleep in impaired functioning and QoL amongst UHR youth.

2.2 **SYSTEMATIC REVIEW AND META-ANALYSIS**

What does the existing evidence tell us about the association between sleep disturbances and psychotic symptoms, functioning and QoL in UHR youth?

There has been a surge in research describing an association between sleep disturbances, psychotic symptoms and functioning in UHR youth (Lunsford-Avery et al., 2017a, Lunsford-Avery et al., 2017c, Lunsford-Avery et al., 2015, Gonçalves et al., 2016, Zanini et al., 2015a, Reeve et al., 2018a, Bradley et al., 2018, Poe et al., 2017, Stowkowy et al., 2020, Morales-Muñoz et al., 2020). However, it is challenging to draw conclusions about the impact of sleep disturbances on outcomes in UHR youth due to small sample sizes and diverse measurements of sleep problems across studies. There is a need to summarise the evidence to establish whether sleep difficulties relate to increased symptom severity, poor functioning and

reduced QoL in UHR youth. Therefore, this thesis will present the findings from a systematic review and meta-analysis which qualitatively assesses the evidence to date, exploring whether specific sleep disturbances are associated with positive psychotic experiences, functioning and QoL. Furthermore, it will quantitatively examine comparable studies through a meta-analysis to explore the strength of the reported relationships.

The hypothesis for the systematic review and meta-analysis is:

1. Self-reported and objectively measured sleep disturbances will be associated with increased positive psychotic symptoms, poorer functioning and reduced QoL cross-sectionally and longitudinally in UHR youth.

2.3 **ALSPAC STUDY**

Are early childhood and adolescent sleep disturbances prospectively associated with persistent PE in adulthood? Is anxiety and/or depression a mediator in the relationship between sleep and PE?

Sleep disturbances in childhood and adolescence have been shown to be associated with later PE at 12 and 18 years old (Fisher et al., 2014, Thompson et al., 2015). However, there is yet to be any investigations into whether this relationship extends beyond 18 years old into early adulthood, which marks the peak onset age for the emergence of severe and long lasting mental health conditions including psychotic disorder (de Pablo et al., 2020). Furthermore, the complexity relating to the persistence of sleep difficulties and their relationship with psychotic experiences that persist into adulthood is yet to be explored. This thesis aims to investigate the longitudinal relationship between early sleep disturbances and subsequent psychotic experiences in adulthood, examining subtypes of sleep problems (including difficulties initiating and maintaining sleep and parasomnias) and their relationship with persistent PE. In addition, this thesis seeks to further understand whether anxiety and depression mediates this relationship as shown in other mental health conditions such as suicide (Littlewood et al., 2017).

The hypotheses for this study are:

Primary hypotheses:

1. Preschool and/or adolescent sleep problems (aged 1.6-5.9 and 12 years old) will be associated with psychotic experiences at 24 years old
2. Preschool sleep problems (aged 1.6-5.9 years) and adolescent parasomnias (12 years old) will be associated with the *persistence* of psychotic experiences during late adolescence/early adulthood (18 and 24 years old)

Secondary hypothesis:

1. Preschool and/or adolescent sleep problems significantly associated with psychotic experiences at 24 years old will be mediated by symptoms of anxiety and depression

2.4 **TRANSITIONS STUDY**

Are there specific sleep problems that are associated with subsequent UHR status, psychotic symptoms, functioning and QoL in a help seeking sample of UK and Australian youth?

Retrospective studies have provided evidence to suggest that sleep disturbances emerge early in psychotic illness, often prior to the first episode of psychosis. However, there is limited prospective evidence to understand the specific types of sleep difficulties reported by at risk youth and how they relate longitudinally to UHR status, severity of psychotic symptoms, functioning and QoL. Furthermore, there are few replication studies examining the long term relationships between these experiences. Therefore, this thesis aims to examine the prospective association between self-report sleep disturbances (sleep quality, duration, chronotype, daytime sleepiness) and UHR status, psychotic experiences, functioning and QoL in an Australian help seeking sample. It also aims to replicate these findings in a UK help seeking sample.

The hypothesis for this study is:

1. Australian and UK help seeking youth who meet **UHR criteria, experience positive psychotic symptoms, poorer functioning and QoL** at 6 and/or 12

month follow up will report reduced sleep quality, lower sleep quantity, persistent daytime sleepiness and a delayed chronotype at baseline.

2.5 **FEASIBILITY STUDY**

Is a CBTi intervention compared to treatment as usual effective in reducing PE longitudinally in a UHR and healthy control sample?

Despite strong signals to indicate that sleep disturbances predate PE in clinical and non-clinical samples, it is not possible to draw definitive conclusions concerning the direction of causality due to the observational nature of existing studies. Therefore, the outline of a feasibility study is presented to assess the effectiveness of a CBTi intervention compared to treatment as usual in a UHR sample, to ascertain whether the manipulation of sleep produces changes in PE, functioning and QoL.

The hypothesis for this study is:

I. There will be improvements in PE, functioning and QoL at 6 and 12 month follow up amongst help seeking youth randomised to receive a CBTi intervention compared to treatment as usual.

Chapter 3. **SYSTEMATIC REVIEW AND META-ANALYSIS**

3.1 **Introduction**

Sleep is a fundamental biological need that is commonly disrupted in individuals that experience psychosis (Rowland and Wickwire, 2018, Kaskie et al., 2017b, Freeman et al., 2015). Research has shown that disturbances to sleep occur early in the course of psychotic illness, often pre-diagnosis, and persist throughout the course of the disorder (Yung and McGorry, 1996a, Cohrs, 2008). Although prevalence rates are difficult to determine, one study reported that 21-100% of individuals experience difficulties with their sleep in the early stages of psychosis, whilst another study reported 77-100% of sleep disturbances occurring before the first episode of psychosis (Tan and Ang, 2001, Yung and McGorry, 1996b). Both the widespread nature of sleep disturbances and the early presence of sleep problems in psychosis including the prodromal period suggests that they are not necessarily a consequence of disease chronicity or medication status (Keshavan et al., 2011, Yung and McGorry, 1996b). Instead, sleep disruptions may be an indicator, or in some cases a marker, of impending deteriorations to mental health and possibly transition to psychosis (Zanini et al., 2013, Poulin et al., 2008). However, the characteristics of sleep that are indicative of poorer mental health outcomes prior to a diagnosis of psychosis remain unclear, particularly in individuals who may be at risk of developing psychosis such as those with an identified at risk mental state (ARMS).

Research suggests that sleep disruptions and functional impairments share a number of key features in ARMS patients; they are often reported prior to diagnosis, are persistent and linked to transition to psychosis (Rapado-Castro et al., 2015, Velthorst et al., 2013, Robustelli et al., 2017). Furthermore, functional deficits are recognised as important for ARMS youth who transition to psychosis and those who do not; as they correlate with neurocognitive impairments, negative symptoms and disorganised behaviour (Cotter et al., 2014, Lin et al., 2011). A link between functional outcomes and sleep has been documented in healthy and clinical populations with poor sleep impacting on daytime functioning and cognitive processes (Anderson and Bradley, 2013). However, little is known about the

relationship between sleep disruptions and functional outcomes in ARMS youth, although both may present as a risk factor for poorer long-term clinical outcomes (Fusar-Poli et al., 2017, Alderman et al., 2015).

The relationship between disturbed sleep and Quality of Life (QoL) in ARMS youth is also an important line of enquiry; as the prevalence and impact of reduced QoL is well documented in ARMS groups (Ruhrmann et al., 2008, Fusar-Poli et al., 2015). Furthermore, poor sleep has been implicated in the sustainment of reduced QoL in patients diagnosed with psychotic illness (Hofstetter et al., 2005a, Ritsner et al., 2004, Afonso et al., 2011). The presence of a relationship between sleep disturbances and QoL in ARMS youth may represent an additional target for intervention or an important measurement for assessing the effectiveness of interventions. However, firstly it is important to define the nature of the relationship that exists between sleep disruptions and QoL prior to a diagnosis of psychosis.

Several systematic reviews have thoroughly examined the relationship between sleep disruptions and psychotic symptoms and illness (Lunsford-Avery and Mittal, 2013, Zanini et al., 2013, Davies et al., 2017, Reeve et al., 2015, Waite et al., 2019). A recent high quality review reported on the nature of sleep disruptions in ARMS and First Episode Psychosis (FEP) samples. In addition to exploring the relationship between disturbances, positive symptom severity, cognitive deficits and levels of distress in these samples (Davies et al., 2017). There have since been a number of new studies published in this area. Therefore, this review will update and extend current knowledge on self-reported and objective measurements of sleep disturbances and how they interact with attenuated psychotic symptoms whilst also exploring interactions with patient QoL and functional outcomes in ARMS youth. We will conduct an exploratory meta-analysis to quantitatively assess whether self-reported general sleep disturbance are problematic in ARMS groups, which to our knowledge has not been carried out before.

The two key aims of this paper are to (i) characterise self-reported and objectively measured sleep disturbances during the ARMS period and to (ii) examine cross-sectional and longitudinal relationships between sleep disturbances and psychotic symptoms, functioning and QoL in ARMS patients.

3.2 **Method**

This review was carried out in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol is registered on PROSPERO (CRD42017069160).

3.2.2 Data sources and search strategy

We conducted electronic searches of the following databases: MEDLINE, Embase, CINAHL, PsycINFO, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL). The reference lists of eligible studies were hand searched to identify further relevant studies. Grey literature including doctoral thesis and conference abstracts were screened for eligibility to reduce the risk of publication bias. No date or publication status restrictions were applied during the searches. Non-English language studies were excluded due to limited resources.

All searches were performed on 10th July and re-ran on 14th February 2020. Search terms were developed with advice from a medical librarian and field experts. A combination of risk terms (e.g., "ultra high risk"), psychosis terms (e.g., 'psycho*) and sleep terms (e.g., 'insomnia') were used in electronic searches (see appendix A).

3.2.3 Eligibility criteria

Eligible studies included at least ≥50% of participants (aged 12-35 years old) assessed to be Ultra High Risk as identified by any standardised measure of At Risk Mental State (including the Comprehensive Assessment of the At Risk Mental State (CAARMS) (Yung et al., 2005a); The Structured Interview for Psychosis-Risk Syndromes (SIPS); the Structured Clinical Interview for DSM Disorders (SCID) (Lobbestael et al., 2011)). Studies that did not involve UHR participants or did not include a formal assessment of the At Risk Mental State were excluded.

All studies reported objective (e.g., actigraphy or polysomnography) or self-reported data (e.g., validated self-reported measures, sleep diaries) on sleep disturbance. Studies not reporting sleep outcomes, disturbances or sleep disorders using validated tools were excluded.

Randomised, non-randomised trials and observational studies (cross sectional and prospective) were included in this review. However, similar to other published systematic reviews and meta-analyses examining risk factors across a range of health

conditions, case control studies involving <20 participants were excluded to reduce the risk of bias (Lankhorst et al., 2012, Sagna et al., 2014, Friedemann et al., 2012, Sangla and Kandasamy, 2021, Lai et al., 2019). Unpublished studies and meeting abstracts were screened but did not meet the inclusion criteria. Non English studies were excluded.

3.2.4 Screening procedure

Search results were imported into reference manager software (endnote) and duplicates removed. One reviewer (LC) screened all titles and abstracts and another member of the team (FE) screened a random 20% of articles. LC and FE independently screened 100% of full text articles; all disagreements were resolved by discussion with a third party (AT).

3.2.5 Quality assessment and risk of bias

The quality of studies was assessed using the Downs and Black quality index tool (Downs and Black, 1998). This is a 27-item checklist for measuring quality with high criterion validity (r=0.90), internal consistency reliability (Cronbach alpha >0.69) and external validity (Cronbach alpha= 0.54). The tool has high test-retest reliability scores for both randomised and non-randomised studies (r: 0.69-0.90) (Downs and Black, 1998). The levels of categories for quality are: excellent (26-28), good (20-25), fair (15-19) and poor (≤14) (Jutai et al., 2009).

3.2.6 Data extraction

Details of eligible studies were recorded using pre-piloted data collection forms. Author details, study details (including year of study, country of study, number and duration of follow up assessments), participant information (including number of participants/age/gender), assessment tools used to assess ARMS/sleep/functioning and QoL and were collected for each study.

3.2.7 Data synthesis and analysis

A narrative synthesis approach (Popay et al., 2006) was adopted for the analysis of studies included in this review. Exploratory meta-analysis was not possible for all included studies due to the heterogeneity of data. Consequently, three studies reporting means and standard deviations from the Structured Interview for Prodromal Symptoms (SIPS) and two studies reporting means and standard

deviations from the Pittsburgh Sleep Quality Index (PSQI) were pooled in two separate exploratory meta-analyses.

Random effects models (Revman version 5.3) were used for the quantitative synthesis of comparable data which did not involve overlapping samples. Heterogeneity of studies was examined using the I^2 statistic.

3.3 **Results**

3.3.2 Search yield

Database searches and retrieval from other sources revealed 7825 articles; following the removal of duplicates 6585 papers were left of which 6451 were excluded at title and abstract stage. The remaining 134 articles were assessed at full text level for eligibility. Full text agreement between reviewers was high (k =0.8). One hundred and seventeen papers were excluded following full text review. Sixteen studies provided data on sleep in ARMS samples and were included in the final review (see Figure 2).

FIGURE 2. PRISMA DIAGRAM

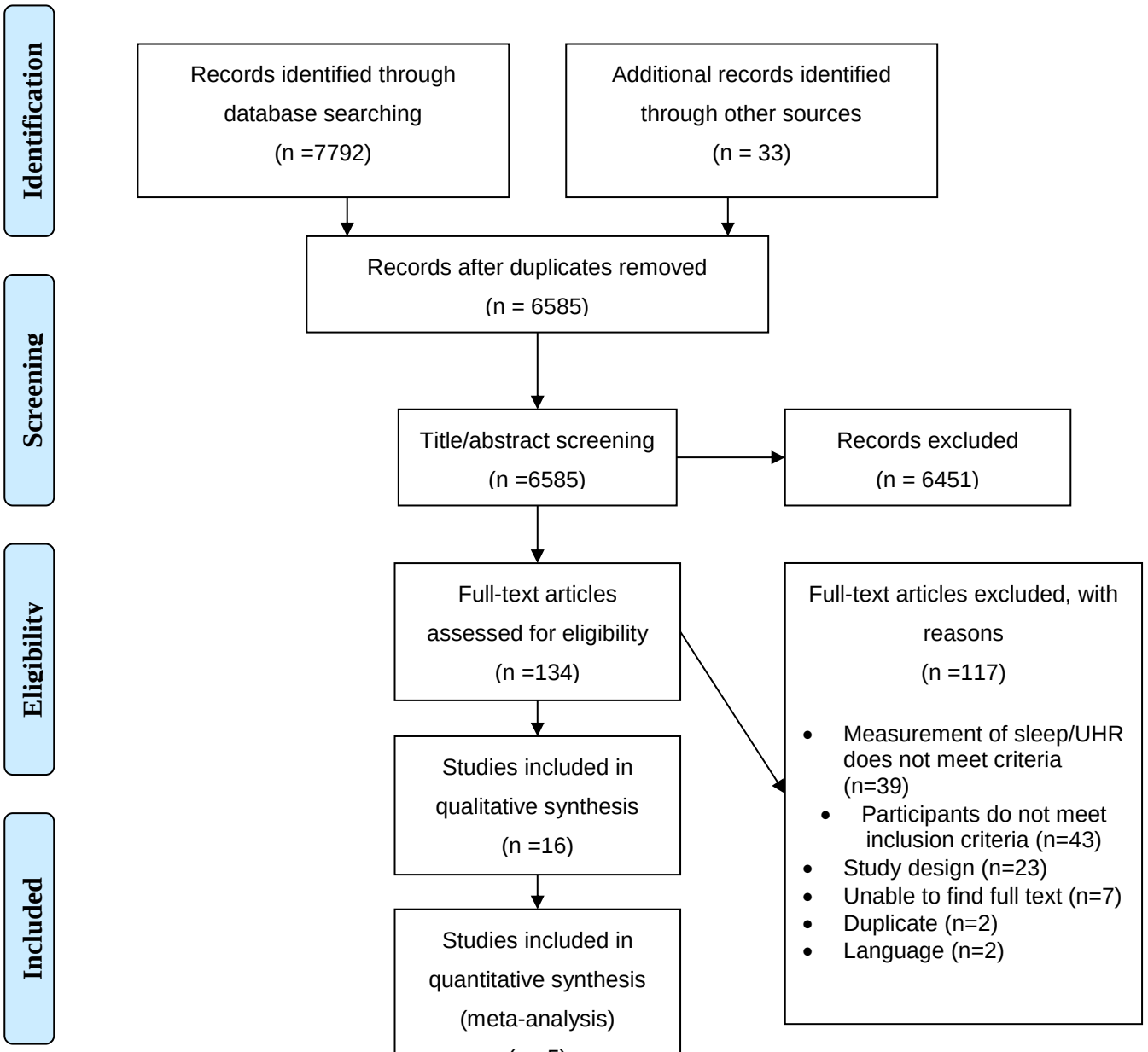


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

3.3.3 Study and participant characteristics

The included studies involved 1962 at risk participants from the USA and Canada (n=1459), Europe (n= 601), Brazil (n=20) and Australia (n=10). Study designs varied and included seven cross-sectional studies, seven cohort studies and two RCT's (see table 1). Follow up periods for longitudinal studies ranged from 1 to 8.9

years and outcomes were based on psychotic symptoms, conversion to psychosis and psychosocial functioning. Six studies did not include a control group, however those who did (n= 10) (Castro et al., 2015, Lederman et al., 2017, Lunsford-Avery et al., 2013, Michels et al., 2014, Tso et al., 2017, Zanini et al., 2015b, Lindgren et al., 2017, Lunsford-Avery et al., 2015, Lunsford-Avery et al., 2017b, Goines et al., 2019) included a wide spectrum of participants including: healthy controls, healthy relatives, first episode psychosis patients, and individuals diagnosed with psychotic disorder (see table 1).

Four studies were produced by the Adolescent Development and Prevention Treatment lab at the University of Colorado Boulder (Lunsford-Avery et al., 2013, Lunsford-Avery et al., 2017b, Lunsford-Avery et al., 2015, Lunsford-Avery et al., 2017a) and two studies from The Program for Recognition and Intervention in Individuals at-risk Mental State (Castro et al., 2015, Zanini et al., 2015b). Despite the overlap in samples, these studies were included in the review due to the reporting of different sleep outcomes. However, these studies were not compared directly in the exploratory meta-analysis to prevent inflation of the reported effect sizes (Higgins and Altman, 2008). Only studies including comparable data without overlapping samples were compared in the meta-analysis.

3.3.4 Sleep related outcomes

Sleep was measured using a range of self-reported measures including the Pittsburgh Sleep Quality Index (n=6), Epworth Sleepiness Scale (n=2), Questionnaire of Morningness and Eveningness (n=2), the Structured Interview for Prodromal Symptoms (SIPS) (n=7), lucid dream and nightmare frequency scales (n=1), the Economic Patient Questionnaire Interview (n=1); and objective measures including actigraphy (n=3) and polysomnography (n=1). The duration of monitoring for actigraphy varied between five (Lunsford-Avery et al., 2015, Lunsford-Avery et al., 2017b) and fifteen consecutive days (Castro et al., 2015) and PSG was two consecutive nights (Zanini et al., 2015b). The reporting of the sleep data varied, for instance some articles included dichotomous outcomes (e.g., poor sleeper and good sleeper) (Lunsford-Avery et al., 2017a, Miller et al., 2003b) and/or continuous outcomes (e.g., means and standard deviations) (Lunsford-Avery et al., 2015, Lunsford-Avery et al., 2017b, Lunsford-Avery et al., 2013, Castro et al., 2015,

Zanini et al., 2015b, Poe et al., 2017, Ruhrmann et al., 2010b, Michels et al., 2014, Grivel et al., 2018, Lederman et al., 2017, Lindgren et al., 2017, Tso et al., 2017).

3.4 **Main Results**

3.4.2 Self-reported and objective and sleep disturbances in ARMS patients

3.4.3 Latency

Three studies reported sleep latency scores in ARMS patients (for definition of sleep latency and other sleep terms, see table 2). (Lunsford-Avery et al., 2013, Zanini et al., 2013, Lederman et al., 2017). Zanini et al. (2015b) revealed significantly higher PSG latency scores in ARMS compared to HC. Interestingly, Lunsford-Avery et al. (2013) also reported higher self-reported PSQI latency scores in ARMS patients compared to HC's. In contrast, Lederman et al. (2017) found no significant difference in the PSQI sleep latency scores of healthy volunteers, ARMS and FEP patients.

3.4.4 Efficiency

Four studies presented sleep efficiency scores from ARMS patients (Lederman et al., 2017, Lunsford-Avery et al., 2015, Lunsford-Avery et al., 2013, Zanini et al., 2015b).There were no significant differences in the PSG sleep efficiency percentages (Zanini et al., 2015b) or actigraphy scores (Lunsford-Avery et al., 2015) of ARMS patients compared to HC's. However, there was an association at trend level between PSQI efficiency and actigraphic efficiency scores among ARMS youth but not HC's (Lunsford-Avery et al., 2015). There were no significant differences in PSQI sleep efficiency scores of ARMS verses HC participants (Lunsford-Avery et al., 2013, Lederman et al., 2017)

3.4.5 WASO

Two studies reported WASO scores of ARMS participants (Lunsford-Avery et al., 2015, Zanini et al., 2015b). Actigraphy WASO scores of ARMS patients was found to be significantly higher than HC's (Lunsford-Avery et al., 2015). However, Zanini et al. (2015b) reported no significant difference in the PSG WASO scores of ARMS youth compared to HC's.

3.4.6 Night time awakenings

Number of night-time awakenings derived from actigraphic measurements revealed no differences in mean scores between ARMS patients and HC participants (Lunsford-Avery et al., 2015). Furthermore, there were no correlations between self-reported PSQI sleep disturbances and number of night time awakenings measured by actigraphy in ARMS and HC participants (Lunsford-Avery et al., 2015). Two studies reported scores from the PSQI sleep disturbance subscale which indicates disruptions caused by environmental/physiological factors. One of these studies did not reveal any significant differences between HC's, and FEP patients (Lederman et al., 2017). In contrast, Lunsford-Avery et al. (2013) reported that ARMS patients endorsed significantly more disturbances than healthy controls on this subscale.

3.4.7 Total Sleep Time

Four studies provided data on Total Sleep Time (TST) (Lunsford-Avery et al., 2015, Lunsford-Avery et al., 2013, Zanini et al., 2015b, Lederman et al., 2017). Polysomnographic TST and actigraphy TST scores were not found to be significantly different between ARMS individuals and HC's (Zanini et al., 2015b, Lunsford-Avery et al., 2015). Similarly, there were no between group differences in PSQI duration scores (Lunsford-Avery et al., 2013, Lederman et al., 2017). Interestingly, Lunsford-Avery et al. (2015) reported a significant relationship between PSQI sleep duration and actigraphy TST in both ARMS and HC participants (Lunsford-Avery et al., 2015).

3.4.8 Movements

Only one study reported on movements during sleep revealing that total night time movements recorded by actigraphy was significantly increased in ARMS patients compared to HC (Lunsford-Avery et al., 2015).

3.4.9 Day time naps

In addition to impaired night time sleep, ARMS participants endorsed significantly longer naps compared to HC's according to actigraphic data (Castro et al., 2015).

3.4.10 General sleep disturbance

Six studies presented findings on self-reported sleep disturbances(Grivel et al., 2018, Lederman et al., 2017, Miller et al., 2003b, Poe et al., 2017, Tso et al., 2017, Zanini

et al., 2015b). Tso et al. (2017) revealed that clinically higher risk patients (global score ≥ 7 on the SOPS) scored significantly higher SOPS sleep disturbance scores compared to clinically lower risk patients (global score < 7 on the SOPS). Grivel et al. (2018) also reported that ARMS patients with any life time trauma endorsed significantly higher SIPS sleep disturbance scores compared to those with no trauma. A further study assessing sleep disturbances using the SIPS revealed one third (37%) of ARMS patients scored between 3 (moderate) and 6 (extreme) on the sleep disturbance SIPS subscale (Miller et al., 2003b). A final study found a significant difference between ARMS and HC's on the SIPS G1 subscale (Poe et al., 2017).

Zanini et al. (2015b) revealed that 75% of ARMS patients and only 30% of the healthy controls scored greater than 5 on the PSQI measure. ARMS patients (mean score 8.0, SD 3.3) were also reported to score significantly higher PSQI scores compared to HC's (mean score 3.9, SD 1.5) (Lederman et al., 2017). A global score of <5 indicates "good" sleep quality commonly reported amongst healthy control subjects in comparison to a score >5 on the PSQI that is suggestive of "poor" sleep often observed in clinical samples (Buysse et al., 1989).

3.4.11 Daytime sleepiness (ESS)

Three studies provided results on daytime sleepiness in ARMS patients (Poe et al., 2017, Lederman et al., 2017, Zanini et al., 2015b). ARMS participants endorsed significantly higher SIPS measured daytime fatigue (Poe et al., 2017) and PSQI daytime dysfunction compared to HC's. Conversely, daytime sleepiness scores derived from the Epworth Sleepiness Scale were not significantly different between ARMS patients and healthy controls (Zanini et al., 2015b).

There are seven items assessing sleep disturbances on the SIPS; with higher scores suggesting higher levels of disturbed sleep (Miller et al., 2003a).

3.4.12 Dreaming and Parasomnia

Only one study reported on dreaming and nightmares using the Lucid dream and nightmare frequency scales, revealing that ARMS patients reported a significantly higher frequency of nightmares compared to HC's (Michels et al., 2014). Dream recall frequency was also found to be highest among ARMS patients compared to healthy controls (Michels et al., 2014).

3.4.13 Circadian rhythm

Four studies reported on circadian rhythm in ARMS patients (Castro et al., 2015, Lunsford-Avery et al., 2015, Poe et al., 2017, Zanini et al., 2015b). Castro et al. (2015) revealed between group differences in the actigraphic autocorrelation function parameter, which is an indication of circadian rhythm fragmentation; values closer to zero suggest a less fragmented rhythm. ARMS participants (mean score: -0.14.SD 0.03) experienced more fragmentation compared to HC's (mean score: -0.11. SD 0.02). However, Lunsford-Avery et al. (2015) did not find this parameter to be significantly different among ARMS individuals (mean score: 20.67. SD 8.37) and HC's (mean score: 20.63. SD 5.42). Participants wore actigraphs for five days in the Lunsford-Avery et al. (2015) study compared to 15 consecutive days in the Castro et al. (2015) study. Compared to HC's a significantly higher number of ARMS participants reported sleep pattern disruption (17.5% of ARMS youth vs 0% HC) and day/night reversal (11.9% of ARMS youth vs 0% HC) as measured by the SIPS (Poe et al., 2017).

3.5 CROSS-SECTIONAL ASSOCIATIONS BETWEEN SLEEP DISTURBANCES, PSYCHOTIC SYMPTOMS, FUNCTIONING AND QOL

3.5.2 Positive symptoms

A total of five studies reported cross-sectional associations between sleep disturbances and positive symptoms (Lunsford-Avery et al., 2015, Lunsford-Avery et al., 2013, Poe et al., 2017, Goines et al., 2019). In one study, SIPS rated sleep disturbances were found to be significantly associated with severity of total positive symptoms ($\boldsymbol{p} < 0.01$) in a large sample of 740 ARMS youth (Goines et al., 2019). These self-reported sleep disruptions were found to relate to the severity of specific attenuated psychotic symptoms; suspiciousness ($\boldsymbol{p} = 0.006$) and perceptual abnormalities ($\boldsymbol{p} = 0.001$). When exploring mediation effects, the researchers revealed that depression held an indirect effect on the relationship between sleep disturbance and persecutory symptoms (b = 0.0537, CI (95%) = 0.0319–0.0787) but the same was not true for perceptual abnormalities or disorganised communication. Similarly, in a large help seeking sample of 194 ARMS patients, SIPS rated sleep pattern disruption (B=3.37, p= < 0.01) and day night reversal (B=3.05, p= < 0.01)

were found to be significantly related to positive psychotic symptoms (Poe et al., 2017). Lunsford-Avery et al. (2015) reported several actigraphic sleep parameters to be associated with baseline positive symptoms including reduced sleep efficiency (***F*** (3, 31) = 8.19, ***p*** < .01), increased WASO (***F*** (3, 31) = 12.50, ***p*** < .01), greater numbers of night time awakenings (F (3, 31) = 2.81, p = .05) and increased movements (***F*** (3, 31) = 7.26, ***p*** < .01) among ARMS and HC participants. Interestingly, TST scores were not associated with positive symptoms (p=0.37). In a study involving an overlapping sample, several circadian rhythm parameters were found to correlate with baseline positive symptoms severity (Lunsford-Avery et al., 2013). These included lower autocorrelation function (p<0.05), lower diurnal activity (p<0.05) and increased intradaily variability (an indication of rest activity fragmentation) (p<0.05). However, self-reported PSQI scores were not found to be associated with SIPS positive symptoms in ARMS participants.

3.5.3 Negative symptoms

Three studies reported on the relationship between sleep disturbances and negative symptoms in ARMS patients (Lunsford-Avery et al., 2017a, Poe et al., 2017, Lunsford-Avery et al., 2013).Negative symptom levels measured by the SIPS were found to be related to decreased sleep duration, increased sleep latency and reduced sleep quality in ARMS patients (Lunsford-Avery et al., 2013). Furthermore, at a trend level ARMS patient with a PSQI score >8 experienced increased negative symptoms compared to those endorsing a score of ≤ 8 on PSQI (Lunsford-Avery et al., 2017a).

Poe et al. (2017) also reported negative symptoms to be associated with several SIPS measured sleep disturbances including daytime fatigue, sleep pattern disruption and day night reversal (B=3.12, p-value=0.02; B=4.48, p-value= < 0.01; and B=5.54, p-value= < 0.01 respectively). Furthermore, insomnia for two days was found to be related to negative symptoms at trend level.

3.5.4 Functional outcomes

Two studies reported on the relationship between sleep disruptions and functional outcomes among ARMS patients (Poe et al., 2017, Lunsford-Avery et al., 2017a). Poe et al. (2017) revealed sleep pattern disruption assessed by the SIPS G1 subscale to be significantly associated with reduced GAF general functioning scores of

ARMS youth. Furthermore, linear regression models revealed insomnia for two days to be related to role functioning and social functioning at trend level (Poe et al., 2017). In relation to psychosocial functioning, ARMS patients defined as poorer sleepers with a score of >8 on the PSQI did not differ significantly to better sleepers that scored ≤8 on the GAF measure (Lunsford-Avery et al., 2017a).

3.5.5 Quality of Life

QoL assessed using the Manchester Short Assessment of Quality of Life scale was not found to be associated with sleep duration or sleep duration range in 160 ARMS patients as measured by the Economic Patient Questionnaire interview. However, the authors acknowledged that the tests may be underpowered due to low completion rates of quality of life measures (Reeve et al., 2018c).

3.6 LONGITUDINAL RELATIONSHIP BETWEEN SLEEP DISTURBANCES, PSYCHOTIC SYMPTOMS, FUNCTIONING AND QOL

3.6.2 Positive symptoms

Six studies reported on sleep disturbances as a longitudinal predictor of positive psychotic symptoms in ARMS patients (Lunsford-Avery et al., 2015, Lunsford-Avery et al., 2017b, Reeve et al., 2018c, Ruhrmann et al., 2010b, Poe et al., 2017, Lindgren et al., 2017). One study provided estimates on ARMS patient sleep duration on a 'good' or 'bad' night over the preceding three month period. Reeve et al. (2018c) reported that shorter sleep duration predicted severity of delusional ideas ($p=0.003$) and hallucinations ($p=0.01$) longitudinally. Delusional ideas remained significant even when controlling for sleep at the later time point ($p= 0.036$). However, when controlling for previous psychotic experience severity these results did not remain significant. Instead the strongest predictor for later psychotic experiences was the presence of previous psychotic experience rather than the occurrence of sleep disturbances.

Interestingly, sleep disturbances assessed by a SIPS score of >2 was included in a prediction model of transition to psychosis at 18-month follow up, in addition to five other variables (such as SIPS positive subscale scores) (Ruhrmann et al., 2010b).

The hazard ratio for sleep disturbances was 2.21 (95% confidence interval 1.034-4.717); suggesting that conversion to psychosis in ARMS patients reporting SIPS sleep disturbance scores >2 was 2.21 times higher than those scoring <2 on the SIPS. On the contrary, a separate study conducted in the USA found that sleep items measured by the SIPS at baseline did not predict conversion to psychosis at 2.5 year follow up (Poe et al., 2017). None of the studies included in this review reported sleep problems at baseline predicting transition to psychosis at follow up.

In one study ARMS patients wore actigraphs for five nights and findings revealed reduced sleep efficiency ($F(4, 18) = 8.27$, $p < .01$), lower total sleep time ($F(4, 18) = 4.39$, $p < .05$) and higher Wake After Sleep Onset ($F(4, 18) = 4.94$, $p < .05$) at baseline to be significantly related to positive symptoms at 12-month follow up (Lunsford-Avery et al., 2015). In a separate study involving the same sample, fragmented circadian rhythm (calculated using rest activity data derived from actigraphic measurements) at baseline correlated with positive symptoms at baseline and one year follow up (Lunsford-Avery et al., 2017b).

Only one study provided data on psychotic symptoms at baseline and sleep disturbances at follow up. This study investigated suicidality, self-harm and psychotic-like symptoms amongst ARMS patients and non-ARMS patients at baseline and sleep disturbances at 2.8-8.9 years follow ups. Findings revealed that self-harm was not significantly related to sleep disturbances (as measured by the SIPS subscales) at follow up (p=0.43) (Lindgren et al., 2017).

3.6.3 Negative symptoms

Two studies reported on the longitudinal relationship between sleep problems and negative symptoms (Lunsford-Avery et al., 2017b, Lunsford-Avery et al., 2015). Self-reported PSQI disturbance scores and actigraphic variables at baseline were not significantly correlated with SIPS negative symptom levels at 12-month follow up (Lunsford-Avery et al., 2015). However, actigraphy measured diurnal activity (indicating the average activity level during the most active 10 hours of the day) predicted the severity of negative symptoms at 12 month follow up (Lunsford-Avery et al., 2017b).

3.6.4 Functional outcomes

One study reported on actigraphic variables predicting functional outcomes in ARMS patients. In this study circadian rhythm variables (such as autocorrelation function which may be used to derive degree of rhythm fragmentation) at baseline were also found to be related to psychosocial functioning levels measured by the Global Assessment of Functioning scale at one year follow up (Lunsford-Avery et al., 2017b).

3.6.5 Quality of Life

None of the included studies provided findings on the longitudinal relationship between quality of life on sleep disturbances in ARMS youth.

TABLE 2. DETAILS OF INCLUDED STUDIES

Author	Year	Country	Study design	ARMS N (male/female)	Comparator N (male/female)	ARMS Assessment Measure	Sleep Instrument	Functioning Assessment Measure	Positive symptoms Assessment Measure	Negative Symptoms Assessment Measure	Quality Score (Downs and Black, 1998)
Castro et al. (2015)†	2015	Brazil	Cross-sectional study	20 At risk for psychosis/BD (13/7)	20 Healthy Controls (13/7)	CAARMS	Actigraphy, PSQI, ESS,QME	NR	NR	NR	10
Lederman et al. (2017)	2017	Australia	Cross-sectional study	10 ARMS (8/2)	10 FEP (8/2); 10 HC (7/3)	CAARMS	PSQI	NR	NR	NR	10
Lunsford-Avery et al. (2013)‡	2013	USA	Cross-sectional study	33 UHR (22/11)	33 Healthy Controls (14/19)	SIPS	PSQI	NR	SIPS	SIPS	12
Lunsford-Avery et al. (2017a)‡	2017	USA	Cross-sectional study	62 UHR (37/25)	none	SIPS	PSQI	GAF	SIPS	SIPS	14
Michels et al. (2014)	2014	Germany	Cross-sectional study	14 UHR (9/5)	17 Schizophrenia (9/8). 17 Healthy Relatives (7/10). 29 Healthy Controls (18/11)	Early Recognition Inventory	Lucid dream and nightmare frequency scales	None reported	Early Recognition Inventory	Early Recognition Inventory	11
Tso et al. (2017)	2017	USA	Cross-sectional study	203 CHR (115/88)	87 CLR (61/26); 44 EFEP (26/18)	SOPS	SOPS	GFS	PANSS	PANSS	15
Zanini et al. (2015b)†	2015	Brazil	Cross-sectional study	20 At risk for psychosis/BD (13/7)	20 Healthy Controls (13/7)	CAARMS	PSG, PSQI,ESS,QME	NR	NR	NR	11

Miller et al. (2003b)¥	2003	USA & Canada	RCT	60 UHR (39/21)	None	SIPS	SIPS	GAF	PANSS	PANSS	13
Reeve et al. (2018c)	2018	UK	RCT	160 ARMS (98/62)	None	CAARMS	Economic Patient Questionnaire Interview	NR	CAARMS	NR	15
Goines et al. (2019)¥	2019	USA & Canada	Cohort Study	740 ARMS (424/316)	280 Healthy Controls 141/139)	SIPS	SIPS	NR	SIPS	SIPS	15
Grivel et al. (2018)	2018	USA	Cohort study	200 UHR (114/56)	None	SIPS	SIPS	GFS	SIPS	SIPS	11
Lindgren et al. (2017)	2017	Finland	Cohort Study	54 CHR (10/44)	107 non-CHR (24/83)	SIPS	SIPS	GFS	SIPS	SIPS	14
Lunsford-Avery et al. (2015) ‡	2015	USA	Cohort Study	36 UHR (19/17)	31 Healthy Controls	SIPS	Actigraphy, PSQI	NR	SIPS	SIPS	14
Lunsford-Avery et al. (2017b) ‡	2017	USA	Cohort Study	34 UHR (15/19)	32 Healthy Controls (16/16)	SIPS	Actigraphy	GAF	SIPS	SIPS	13
Poe et al. (2017)	2017	USA	Cohort study	194 UHR (142/52); 66 Healthy Controls (42/24)	None	SIPS	SIPS	GAF	SIPS	SIPS	13
Ruhrmann et al. (2010b)	2010	Germany, Finland, the Netherlands and England	Cohort study	245 UHR (137/108)	None	SIPS	SIPS	GAF	SIPS	SIPS	16

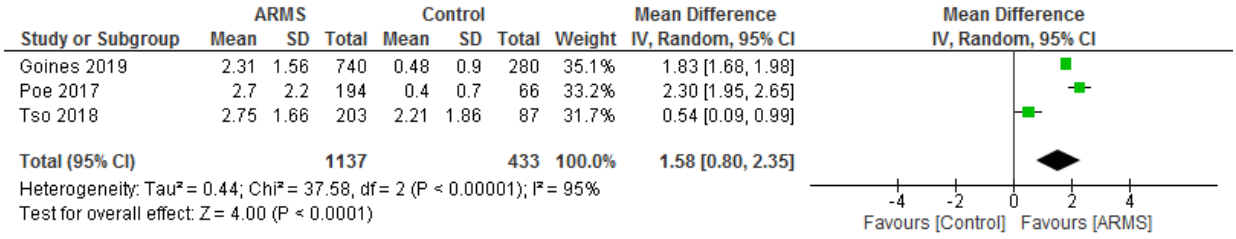
CAARMS: Comprehensive Assessment of the At Risk Mental State; SIPS/SOPS: Structured Interview for Prodromal Symptoms; PSG: Polysomnography; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; QME: Questionnaire of Morningness and Eveningness Scale;; PANSS: Positive and Negative Syndrome Scales; SOFAS Social and occupational functioning assessment scale; GAF: Global assessment of functioning; GFS: Global functioning scales; NR:Not reported; †study produced by the Program for Recognition and Intervention in Individuals at-risk Mental State; ‡ study produced by the Adolescent Development and Prevention Treatment lab; ¥ Data taken from the North American Prodrome Longitudinal Study; ≠Downs and Black Quality score: excellent (26-28), good (20-25), fair (15-19) and poor (≤14)

3.7 **EXPLORATORY META-ANALYSIS EXAMINING SELF-REPORTED SLEEP DISTURBANCES IN ARMS YOUTH**

A comparison between ARMS patients and controls in relation to self-reported sleep disturbances measured by the SIPS was found to be significantly different (see figure 3). The mean difference in score was 1.58 (95% CI 0.80, 2.35) z=4.00, p<0.00001. In the studies by Poe et al. (2017) and Goines et al. (2019) the sleep disturbances of ARMS patients was compared to healthy controls. In the study by Tso et al. (2017) the sleep disturbance scores of 'clinically higher risk' individuals with a score ≥7 on SOPS were compared to 'clinically lower risk' participants, or those scoring <7 on the SOPS. All participants were help seeking in this sample. The clinical diversity between the control groups may explain the high I^2 value (I^2=95%).

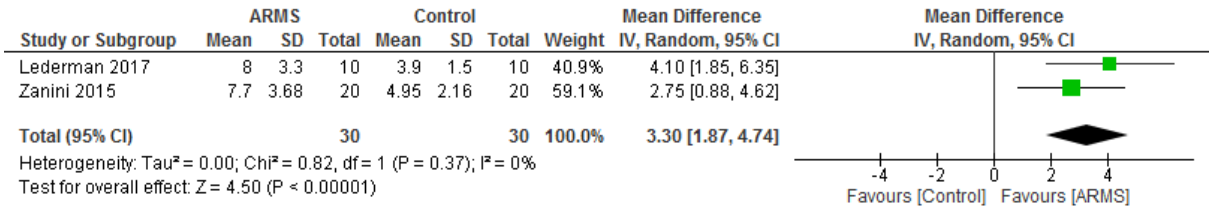
The mean difference in score remained significant when the study by Tso et al. (2017) was excluded from the analysis; mean difference in score was 2.04 (95% CI 1.58, 2.49) z=8.73, p<0.00001 (I^2=83%).

FIGURE 3. SLEEP DISTURBANCE (SIPS)



Two studies were included in the meta-analysis for sleep disturbances measured using the PSQI (see figure 4) (Lederman et al., 2017, Zanini et al., 2015b). The ARMS group and healthy controls differed significantly and there was no significant heterogeneity between the studies. The mean difference in score was 3.30 (95% CI 1.87, 4.74) z=4.50, p<0.00001, suggesting that at-risk youth experienced significantly higher levels of sleep disturbances compared to healthy controls.

FIGURE 4. SLEEP DISTURBANCE (PSQI)



3.8 **RISK OF BIAS ASSESSMENT**

Quality scores are summarised in Table 2. Overall scores were heavily influenced by study design; for instance observational studies scored lower on questions relating to internal validity bias (e.g., studies that did not include a comparator group could not receive points on questions relating to selection bias). Several studies did not include follow up assessments which impacted on the risk of bias scores. All studies generally reported insufficient information on power calculations. Grey literature including doctoral thesis and conference abstracts were screened for eligibility. However, studies did not meet criteria due to participants not meeting UHR criteria. The majority of studies included were considered to be low quality according to the Downs and Black checklist.

3.9 **Discussion**

3.9.2 Summary of findings

This review builds on previous research examining the significance of sleep disturbances in psychotic illness, through highlighting that sleep disruptions are present in at risk for psychosis groups and that they are associated with psychotic symptoms and functional outcomes. A strength of this review is the inclusion of the exploratory meta-analysis which revealed poorer global sleep quality among ARMS patients.

3.9.3 Self-reported sleep disturbances in ARMS patients

This review has highlighted that ARMS patients reported higher levels of general sleep disturbances, increased night time disruption, and increased nightmares. However, sleep efficiency and sleep duration were not reported to be reduced in ARMS groups. These findings are important as they demonstrate distinctions between self-reported sleep problems in ARMS youth. The meta-analyses results show that global self-reported sleep quality is significantly reduced in ARMS and

these disruptions are detectable by both the PSQI and the SIPS mental health tool. Interestingly, the PSQI global scores of the ARMS samples are comparable to those seen in other clinical groups (e.g., cut off score of 5 for students; >6 for adults with back pain; ≥8 for adults with TBI) (Mollayeva et al., 2016). However, as has been highlighted in research involving schizophrenia patients (Faulkner and Sidey-Gibbons, 2019) it is important to establish the validity, utility and cut-off scores of self-reported sleep tools such as the PSQI and SIPS in ARMS youth.

3.9.4 Objectively measured sleep disturbances in ARMS patients

Several objectively assessed parameters of sleep were found to be disrupted in ARMS youth including quantity of sleep, (PSG latency, daytime naps, night time movements) and circadian rhythm in ARMS individuals. However, sleep efficiency, duration and night time awakenings were not found to be significantly reduced in ARMS patients compared to controls. These findings should be interpreted with caution as a small number of included studies (n=3) used PSG or actigraphy to assess sleep disturbances in ARMS youth. It is important to acknowledge the significant challenges associated with conducting such studies, therefore exploration of the macro and micro architecture of sleep in such a small number of studies provides significant gains in knowledge. Research has demonstrated that the validity of self-report measurements of sleep, such as PSQI sleep duration, is comparable to actigraphic measurements in ARMS groups (Lunsford-Avery et al., 2015). However, there is still a need to better understand the disruptions to sleep architecture that cannot be assessed through self-report sleep measures. Therefore, this review calls for further robust research involving gold standard sleep assessments such as PSG in ARMS patients.

3.9.5 Cross-sectional associations between sleep disruptions and the ARMS

This review has demonstrated that several sleep parameters (including reduced sleep efficiency, increased WASO and increased night time awakening and movements), are related to positive symptoms. Whilst increased latency, duration and quality were reported to be associated with negative symptoms. These findings complement previous research focused on patients with psychotic disorder (Reeve et al., 2015, Blanchard et al., 2020a, Blanchard et al., 2020b) as they show that a relationship

between attenuated psychotic symptoms and sleep disturbances is present prior to diagnosis of psychotic disorder. The relationship between sleep impairments and negative symptoms is a particularly interesting and under researched area in ARMS patients. The timing of the psychosis prodrome may coincide with a period whereby negative symptoms and sleep problems may be entangled with social and developmental changes. Consequently, it is crucial that our knowledge around the relationship between sleeping difficulties and negative symptoms is developed to support early detection of such phenomena in adolescents and young adults.

3.9.6 Longitudinal relationship between sleep disruptions and the ARMS

The findings from longitudinal studies included in this review highlight the relationship between disrupted sleep quality (e.g., sleep efficiency), quantity of sleep (e.g., Wake After Sleep Onset, number of awakenings, total sleep time), the rhythm of sleep/rest activity levels (e.g., fragmented circadian rhythm, sleep pattern disruption and day night reversal) and increased positive symptoms across time. These findings can be explained by the concept of shared mechanisms underlying circadian misalignment and dysfunctional neurotransmitter thought to be implicated in the expression of schizophrenia and circadian pathways (Wulff et al., 2012) Dopaminergic pathways and dopamine receptor activity are of particular interest as they have been implicated in the maintenance of psychosis whilst also being linked to sleep and circadian rhythm disturbance in the presence of genetic vulnerability and psychological or environmental stressors (Yates, 2016). This review calls for further experimental studies investigating pathways involved in sleep dysfunction and psychopathology.

Understanding whether sleep disturbances represent the emergence of long-term sleep difficulties or a sleep disorder in ARMS patients is another important line of enquiry; particularly as research has shown that ARMS youth experience outcomes which are broader than transition to psychosis such as functional impairment (Addington et al., 2011, Carrión et al., 2013). Therefore, increased understanding of the trajectory of ARMS youth, not just in relation to mental health outcomes but also other long-term difficulties such as sleep disorders are important when considering

appropriate treatments and the priorities of sleep interventions in clinical practice (Reeve et al., 2018d, Cosgrave et al., 2018, Freeman et al., 2017, Ohayon, 1997).

3.9.7 Sleep disruptions, functional outcomes and QoL in ARMS patients

Few studies included in this review presented evidence on the relationship between sleep disturbances and functional outcomes during the ARMS period. Studies that did, reported correlations between sleep pattern disruption and general functioning; in addition to circadian rhythm variables predicting long term psychosocial functioning levels. These findings support research showing that sleep difficulties are related to lower functioning in schizophrenia spectrum disorders and that improving sleep could improve levels of functioning independent of other treatments (Laskemoen et al., 2019).

It is also a surprising finding from this review that only one study reported on the cross-sectional association between sleep disturbances and QoL in an at risk samples, with no significant associations reported. This is unexpected as poor sleep has been implicated in sustaining reduced QoL and difficulties in coping (Hofstetter et al., 2005). Furthermore, the profound impact of sleep and circadian rhythm disruptions on quality of life and employability are both understudied and of high importance (Hofstetter et al., 2005a, Yates, 2016). Understanding the subjective experience of a patient's life beyond the clinical symptoms is in some cases more valuable than clinical care for individuals experiencing mental health problems (Sagayadevan et al., 2018)(Katshnig 2006; Sagayadevan 2018). Therefore, there is a need for research which includes well defined and carefully measured QoL domains along with effective measurements of sleep to explore their relationship further.

3.9.8 Strengths and limitations

The review must be interpreted in light of the following limitations. Studies included in this review were highly heterogeneous in relation to the methodological characteristics, reflecting the broad understanding of sleep in ARMS individuals and the diversity in how sleep is measured. Furthermore, the reporting of descriptive statistics (e.g., means and standard deviations) was not consistently stated across studies. The consequence of this limitation was evident in the quantitative synthesis and meta-analysis whereby both meta-analyses only included two or three studies,

resulting in an inability to conduct subgroup analyses. The small sample sizes in the meta-analysis and the heterogeneity of comparison groups are likely contributors of the wide confidence intervals and high I statistic (see figure 3). Although this reduces the generalisability of the findings, the meta-analyses results are exploratory and hypothesis generating rather than conclusive. Therefore, the findings from this review provide some advances in knowledge in an area where we understand very little about the relationship between sleep disruptions in youth at risk for psychosis.

A second limitation is the unquestionable challenge of ascertaining the direction of causality between sleep disturbances and psychotic illness. This review has provided cross-sectional evidence highlighting associations between sleep disturbances and psychotic symptoms. However, there is a need for further prospective studies which repeatedly assess sleep disturbances using robust self-report and objective tools, assessments of mental health status and related variables including premorbid functioning, personality characteristics, life events and symptoms (Mason et al., 2004).

A third limitation is the quality of studies included according to the Downs and Black quality index tool. The majority of studies were assessed to be low quality and scores were largely influenced by study design. Consequently, further high quality research is needed to better assess the relationship between sleep disturbances and the at risk mental state.

3.9.9 Clinical and research implications

Research has shown that clinicians in mental health teams often assess sleep problems informally, with no treatment offered or basic sleep hygiene and/or pharmacology rather than recommended CBT treatments for individuals with persistent insomnia (O'Sullivan et al., 2015, Rehman et al., 2017). Sleep problems are often seen as secondary or corollary to the psychiatric symptoms and therefore not given adequate focus. Treatment for sleep problems are often limited by service level challenges (such as lack of time and training), patient factors (including lifestyle) and environmental issues (e.g., inpatient settings). Given the effectiveness of psychological treatments such as Cognitive Behavioural Therapy for Insomnia (Bradley et al., 2018) and the impact of sleep disturbances on psychopathology and functioning, there is a strong need to recognise and treat sleep disturbance using

effective and inexpensive interventions, early in the course of mental illness (Harvey et al., 2011).

The findings from this review also have important implications for future research. It is evident that the relationship between sleep disturbances and early symptoms is complex and the mechanisms and mediating factors between these experiences are yet to be fully understood. Further research examining disruptions to sleep architecture (e.g., sleep spindles) in ARMS patients is key, particularly as research has suggested that there are significant impairments in schizophrenia patients (Manoach et al., 2014, Wamsley et al., 2012, Ferrarelli et al., 2007, Poulin et al., 2003, Manoach et al., 2016) and that spindles and slow waves may be valid biomarkers for schizophrenia (Zhang et al., 2019b). Therefore, there is a need for further high-quality experimental studies utilising well-powered, accurate and practical methods involving early course psychosis patients to explore the structure of sleep. For instance, recent research has shown afternoon naps to be correlated with nocturnal spindle density in schizophrenia patients; highlighting an alternative method for assessing the spectral content of sleep (Mylonas et al., 2019).

3.9.10 Conclusions

Our review suggests that young people at risk for psychosis experience increased levels of self-reported and objectively measured sleep disturbances compared to healthy controls, including poorer global sleep quality (as measured by the PSQI and SIPS). Furthermore, there is evidence that sleep disturbances at baseline are associated with higher levels of positive psychotic symptoms over time. However, due to the limited number of longitudinal studies in this area, further research is needed to build our understanding of how much sleep disturbances during the at risk period worsen or contribute to increased psychotic symptoms at later time points. This is key to establishing the relative importance of services prioritising sleep disturbance treatments in ARMS patients.

Chapter 4. **ALSPAC STUDY**

4.1 **Introduction**

Sleep disturbances during childhood are common and often resolve spontaneously without intervention (Touchette et al., 2005, Galland et al., 2012). However, those that are persistent and frequent are associated with the development of later psychopathology including psychotic-like experiences (Jeppesen et al., 2015). Previous research exploring data from the Avon Longitudinal Study of Parents and Children (ALSPAC) has shown that children, aged 2.5 and 9 years old, experiencing frequent nightmares were more likely to report psychotic-like symptoms at age 12 (Fisher et al., 2013b). Similarly, nightmares at 12 years old were also associated with an increased risk of psychotic-like symptoms at aged 18 (Thompson et al., 2015). Such findings suggest that nightmares during childhood may represent an important and clinically significant indicator for risk of psychotic experiences in adolescence.

The relationship between childhood sleep disturbances and the presence of psychotic experiences beyond the age of 18 is still yet to be explored. The incidence of psychotic experiences often peaks during adolescence to early adulthood (McGrath et al., 2016) and sleep disturbances frequently co-occur with psychotic-like experiences during this time (Taylor et al., 2015). Importantly, the transition from childhood to adulthood is a sensitive developmental period as biological, psychological and social risk factors can result in the emergence of mental health difficulties (Paus et al., 2008). As young people enter into adulthood, common developmental experiences such as sleep problems and psychotic experiences can be a signal of underlying difficulties that may be responsive to intervention (Freeman et al., 2015).

Understanding the risk factors for psychotic experiences are important for improving knowledge around mechanisms and function in clinical populations (Brederoo et al., 2021). Psychotic-like experiences such as hallucinations are largely viewed as common across the general population, with 5-15% of individuals reporting at least one experience during their lifetime (Brederoo et al., 2021). However, approximately 80% of these experiences are transient and represent normal developmental experiences (Zammit et al., 2013). Several studies have highlighted that psychotic

experiences that are persistent in nature are linked to poorer psychological outcomes including transition to psychosis and risk for non-psychotic illness (Kaymaz et al., 2012, Werbeloff et al., 2012, Fisher et al., 2013a, Kelleher et al., 2012). To demonstrate this, one longitudinal study (8.4 year follow up) involving 845 adolescents aged 14-17 years old, examined the relationship between subclinical psychotic experiences and later clinical psychosis. Findings revealed a dose response relationship between psychotic experiences and frank psychosis with just over one third of frank psychosis reported at time point 3 preceded by subclinical psychotic experiences (OR = 9.9 [95% CI = 2.5–39.8], PP = 27%)(Dominguez et al., 2011) (Dominguez et al., 2011). The authors concluded that psychotic experiences are commonly reported across the developmental trajectory but those that persistent are associated with a risk of psychotic disorder, supporting the psychosis proneness-persistence impairment model of psychotic disorder (Dominguez et al., 2011). To explain the association between PE and clinical psychosis, the authors hypothesized that psychotic experiences may become persistent through the interaction between an over-sensitised dopamine system and environmental risk factors (including stressful life events and substance misuse) (Dominguez et al., 2011). The endorsement of psychotic experiences in both clinical and non-clinical groups can be explained by the concept of a psychosis existing on an etiological continuum, with the same genetic and environmental risk factors for both subthreshold and persistent psychotic experiences (Zavos et al., 2014). Therefore, studying the expression of psychotic experiences in non-clinical samples allows the role of *persistent* low level psychotic experiences that emerge prior to the development of clinical disorder to be explored to better understand the trajectory and early stages of psychotic illness.

Several studies have started to unpick the relationship between sleep disruptions and psychotic experiences through considering mediating factors (Reeve et al., 2018a, Reeve et al., 2018b, Freeman et al., 2017, Ered et al., 2018). One experimental sleep restriction study, involving 68 non-clinical participants aged 18-30 years old, found that sleep problems such as insomnia in adulthood play a causal role in the expression of psychotic experiences via the route of negative affect (Reeve et al., 2018a). In this study, participants in the sleep-restricted group were limited to 4 hours sleep over 3 nights and were found to experience higher levels of paranoia,

hallucinations and cognitive disorganisation compared those in the control group (who had no restrictions on sleep duration). The authors concluded that sleep loss increased depression, anxiety and/or stress which can lead to the onset of paranoia, hallucinations and cognitive disorganisation (Reeve et al., 2018a). This study demonstrates that the relationship between sleep and psychotic experiences is not necessarily direct and implicates affect as a potential pathway.

Despite growing evidence to suggest that sleep problems pre-date psychotic experiences and their relationship is potentially mediated by negative affect, it still remains unclear whether sleep problems in childhood and adolescence are associated with psychotic experiences that persist into adulthood. Furthermore, it is unclear whether *all* early sleep disruptions are associated with psychotic experiences that persist into adulthood (e.g., are difficulties initiating sleep and nightmares both risk factors for later psychotic experiences) and factors mediating this long term relationship are yet to be tested. Therefore, this chapter will explore the longitudinal associations of childhood and adolescent sleep problems between the ages 1.6 and 12 years old with self-reported Psychotic Experiences (PE) at 18 and 24 years old. The hypotheses for this study are:

<u>Primary hypothesis:</u>

(i) Preschool and/or adolescent sleep problems (aged 1.6-5.9 and 12 years old) will be associated with psychotic experiences at 24 years old

(ii) Preschool sleep problems (aged 1.6-5.9 years) and adolescent parasomnias (12 years old) will be associated with the *persistence* of psychotic experiences during late adolescence/early adulthood (18 and 24 years old)

<u>Secondary hypothesis:</u>

(i) Preschool and/or adolescent sleep problems significantly associated with psychotic experiences at 24 years old will be mediated by symptoms of anxiety and depression

4.2 **METHOD**

4.2.2 Study design

This ALSPAC study is a multigenerational prospective birth cohort study involving parents and children from the South West of England in the UK. This study is one of several studies forming the European Longitudinal Study of Pregnancy and Childhood (ELSPAC) first developed by the World Health Organisation in 1985, with the aim of understanding the factors contributing to the health and wellbeing of parents and children in Europe (Golding, 1989). Other countries involved in ELSPAC include Czech Republic, Isle of Man, Russia, Slovakia and Ukraine. The ALSPAC study received ethical approval from the ALSPAC law and ethics committee and local research and ethics committees (Bristol and Weston, Southmead and Frenchay).

4.2.3 Participants

The data in this study is derived from the ALSPAC. Participants were invited to take part whilst pregnant and due to give birth between 1 April 1991 and 31 December 1992 (Boyd et al., 2013). In line with the original eligibility criteria, a second wave of recruitment occurred when the children from the initial phase were approximately 7 years old. This additional phase of recruitment aimed to increase the overall sample, encouraging participants who did not join the original cohort to take part in the study. All participants were living in the Avon area of the UK at the time of study. As of April 2021, participants have been followed for 30 years.

4.2.4 Procedure

Recruitment to the study began from September 1990 following local advertisements at ultrasound test centres and maternity healthcare professionals discussing the details of the study with patients (Golding et al., 2001). Participants were invited to complete postal questionnaires during the antenatal period (<10-40 weeks of pregnancy), relating to the health and development of mother and child. Questionnaires for the mother's current partner were also sent by post along with questionnaires for mothers. Quarterly questionnaires were sent to parents regarding children to collect data on home and school environment, health and behaviour and attitudes and activities (Golding et al., 2001). Annual self-report questionnaires relating to parent health and lifestyle were also sent by post. Teachers completed

questionnaires concerning behaviour and abilities for children between 7-8 years old. From the age of 7 years old, children attended annual face-to-face health clinics to complete psychological and physical assessments (ALSPAC, 2020, Golding et al., 2001). A range of phenotypic, environmental, genetic data and links to health and social records are collated as part of the study, including 68 data collection time points between birth and 18 years old, resulting in 34 child completed questionnaires, 9 clinical assessments and 25 questionnaires about children completed by parents (Boyd et al., 2013).

4.2.5 Measures

4.2.6 Dependent variables

4.2.6.1 Psychotic experiences at 24 years old

The psychosis-like symptoms semi-structured interview (PLIKSi): The PLIKSi is a semi structured interview designed to assess psychotic experiences occurring over the past six months, including hallucinations, delusions, and thought interference (e.g., *Auditory hallucinations* : "Since age 12, have you ever heard voices or sounds that other people could not hear?" *Delusions*: "Since age 12, have you ever felt that you were under the control of some special power?" *Thought disorder:* "Since age 12, have you ever felt that your thoughts were broadcast out loud so that other people knew what you were thinking?"). Twelve key questions are included, of which seven are taken from the Diagnostic Interview Schedule for Children-Iv (DISC-IV) and five from the Schedules for Clinical Assessment in Neuropsychiatry version 2.0 (SCAN 2.0). Responses were coded as (a) present, (b) suspected or (c) definitely present (Horwood et al., 2008, Zammit et al., 2013). The main outcome was the presence of a definite or suspected PE at 18 or 24 years old, to ensure findings would be comparable with a previous study examining PE at 18 years old in the ALSPAC sample (Thompson et al., 2015) . The kappa values for the interrater reliability and test –retest reliability was 0.83 and 0.76 respectively (Thompson et al., 2015, Zammit et al., 2013). The PLIKSi includes probing questions to enable trained administrators of the interview to delineate and record sleep disturbances that occur during sleep onset (hypnogogic), sleep offset (hypnopompic) or when experiencing fever. The distinction between PE attributed to sleep or fever were recorded and

coded separately to those that were not and were not used in the analyses for this study.

Persistence of PE: A new variable was created to capture the incidence and persistence of psychotic experiences not attributable to sleep or fever. The PLIKSi includes probing questions to enable trained administrators of the question to delineate and record sleep disturbances that occur during sleep onset (hypnogogic), sleep offset (hypnopompic) or when experiencing fever. As described in the introduction section, persistent PE are associated with increased risk of psychosis and are therefore of significant interest (see chapter 1). The PLIKSi was conducted with participants at 18 and 24 years old. Therefore, data derived from these time points were (a) none-no psychotic experiences at 18 or 24 years; (b) incident-suspected or definite psychotic experience at 18 *or* 24 years old. (c) persistent-suspected or definite psychotic experience at 18 *and* 24 years old.

4.2.7 Independent variables

4.2.7.1 Infancy, toddlerhood and preschool sleep disturbances

Early childhood sleep: Sleep disruptions between the ages of 1.6-5.9 years were reported by mothers via postal questionnaires. Difficulties falling asleep, night awakenings and nightmares were reported at 18 months, 30 months, 3.5 years, 4.8 years, and 5.9 years. Questions included "In past year has your child regularly had difficulty going to sleep?", "In the past year, has your child regularly woken in the night?" and "In the past year, has your child regularly had nightmares?" (See appendix 2 for sleep questions). Parental responses for sleep questions at each time point were recorded as (a) no did not happen; (b) yes, worried parent greatly; (c) yes, worried parted a bit; (d) yes, did not worry parent. It is acknowledged that the threshold for reporting sleep disruptions may have varied across parents, however similar research involving the ALSPAC sample has included these sleep items when examining sleep difficulties during childhood (Lereya et al., 2017). Sleep domains were operationalised as (a) absent; (b) present at one time point; (c) present at two time points; or (d) present at three or more time points.

4.2.7.2 Adolescent sleep difficulties

Adolescent sleep: As part of the semi structured face to face interviews during clinic visits at 12 years old, participants were asked several questions relating to parasomnias (nightmares, night terrors and sleep walking) occurring over the last 6 months (e.g., "Since your 12th birthday have you had any dreams that woke you up? Were they frightening?", "Has anyone ever told you, since you were 12, that you got out of bed and walked around while you were fast asleep?", "Has any one ever told you, since you were 12, that you scream out at night, sit up in bed, seem to fight or wrestle with unseen creatures or shout at them in your sleep? Describe"). All interviews were conducted by psychology graduates supervised by consultant psychiatrists. Responses were scored according to the DSM-IV criteria for sleeping disorders as (0) not present, (1) suspected, (2) definitely present. Interrater reliability was strong at 0.72 (Thompson et al., 2015). (Horwood et al., 2008, Zammit et al., 2013). For consistency, the presence of a definite or suspected parasomnia was used in the main analyses, to ensure findings would be comparable with a previous study examining parasomnias and PE in the ALSPAC sample (Thompson et al., 2015)

4.2.8 Confounding and mediating variables

The Development and Well-being Assessment (DAWBA): The DAWBA is a set of 20-25 structured interview and questionnaires administered to children (5-16 years old), parents and teachers to obtain ICD-10 and DSM-IV psychiatric diagnoses. The various types of information (concerning emotional, behavioural, and hyperactivity disorder) are triangulated by a computer package to elicit a likely diagnoses which is then interpreted by a trained practitioner (Goodman et al., 2000). Responses are recorded in bands (level 0- level 5) according to the likelihood of having a disorder, with higher bands indicating the prevalence of the assessed disorder (Goodman et al., 2011). The DAWBA has been shown to be valid in British and Norwegian children (Goodman et al., 2011). As included in previous analysis involving this sample (Thompson et al., 2015), any psychiatric disorder at 7 years old and any anxiety disorder at 10 and 15 years old and depression symptoms at 17 years old identified by the DAWBA was included as a confounding variable in the analyses for this study.

The Short Moods and Feelings Questionnaire (SMFQ): The SMFQ is a widely used questionnaire assessing depressive symptoms over the last two weeks and has been used in a similar study involving the ALSPAC sample (Thompson et al., 2015). The SMFQ includes 13 questions rated on a 3 point scale (not true, sometimes true and true) with scores calculated out of a total score of 26, with higher scores indicating more severe symptoms. A validated cut-off for total score reported in previous research (Thompson et al., 2015) was used to code depressive symptoms as subthreshold or clinical level symptoms. A score of <11 was indicated that symptoms were below clinical threshold symptoms and ≥11 indicated clinical symptoms. This measure has a good Cronbach's alpha score (α = .88 to .89); convergent validity across three time points (.50) and criterion validity with the Mood and Feelings Questionnaire (r = .95 to .96, p < .001) (Thabrew et al., 2018). Parents completed this measure at 9 and 11 old. Participants with more than one question on the measure not completed were omitted from the analyses.

The Upsetting Events Questionnaire (UEQ): Physical and sexual child abuse was assessed through one item ("he/she was sexually abused" and "he/ she was physically abused") at 2.5 years old, 3.5 years old, 4.8 years old, 5.8 years old and 6.8 years via parental postal questionnaire. In line with previous studies in this cohort, a new variable was created to capture physical or sexual abuse at any one time point as present or absent (Lereya et al., 2017).

The Wechsler Intelligence Scale for Children-III (UK version): The WISC-III is a widely used standardised global assessment of intelligence assessing verbal comprehension, perceptual organisation, freedom from distractibility and processing speed in children between 6 to 16 years old (Woolger, 2001). Overall IQ scores range from 40 to 160, with higher scores indicating higher IQ. The WISC-III was administered at 8 years old (see appendix 3 for an overview of variables included in the analyses).

4.2.9 Data analysis

All analyses were conducted using SPSS, version 27. Firstly, a series of separate logistic regression analyses were conducted to assess whether persistent sleep disturbances (difficulties falling asleep, night awakening) and nightmares during childhood (1.6-5.9y) and adolescence (12y) predicted psychotic experiences at 24

years old. Secondly, several multinomial regression models were constructed to test whether childhood and adolescent sleep difficulties were associated with later psychotic experiences at (i) 18 or 24 years (incident) or (ii) 18 years and 24 years (persistent).

All regression models accounted for confounding variables (sex, IQ at 8 years [WISC-III], physical/sexual abuse [2.6y-6.9 years], DSM-IV psychiatric disorder at 7 years [DAWBA], DSM-IV anxiety disorder at 10y [DAWBA], depression score at 10y [SMFQ], baseline maternal educational level [childhood sleep difficulties only]). Only cases with available data for both predictor and outcome were included. To reduce the effects of attrition bias and to take into account participants lost to follow up all regression analyses were performed with inverse probability of response. A probability of response for each case was calculated using a logistic regression model (Kinner et al., 2007). Essentially, the probability of each participant having complete data was calculated and this estimate or weight is then applied to the regression models (Mansournia and Altman, 2016). Complete case analysis, multiple imputation and full-likelihood methods are alternative approaches to inverse probability weighting when handling missing data. Inverse probability weighting was adopted to include the maximum number of participants possible and to reduce the risk of bias associated with restricting the analysis to complete cases (Seaman and White, 2013). This was especially important as previous studies involving the ALSPAC sample have reported significant difference between drop out and followed up participants (Winsper et al., 2020). Furthermore, compared to multiple imputation, as an alternative missing data method, inverse probability weighting was most appropriate for use on this longitudinal dataset as several variables were assessed at each time point between 1.6 years-24 years, consequently missing values across variables and participants which would have required significant imputation. In such instances inverse probability weighting is recommended (Seaman and White, 2013) and has been conducted in studies involving the ALSPAC sample (Thompson et al., 2015, Winsper et al., 2020). Triplets (n=3) and quadruplets (n=1) are not included in the analyses from this study.

Participants lost to follow up are a common feature across longitudinal studies, therefore logistic regression analyses were conducted to ascertain factors that

differed significantly between those that were retained in the final analyses at 24 years compared to those that were lost to follow up. Missing values analysis was conducted on sex, ethnicity, mothers educational level, emotional difficulties at 42 months, sleep difficulties at 42 months, presence of childhood abuse between 18m-5.9y (dichotomised as yes/no for physical or sexual abuse), IQ at 8 years old, low birthweight (dichotomised as yes or no based on cut off score of 2500g) and prematurity (dichotomised as yes or no based on length of gestation <37 weeks or >37 weeks) were conducted. Odds ratios and 95% confidence intervals are reported for regression models.

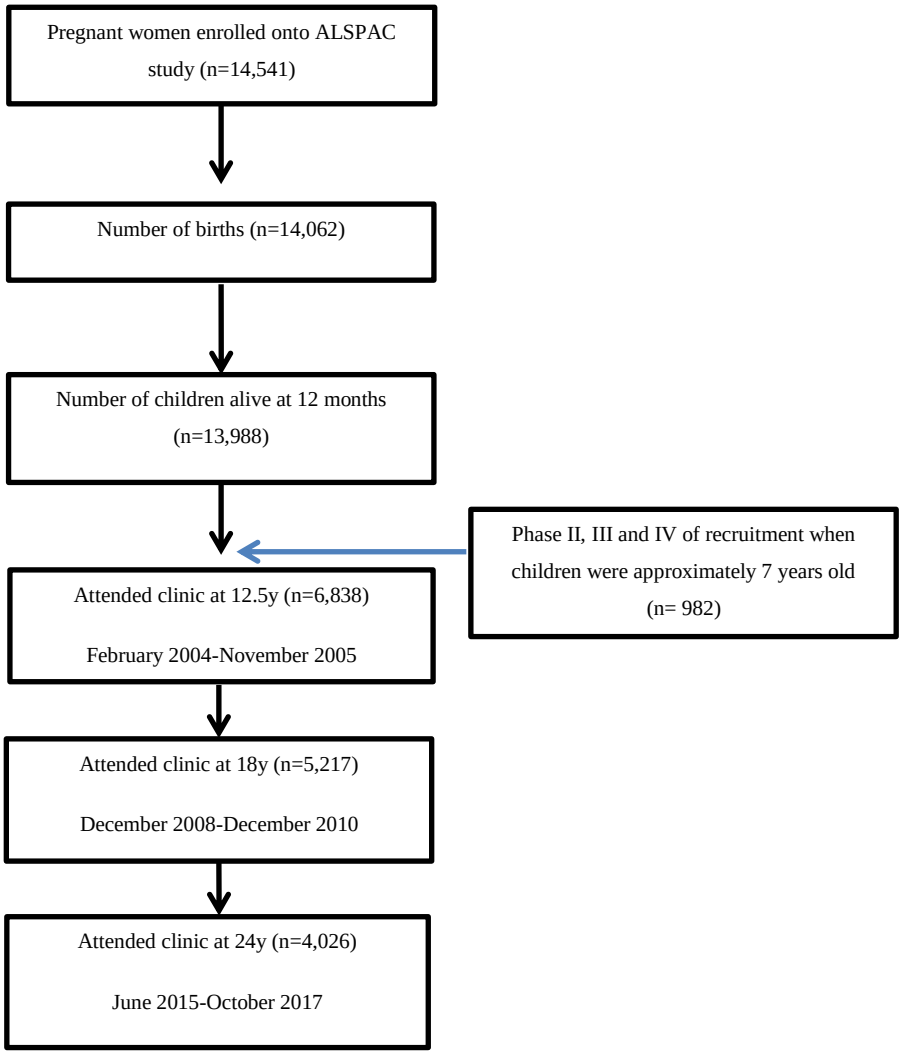
To examine direct, indirect and total associations between sleep problems and psychotic experiences at 24 years, path analyses were conducted using SPSS AMOS-27. Self-reported depression symptoms at 17 years (DAWBA) and anxiety diagnosis (DAWBA) at 15 years were included as mediators in the pathway. As seen in similar studies in this cohort (Morales-Muñoz et al., 2020, Winsper et al., 2020), the following covariates were included in the analysis: sex, childhood abuse and IQ at 8 years old. Missing data was computed using the full maximum likelihood method in AMOS-27, consequently bootstrapped bias-corrected 95% confidence intervals and statistical significance values are reported. The full maximum likelihood method is a statistical approach which involves estimating the distribution and parameters of a model that best fits the data(Pan and Fang, 2002). It is effective when analysing incomplete datasets and is an efficient and flexible approach appropriate for large samples (Hartley, 1958, Arbuckle, 2011).

4.3 **RESULTS**

4.3.2 Study participants

14,541 pregnant women enrolled onto the study, with 13,988 children recorded at 1 years old (13,978 of these children originated from the initial cohort). At 12.5 years old just under half of the sample attended the clinic assessment (n=6,838). At 24 years old, 26% of the total sample attended the clinic (n=4,026) (see Figure 5).

FIGURE 5. FLOW CHART OF STUDY PARTICIPANTS



4.3.3 Sample characteristics

The participating group included a higher percentage of female participants (62.5%) compared to the total sample and non-participating group, see Table 3. The majority of the included group were born within a normal birthweight range at full term. The maternal educational level was mostly 'O' level or above (85.6%) and most parents were homeowners (85.5%). Childhood abuse between 2.6 and 6.9 years was reported by 9.6% of the total sample.

TABLE 3. SOCIODEMOGRAPHIC INFORMATION FOR TOTAL SAMPLE, PARTICIPATING AND NON-PARTICIPATING GROUPS

	Total sample*	**Participating group[1]**	**Non-participating group**
Childs sex (n=13,954)			
Male (n, %)	7,205 (51.6)	1,359 (37.5)	5,846 (58.1)
Female (n, %)	6,749 (48.4)	2,235 (62.5)	4,514 (41.9)
Childs ethnicity (n=12,330)[2]			
White (n, %)	12,006 (97.4)	3,406 (97.8)	8,600 (97.2)
Non-white (n, %)	324 (2.6)	78 (2.2)	246 (2.8)
Childs birthweight (n=5,101)			
Low birthweight (<2500g) (n, %)	381 (7.5)	82 (5.8)	299 (8.1)
Normal range (>2500g) (n, %)	4,720 (92.5)	1,322 (94.2)	3,398 (91.9)
Gestation of pregnancy (n=13,903)			
Premature (<37 weeks) (n, %)	779 (5.6)	171 (4.8)	608 (5.9)
Full term (>37 weeks) (n, %)	13,124 (94.4)	3,417 (95.2)	9,707 (94.1)
Maternal educational level (n=11,650)			
Below O Level (n, %)	2,965 (25.5)	491 (14.4)	2,474 (30.0)
O level or above (n, %)	8,685 (74.5)	2,910 (85.6)	5,775 (70.0)
Parental home ownership (n=13,058)			
Mortgage (n, %)	9,567 (73.3)	2,986 (85.5)	6,581 (68.8)
Renting (n, %)	3,491 (26.7)	505 (14.5)	2,986 (31.1)
Childhood abuse (2.6y-6.9y) (n=11,334)[3]			
Yes (n, %)	1,107 (9.6)	347 (9.3)	760 (9.6)
No (n, %)	10,508 (90.4)	3,377 (90.7)	7,131 (90.4)
Emotional difficulties[4] at 3.6y (n=3,237) mean (SD)	2.56 (1.7)	2.52 (1.6)	2.57 (1.7)
IQ at 8y (n=3,124) mean (SD)	104.1 (16.4)	108.2 (15.8)	101.1 (16.3)
Sleeping difficulties score[5] at 42 months (n=3,239) mean (SD)	2.9 (1.9)	2.7 (1.9)	3.0 (1.9)

*Includes whole cohort excluding triplets and quadruplets, plus children joining from 7 years onwards. The numbers of participants reported for each variable varies due to missing data. [1]Completed PLIKSi session at 24 y [2] non-white ethnic group includes: Black Caribbean, Black African, Other Black, Indian, Pakistani, Bangladeshi, Chinese, Other.[3] Childhood abuse includes both physical and sexual abuse.[4] Emotional difficulties score derived by summing the emotional difficulty items from The Revised Rutter Parent Scale for Preschool Children.[5]The sum of sleeping problems (0-7, responses yes not worried/worried a bit/ worried greatly/ didn't happen) (item is the sum of several variables assessing : refusal to go to bed, waking very early/ after a few hours of sleep, difficulty going to sleep, experienced nightmares, getting up after being put to bed, night time awakening).

4.3.4 Participating compared to none participating group

Logistic regression analysis was conducted to assess the impact of sociodemographic and clinical factors on completion of the PLIKSi at 24 years old. The model

contained 9 factors (sex, ethnicity, IQ at 8, maternal education level, maternal homeownership, sleep difficulties at 42 months, prematurity, child abuse, emotional difficulties at 42 months). The full model including all predictors was statistically significant x^2 (8, n=5,873) = 588.33, p<0.001, indicating that the model was able to detect a difference between the participating and non-participating group. Five sociodemographic and clinical variables contributed significantly to the model: sex OR: 2.33. p<0.001, maternal educational level OR: 1.76. p<0.001, IQ at 8 years old OR: 1.03. p<0.001, emotional difficulties at 42 months OR: 1.04, p=0.021, sleeping difficulties score OR: 0.96, p=.006. These findings suggest that non-participating group had a lower IQ score at 8 years, higher emotional difficulties score at 42 months, increased sleeping difficulties at 42 months and a lower maternal educational level. The strongest predictor was sex with an odds ratio of 2.33, suggesting that males were more than twice as likely to be non-participators at 24 years old compared to females (see Table 4).

TABLE 4. COMPARISON BETWEEN PARTICIPATING AND NON-PARTICIPATING GROUPS

	Non-participating group		**Participating group[1]**		**Non-participating versus participating**	
	Mean	SD	Mean	SD	OR (95% CI)	p
IQ at 8 years[2]	101.1	16.3	108.2	15.8	1.03 (1.02-1.03)	<0.001
Emotional difficulties score[3] at 42 months	2.6	1.7	2.5	1.6	1.04 (1.01-1.07)	0.021
Sleeping difficulties score at 42 months[4]	3.0	1.9	2.7	1.9	0.96 (0.93-0.99)	0.006
	Non-participating group		**Participating group**			
	n	%	n	%		
Ethnicity (white)	8,600	97.2%	3,406	97.8%	0.77 (0.49-1.20)	0.250
Maternal educational level (above O level)	5,775	70%	2,910	85.6%	1.76 (1.51-2.02)	<0.001
Sex (male)	5,888	56.5%	1,459	37.5%	2.33 (2.09-2.60)	<0.001
Childhood abuse (no)	7,131	90.4%	3,377	90.7%	.92 (0.77-1.09)	0.356
Premature (no)	9,707	94.1%	3,417	95.2%	1.06 (0.83-1.37)	0.643

[1]Completed PLIKSi session at 24y (n=3,889). [2]IQ measured by the Wechsler Intelligence Scale for Children (WISC) **(**n=3,124) includes overall score of verbal and performance subtests.[3]Emotional difficulties score (n=3,237) derived by summing the emotional difficulty items from The Revised Rutter Parent Scale for Preschool Children. [4]The sum of sleeping problems (n=3,239) (0-7, responses yes not worried/worried a bit/ worried greatly/ didn't happen) (item is the sum of several variables assessing : refusal to go to bed, waking very early/ after a few hours of sleep, difficulty going to sleep, experienced nightmares, getting up after being put to bed, night time awakening).

4.3.5 Psychotic experiences reported at 24 y group

Table 5 shows a breakdown of psychotic experiences reported at 24 years old. Most participants did not report any psychotic experience at 24 years (n=3,480, 89.5%). However, suspected/definite visual hallucinations were endorsed by the largest number of participants (n=246, 6.3%) and thought withdrawal by the fewest (n=3, 0.1%).

TABLE 5. PSYCHOTIC EXPERIENCES (PE) REPORTED AT 24 YEARS

	PE not present n (%)	PE suspected/definite n (%)
Visual hallucination	3,637 (93.5)	246 (6.3)
Auditory hallucinations	3,641 (93.6)	239 (6.1)
Tactile hallucinations	3,657 (94.0)	230 (5.9)
Olfactory hallucinations	3,768 (96.9)	121 (3.1)
Visual illusions	3,754 (96.5)	119 (3.0)
Delusions of being spied on	3,788 (97.4)	96 (2.5)
Delusions of persecution	3,831 (98.5)	51 (1.3)
Delusions of thoughts being read	3,863 (99.3)	22 (0.6)
Delusions of reference	3,857 (99.2)	28 (0.8)
Delusions of control	3,874 (99.6)	8 (0.2)
Delusions of grandiose ability	3,858 (99.2)	26 (0.7)
Thought broadcasting	3,869 (99.5)	15 (0.4)
Thought insertion	3,871 (99.5)	14 (0.4)
Thought withdrawal	3,881 (99.8)	3 (0.1)
Any psychotic experience	3,480 (89.5)	409 (10.5)

Notes: Psychotic Experiences (PE) are assessed using the Psychosis-Like Symptoms Semi-Structured Interview (PLIKSi)

4.3.6 Childhood and adolescent sleep profiles

The number of participants experiencing sleep disturbances during childhood and adolescence are presented in Table 6. It shows that 62% experienced nightmares, 70.9% endorsed sleep difficulties, and 70.3% of the total sample was found to have night awakenings during childhood. During adolescence, 36.7% of the total sample reported a parasomnia (nightmares, night terrors or sleep walking). More specifically, 29.7% of the total sample reported nightmares, 11.4% had night terrors and 3.7% experienced sleep walking.

TABLE 6. SLEEP DIFFICULTIES IN PARTICIPANTS WITH NONE OR SUSPECTED/DEFINITE PSYCHOTIC EXPERIENCES (PE) AT 24 YEARS OLD

	Total sample	No PE	Suspected PE/ Definite PE
Nightmares (1.6-5.9y) *n (%)*			
Present	2,172 (62.2)	1,941 (62.1)	231 (63.6)
Absent	1,318 (37.8)	1,186 (37.9)	132 (36.4)
Sleep difficulties (1.6-5.9y) *n (%)*			
Present	2,475 (70.9)	2,215 (70.8)	260 (71.6)

Absent	1,018 (29.1)	915 (29.2)	103 (28.4)
Night awakening (1.6-5.9y) *n (%)*			
Yes	2,453 (70.3)	2,194 (70.1)	259 (71.3)
No	1,038 (29.7)	934 (29.9)	104 (28.7)
Any childhood sleep difficulties			
Yes	2,945 (85.7)	2,638 (85.6)	307 (86.2)
No	491 (14.3)	442 (14.4)	49 (13.8)
Nightmares at 12y *n (%)*			
Yes	891 (29.7)	778 (28.9)	113 (36.7)
No	2,041 (67.9)	1,852 (68.7)	189 (61.4)
Maybe	72 (2.4)	66 (2.4)	6 (1.9)
Night terrors at 12y *n (%)*			
Yes	343 (11.4)	302 (11.2)	41 (13.3)
No	2,603 (86.5)	2,346 (89.9)	257 (83.4)
Maybe	63 (2.1)	53 (2.0)	10 (3.2)
Sleep walking at 12y *n (%)*			
Not present	2,730 (90.7)	2,453 (90.8)	277 (89.9)
Suspected	167 (5.6)	148 (5.5)	19 (6.2)
Definitely present	112 (3.7)	100 (3.7)	12 (3.9)
Any parasomnia at 12y			
Yes	1,157 (36.7)	1,014 (35.7)	145 (45.0)
No	2,003 (63.3)	1,826 (64.3)	177 (55.0)

Notes: Psychotic Experiences (PE) are assessed using the Psychosis-Like Symptoms Semi-Structured Interview (PLIKSi

4.4 **MAIN ANALYSIS**

4.4.2 Childhood sleep disturbances and psychotic experiences at 24 years old

The prospective associations between childhood sleep disturbances and psychotic experiences at 24y are shown in table 7. This analysis included participants with PE data at 24y *and* sleep difficulties, night awakening or nightmares data during childhood. Both unadjusted and adjusted models show that the presence of *childhood* sleep difficulties, night awakening and nightmares were not significantly associated with suspected/definite psychotic experiences at 24 years old.

Nightmares at 12 years were significantly associated with psychotic experiences at 24 years old when confounding variables were accounted for (OR: 1.50, CI: 1.12-2.03). However, night terrors and sleep walking at 12 years old were not found to be significantly associated with psychotic symptoms at 24 years (

Table 7).

TABLE 7. PRESENCE OF CHILDHOOD AND ADOLESCENT SLEEP PROBLEMS AND DEFINITE OR SUSPECTED PE'S AT 24 EXCLUDING DISRUPTIONS RELATED TO SLEEP AND FEVER

	Psychotic Experience at 24, OR (95% CI)

	n	Model A[1]	Model B[2]
Sleep difficulties (1.6-5.9y)			
No	660	Reference	Reference
Yes	1,567	1.00 (0.80-1.25)	1.10 (0.88-1.37)
Night awakening (1.6-5.9y)			
No	1,788	Reference	Reference
Yes	437	1.22 (0.96-1.55)	1.18 (0.92-1.50)
Nightmares (1.6-5.9y)			
No	815	Reference	Reference
Yes	1,412	1.08 (0.88-1.33)	1.14 (0.92-1.41)
Nightmares (12y)			
No	2,155	Reference	Reference
Yes	227	**1.49 (1.01-2.00)**	**1.50 (1.12-2.03)**
Night terrors (12y)			
No	2,157	Reference	Reference
Yes	227	1.04 (0.65-1.68)	1.05 (0.66-1.69)
Sleep walking (12 y)			
No	2,157	Reference	Reference
Yes	227	1.25 (0.85-1.84)	1.23 (0.83-1.81)

[1]Model A shows unadjusted analysis. [2]Model B adjusts for sex, IQ at 8 years (WISC-III), physical/sexual abuse (2.6y-6.9 years), DSM-IV psychiatric disorder at 7 years (DAWBA), DSM-IV anxiety disorder at 10y (DAWBA), depression score at 10y (SMFQ), baseline maternal educational level (childhood sleep difficulties only).

4.4.3 Childhood sleep disturbances and psychotic experiences at 18 and 24 years old

Multinomial regression analyses were performed to examine the prospective association between difficulties initiating and maintaining sleep during childhood and the occurrence and persistence of PE's between 18 - 24 years old (table 8). Findings revealed that persistent sleep difficulties, night awakenings and nightmares between 1.6-5.9y were significantly associated with suspected/definite psychotic experiences at one time point (18 or 24y) but not with persistent PE's (18 and 24y) when accounting for potential confounders (see.

Table 8).

TABLE 8. PRESENCE OF CHILDHOOD SLEEP DISTURBANCES, NIGHTMARES AND DEFINITE OR SUSPECTED PE'S AT 18-24Y EXCLUDING PE'S RELATED TO SLEEP ONSET, OFFSET AND/OR FEVER

	Model A			Model B		
	None	**Transient 18 or 24**	**Persistent 18 and 24**	**None**	**Transient 18 or 24**	**Persistent 18 and 24**
Sleep difficulties (1.6-5.9y)	Reference	**1.17 (1.10-1.25)**	1.10 (0.99-1.22)	Reference	**1.15 (1.06-1.24)**	0.95 (0.83-1.09)
Night awakenings (1.6-5.9y)	Reference	**1.08 (1.00-1.15)**	0.99 (0.89-1.09)	Reference	**1.09 (1.00-1.18)**	0.96 (0.85-1.09)

Nightmares (1.6-5.9y)	Reference	**1.25 (1.17-1.33)**	**1.16 (1.04-1.29)**	Reference	**1.24 (1.14-1.34)**	0.98 (0.86-1.13)

Boldface type indicates significant associations at p<0.05. The reference category is the absence of psychotic experiences between 18-24y. [1]unadjusted analysis. [2]Adjusted for sex, IQ at 8 years (WISC-III), physical/sexual abuse (2.6y-6.9 years), DSM-IV psychiatric disorder at 7 years (DAWBA), DSM-IV anxiety disorder at 10y (DAWBA), depression score at 10y (SMFQ), baseline maternal educational level.

4.4.4 Adolescent parasomnias and psychotic experiences at 18 and 24 years old

When exploring the prospective association between parasomnias at 12 years old and the presence or persistence of psychotic experiences between 18 and 24 years, both nightmares and night terrors were significantly associated with psychotic experiences at 18 or 24 (see Table 9). Nightmares were the only parasomnia to be significantly associated with psychotic experiences at both 18y and 24y when accounting for potential confounders in the analysis. Sleep walking at 12y was not found to be significantly associated with psychotic experience at 18 or 24y in the adjusted analysis.

TABLE 9. PARASOMNIAS AT 12Y AND PSYCHOTIC EXPERIENCES AT 18-24Y

		Model A[1]			**Model B[2]**	
	None	**Transient 18 or 24**	**Persistent 18 and 24**	**None**	**Transient 18 or 24**	**Persistent 18 and 24**
Nightmares at 12y	Reference	**1.63 (1.48-1.78)**	**1.90 (1.65-2.18)**	Reference	**1.60 (1.43-1.79)**	**1.67 (1.41-1.99)**
Night terrors at 12y	Reference	**1.33 (1.13-1.57)**	**1.53 (1.21-1.93)**	Reference	**1.29 (1.06-1.57)**	1.14 (0.81-1.59)
Sleep walking at 12y	Reference	**1.23 (1.10-1.38)**	1.10 (0.91-1.33)	Reference	1.22 (1.06-1.40)3	1.07 (0.84-1.36)

Boldface type indicates significant associations at p<0.05. The reference category is the absence of psychotic experiences between 18-24y. [1]unadjusted analysis. [2]Adjusted for sex, IQ at 8 years (WISC-III), physical/sexual abuse (2.6y-6.9 years), DSM-IV psychiatric disorder at 7 years (DAWBA), DSM-IV anxiety disorder at 10y (DAWBA), depression score at 10y (SMFQ).[3]p=0.05

4.5 **SECONDARY ANALYSIS**

To further explore the relationship between adolescent nightmares and psychotic experiences at 24 years, an exploratory path analysis was conducted (see Figure 6). The association between nightmares at 12y was mediated by both anxiety and depression disorder at 15 years old and 17 years old respectively. The results also revealed a direct effect between nightmares at 12 years and PE at 24 years (β=0.078,

p<0.001). The indirect pathway to psychotic experiences also revealed a statistically significant finding (bias corrected CI, 0.05-0.06, p=0.01) (see Table 10). However, goodness of fit indicators did not reach the recommended threshold for good model fit ($x^{2=}$=52.39, df =10, p<0.001, root mean square error of approximation=0.057; comparative fit index =0.839*)* therefore the results should be interpreted with caution.

FIGURE 6. PATH DIAGRAM SHOWING DIRECT ASSOCIATIONS BETWEEN NIGHTMARES (12Y) AND PSYCHOTIC EXPERIENCES (24Y)

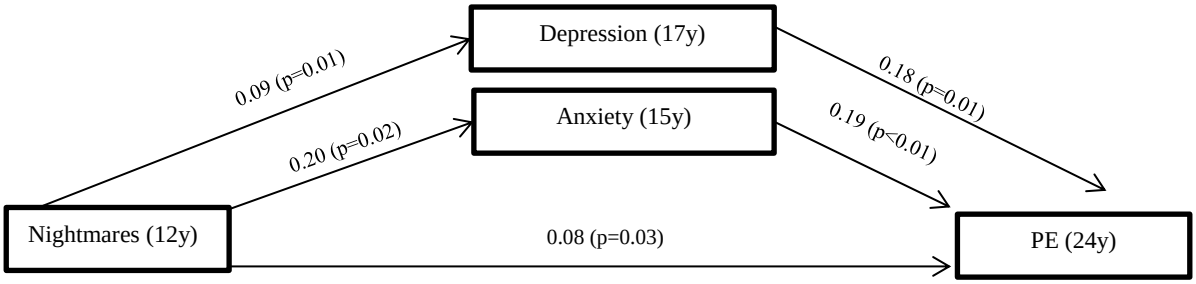


Figure 6 details the direct associations between nightmares at 12y (exposure variable); anxiety disorder at 15y and depression diagnosis at 17y (mediating variable); and psychotic experiences at 24y (outcome variable). This path analyses also included sex, IQ (8y) childhood abuse as covariates. Significant pathways are represented by solid arrows.

TABLE 10. DIRECT AND INDIRECT ASSOCIATIONS BETWEEN NIGHTMARES (12Y) AND PSYCHOTIC EXPERIENCES (24Y)

	Anxiety at 15 years	**Depression at 17 years**	**Psychotic experiences at 24 years**
Direct associations			
Nightmares at 12 years	0.20 (CI., 0.17-0.22) p=0.02	0.09 (CI., 0.06-0.11), p=0.01	0.08 (CI.,0 .10-1.60), p=0.03
Anxiety at 15 years	n/a	n/a	0.19 (CI., 0.17-0.23), p<0.001
Depression at 17 years	n/a	n/a	0.18 (CI., 0.15-0.22), p=0.01
Indirect association			
Nightmares at 12y	n/a	n/a	0.05 (CI., 0.05-0.06), p=0.01

Details standardised regression weights, confidence intervals and significance values for direct and indirect pathways.

4.6 **DISCUSSION**

4.6.2 Main findings

This study aimed to examine the longitudinal associations between sleep problems and psychotic experiences in a large birth cohort sample. Findings revealed that persistent nightmares and difficulties initiating and maintaining sleep during childhood were associated with an increased the risk for later psychotic experiences

at one time point (18 or 24 years old) (OR: 1.15, CI: 1.06-1.24). Furthermore, adolescent nightmares (but not night terrors or sleep walking) were found to be significantly associated with persistent psychotic experiences at 18 and 24 years old. Importantly, nightmares in childhood and adolescence were consistently found to relate to the occurrence of later psychotic experiences. These findings support previous research in this area which show that early sleep difficulties present prior to and may be a potential risk factor for later psychotic experiences (Thompson et al., 2015, Fisher et al., 2014).

Childhood sleep disturbances were shown to be consistently associated with the incidence, but not persistence, of psychotic experiences at 18 and 24 years old. This suggests that preschool sleep problems are important when considering who is likely to experience later psychotic experiences but it may not be an indicator of who will experience sustained PE's. These findings add to recent research revealing that the presence and stability of childhood sleep problems (between 9-11 years) are related to later psychological difficulties (Shimizu et al., 2021). The results from this ALSPAC study demonstrate that *early* childhood sleep disturbances are also relevant to later psychological outcomes and that there are nuances in how early sleep difficulties relate to risk of PE's at two very different life stages. Psychotic experiences at 18 may coincide with a transitional period where by young people are entering into employment or training and gaining increased independence socially. Experiences of paranoia, hallucinations and/or cognitive disorganisation during this stage of life may create difficulties whilst navigating through the complexities of entering adulthood, particularly if additional risk factors for mental health difficulties also present (e.g., adverse social experiences). It is possible that early sleep problems may be a marker of response to stress, similar to early PE's. However, later sleep problems are an early marker for later psychological difficulty as reported by Shimizu et al. (2021). Therefore, the timing of sleep difficulties may represent different markers (e.g., stress response vs impending psychological difficulty).

Similarly, this study found that adolescent parasomnias (with the exception of sleep walking) were associated with an incidence of psychotic experiences at 18 *or* 24 years old. Interestingly, the moderate odds ratios and lack of statistical significance at 24 years old (.

Table 8) suggest that adolescent parasomnias may be more relevant to risk of PE at 18 rather than 24 years old. This finding is compatible with previous research demonstrating that most subclinical psychotic experiences in the general population spontaneously resolve without treatment or intervention, as they represent normal developmental phenotype (Dominguez et al., 2011, Kelleher et al., 2012). In a general population sample such as ALSPAC, which predominantly includes participants that report fewer environmental risk factors (e.g., socio economic status, childhood abuse (Kırlı et al., 2019, Kounali et al., 2014, Cosgrave et al., 2021) for persistent or extreme psychotic experiences, it is expected that persistent PE's will be reported by a small group of individuals and that the 'incident' category of PE will be largely benign in nature.

The findings presented in this study both support and extend previous research by Thompson et al. (2015). Specifically, nightmares during childhood and adolescence are shown to be associated with the incidence and persistence of psychotic experiences between 18 and 24 years. The association at 24 years old is a novel finding which shows that adolescent nightmares are related to outcomes in early adulthood. This is unsurprising as during childhood, nightmares are often considered to be common and reported to occur in at least 75% of children (Mindell and Barrett, 2002). However, the frequency and persistence beyond childhood can be problematic and associated with other difficulties (Gregory and Sadeh, 2012, Barclay and Gregory, 2013, Medicine, 2005). Studies seeking to understand the relationship between nightmares and psychotic experiences have suggested that although they are physiologically distinct from one another (e.g., nightmares activate the pre-frontal area in "closed-loop circuits", whereas hallucinations are linked to anterior frontal areas and posterior sensory arears (Koopman-Verhoeff et al., 2019)), psychotic experiences and nightmares display phenomenological similarities (e.g., low in meta-cognitive awareness but high in sensory experience) which may explain their co-occurring nature(Koopman-Verhoeff et al., 2019). An alternative explanation lies in biases in the cognitive appraisal of unusual experiences in waking and dreaming life. Individuals experiencing psychotic symptoms and/or persistent nightmares may be prone to appraising the world around them in a persecutory or delusional way (Rek et al., 2017). This would also explain the preoccupation, distress and deteriorations

to functioning that are often seen in individuals experiencing severe psychotic experiences and persistent nightmares (Rek et al., 2017). Further research into the role of cognitive appraisal would be a fruitful line of enquiry in this area, to better understand the factors responsible for this association.

This study also revealed that anxiety and depression mediated the relationship between nightmares at 12y and psychotic experiences at 24y (see Figure 6). This finding fits with a recent study involving analysis of the ALSPAC sample by Morales et al., (2020). The authors reported depression as a mediating factor between sleep behaviours (night awakening at 18 months old and sleep routine at 5.8 years old) and psychotic symptoms at 12 years old. The authors suggest that the role of depression can be understood in the context of dopamine and serotonin neurotransmitters which are implicated in the sleep-wake cycle, the emergence of depression and psychotic illness (Morales-Muñoz et al., 2020). Such population based research provide important insights into how sleep and psychotic experiences interact over time, indicating that the relationship is complex and often involves other factors such as affect.

4.6.3 Implications

Across our lifespan and stages of life we spend a significant amount of time asleep (Ohayon et al., 2004, D'Ambrosio and Redline, 2014). The adolescent period is particularly important as the transition from childhood to adulthood results in changes to sleep (including circadian phase delay), physical, emotional and social wellbeing which can have lasting effects into adulthood (Sadeh et al., 2009, Telzer et al., 2015, Carskadon, 2002, Carskadon, 2011). Understanding the factors that may be detrimental to later health and functioning are critical in promoting public health and preventing burdensome disorders and psychological difficulties. This study provides evidence to suggest that sleep difficulties, specifically nightmares, during the adolescent period may have both short term (distress and disruptions to other aspects of sleep) and long term implications (e.g., risk for psychotic experiences in adulthood that could increase the chances of other mental health difficulties). A robust meta-analysis combining the findings from randomised control trials described psychological (e.g., lucid dreaming therapy and Image Rehearsal Therapy [IRT]) and pharmacological interventions (e.g., prazosin and cyproheptadine) as

being beneficial in the treatment of nightmares; with not all interventions providing equal improvements (Augedal et al., 2013). Several mechanisms have been proposed to explain the effectiveness of psychotherapies for nightmares including: increasing feelings of mastery, providing an opportunity for emotional processing to dismantle the fear structure, reorganisation of beliefs, rebuilding sleep functions, reducing arousal and avoidance(Rousseau and Belleville, 2018). There is a need for further research into such mechanisms and effective interventions for specific disruptions to childhood and adolescent sleep such as nightmares, which may have the long term benefit of reducing the chances of potentially negative psychological experiences such as PE's.

In addition to considering effective interventions in this area, there is also a need for further research exploring which groups of children and adolescents would benefit most from sleep interventions. Whilst providing treatment to all children and/or adolescents experiencing nightmares could be beneficial at an individual level, the associated costs to services may outweigh any long term benefits if routinely offered. The threshold for determining at which point nightmares require intervention to prevent longer term difficulties requires further investigation; particularly as for many young people nightmares spontaneously resolve without intervention and represent normal developmental phenomenon.

4.6.4 Strengths and Limitations

This study involves data collected from a large and well-designed longitudinal birth cohort study, with parents and children followed up over a period of 24 years. The assessment of sleep and psychotic experiences are repeated across time to enable a robust analysis involving multiple measurements of the exposure and outcome variables. Exploring the various facets of sleep rather than sleep as a whole is also a fundamental aspect of exploring the temporal relationship between sleep and psychotic experiences.

Although this study presents several important findings, it is important to acknowledge the limitations. Firstly, the ALSPAC sample is a largely homogenous group (e.g., ethnicity, homeownership status and educational level) at enrolment (see Table 3). Previous research has demonstrated differences in sleep quality and quantity and the prevalence of psychotic experiences across gender, ethnic groups

and socioeconomic status (Patel et al., 2010, Whinnery et al., 2014, Oh et al., 2014, Cosgrave et al., 2021). Therefore it would be important to replicate these findings in a more diverse sample. Secondly, analysis of demographic factors relating to participating and the non-participating group indicated a risk of introducing a self-selection bias. To compensate for this, inverse probability weighting was incorporated into the regression analyses. Whilst this approach is reported across similar studies (Fisher et al., 2014, Thompson et al., 2015, Morales-Muñoz et al., 2020), it is not possible to eradicate bias completely and so findings should be interpreted in light of this. A third limitation is the size of the 24 years group included in the regression analyses (see tables 7-9). Attrition is a common challenge in large birth cohort studies and can not only contribute to bias, but it may reduce the statistical power to detect significant differences between groups contributing to larger confidence intervals and an inability to carry out further subgroup analysis. Therefore, it is important to recognise the reduced sample size at 24 years and the impact that this could have on detecting significant differences. A fourth limitation relates to the availability of data and consequently the variables used to represent several constructs in this study including socioeconomic status, anxiety and depression. An overall measurement of socioeconomic status was not available in this study and consequently mother's educational level was used as a sole indicator. Socioeconomic status has been shown to impact on sleep and risk of PE (Mezick et al., 2008, Newbury et al., 2018) therefore results should be interpreted in light of this. Fifth, this study did not have access to data on the frequency or distress associated with sleep disturbances and parasomnias, at each time point, which would have provided further insight into the quality of the experiences. This should be a priority for future research in this area to explore. In addition, the presence of sleep difficulties during childhood was reported by parents who may have held different perceptions or thresholds for sleep difficulties. This is an important consideration for the findings in this study as it is possible that parents may have over or under reported sleep difficulties during the childhood period. Future research should seek to include objective measurements of sleep which are analysed in conjunction with self-report measures to address this limitation. Finally, the secondary exploratory path analysis did not reveal a good model fit according to goodness-of-fit indices. Modifications to the model on the same dataset may have improved the overall fit,

with several iterations producing improved results by chance. However, these findings could fail to be replicable in other samples (e.g., model fit could be consistent with the data but not the real world) (Schermelleh-Engel et al., 2003). The purpose of the path analysis was exploratory in nature and it is possible that the model may have been over simplistic in examining the complex longitudinal relationship between nightmares at 12 years old and PE at 24 years old. There may be a host of biological and psychosocial factors also impacting on the independent, dependent and mediating variables. Therefore, future research should seek to explore more comprehensive models to explore this complex relationship. However, this exploratory analysis provided an opportunity to use a new data analysis package (AMOS) and a new statistical method (structural equation modelling).

4.6.5 Conclusion

This study is one of few studies examining the longitudinal association between early sleep disturbances and later psychotic experiences in a large population-based cohort. Furthermore, this is the first study to examine relationship between sleep difficulties and PE beyond the adolescent period within the ALSPAC sample. It highlights that difficulties initiating and maintaining sleep in addition to parasomnias during childhood and adolescence are associated with the incidence of psychotic experience at 18 or 24 years. Only nightmares at 12 years were associated with persistent psychotic experiences. This study provides evidence that sleep problems may be indicative of increased risk of psychotic experiences. However, these experiences do not necessarily persist beyond 18 or 24 years old, with the exception of nightmares which warrant further investigation.

Chapter 5. **TRANSITION STUDY**

5.1 **INTRODUCTION**

There has been a surge of interest surrounding the relationship between sleep and mental health difficulties over the last two decades; with 1,200 new studies published in this area between 1980- 2018 (Carskadon and Barker, 2020). The steady increase in attention overlaps with an update to the diagnosis and treatment of sleep related disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Seow et al., 2018). Unlike its predecessors, the DSM-5 includes 'insomnia disorder' as a new diagnostic category. Arguably, this new category represents a shift in the conceptualisation of sleep disturbances, from a consequence of psychiatric illness to an important clinical entity to be treated in its own right (see chapter 1 of this thesis for a more detailed discussion on the shift in how sleep is viewed within Psychiatry) (Seow et al., 2018). A further significant addition to the DSM-5 (conditions for further study) is the 'Attenuated Psychosis Syndrome' (APS) (Tsuang et al., 2013, Yung et al., 2012). This new category describes psychotic symptoms such as hallucinations and delusions that do not reach the threshold for diagnosis of psychotic disorder but represent an increased risk for transitioning to psychosis (Samiotakis et al., 2017) (see chapter 1 of this thesis for further discussion on APS and risk for psychosis). Together, these developments in the DSM-5 highlight the clinical value in identifying and treating sleep difficulties and in undertaking further high quality research into APS.

The Ultra High Risk (UHR) criteria overlaps with the APS construct as a operationalised criteria designed to identify individuals at risk of developing frank psychosis in the near future (Fusar-Poli et al., 2012, Schiffman and T CARPENTER, 2015, Yung et al., 2003, Yung et al., 2005a). The early identification and treatment of youth at risk for psychosis is crucial to closing the gap between symptom onset and commencement of treatment (or the 'duration of untreated psychosis' (discussed in chapter 1 of this thesis) and improving patient outcomes including better treatment response, improved quality of life and lower mortality rates following a diagnosis of psychotic disorder (Schiffman and T CARPENTER, 2015). Consequently, it has

become paramount for help seeking youth presenting to services with subthreshold psychotic symptoms to be screened for psychosis risk using well-validated tools.

Research has shown that sleep disturbances are widely reported amongst UHR youth (Clarke et al., 2020, Davies et al., 2017). Whilst sleep problems have been historically viewed as a non-specific symptom and a by-product of psychosis, there is growing evidence that they appear early and there are nuances in how different sleep domains relate to subgroups of psychotic symptoms (Clarke et al., 2020). The systematic review presented in chapter 3 of this thesis highlights that sleep duration, quality and timing of sleep all relate to positive psychotic symptoms and functioning in different ways. To explain this relationship, Lunsford-Avery and A. Mittal (2013) postulate a neurodevelopmental diathesis stress model (Lunsford-Avery and A. Mittal, 2013) which suggests that sleep disturbances contribute to the onset of psychosis at numerous points throughout development. The theory highlights that sleep disturbances and psychosis share a number of genetic (e.g., Snap-25 and CLOCK genes) and early environmental risk factors (e.g., prenatal malnutrition, hypoxia and stress). When these early vulnerabilities interact with neuromaturational, endocrine and psychosocial stressors during the adolescent period they create the perfect storm for an over-sensitised Hypothalamic-Pituitary-Adrenal (HPA) system and functional and structural brain changes (e.g., atypical synaptic pruning and white matter growth). Dysfunctional sleep is posited to negatively affect the biological stress response (including cortisol secretion), in addition to adversely impairing neurodevelopment during the adolescent period. The consequences of impaired stress response are instrumental in driving attenuated psychotic symptoms through the interaction between cortisol and dopamine. Furthermore, structural changes to areas of the brain implicated in sleep such as the thalamus and thalamo-cortico connections are also seen during this adolescent phase, feeding into a vicious cycle. Sleep disturbances then negatively impact cognitive functioning (including memory consolidation) and increase stress to further perpetuate the cycle. Essentially, sleep dysfunction is implicated in the pathophysiology of psychosis through negatively impacting cognitive (e.g., memory consolidation), biological (e.g., endocrine systems) and psychosocial (e.g., resilience) domains integral to the expression of psychosis. This study will test one

aspect of this theory by exploring whether increased sleep disturbances are prospectively associated with attenuated psychotic symptoms during the adolescent period.

Whilst approximately one third of UHR youth transition to psychosis, research suggests that around two thirds experience a range of other adverse outcomes including significant and long lasting impaired social and occupational outcomes (Malhi and Bell, 2019). At a patient level the costs of such impairments can be grave, with individuals struggling to maintain core aspects of everyday life including critical relationships with friends and family, in addition to difficulties retaining employment which bring not only financial gains but psychological benefits (Robustelli et al., 2017, Lee et al., 2017, Hodgekins et al., 2015, Singh et al., 2021). Therefore, it is unsurprising that functioning is viewed by clinicians and patients an important outcome with far reaching consequences. The systematic review in chapter 3 describes a small number of studies (n=2) that report on the relationship between sleep disturbances and functional outcomes in UHR youth, highlighting circadian rhythm variables (including sleep pattern disruption) to be associated with long term psychosocial functioning levels. A developmental psychopathology model proposed by Beebe (Beebe, 2011) provides a framework for understanding how poor sleep could drive functional difficulties. It postulates that genetic and environmental factors drive pronounced neurodevelopmental changes during childhood and adolescence, which do not occur at any other time over the lifespan. This sensitive period is vulnerable to stress or toxins which can lead to abnormal neural connections impacting on cognitive, behavioural or emotional domains. Dysfunctional sleep is identified as one such stressor which can alter neural plasticity, impair learning and disrupt behavioural functioning in children. Notably, it is the extended exposure, even at a low level, that is hypothesised to affect neurodevelopment and result in later poor functional outcomes (Beebe, 2011). As the brain is undergoing significant changes, critical functional skills are also developing during childhood and adolescence such as academic and social skills. Prolonged sleep disturbances may hamper a child or adolescents engagement with the environment and therefore interrupt or delay the development of such life skills and functional development. This model explains a complex relationship; suggesting that

sleep disturbances are detrimental to functional capabilities when extended sleep problems act as a stressor on the developing brain and impede an individual's capacity to engage and learn critical skills in the environment (Beebe, 2011). This current study seeks to test Beebe's developmental framework through assessing the impact of poor sleep quality and quantity on role and social functioning in late adolescence to early adulthood.

There is a dearth of evidence concerning the relationship between sleep and Quality Of Life (QoL) in ARMS youth (see systematic review, chapter 3 of this thesis). Research has reported that QoL is an imperative outcome for patients experiencing psychiatric disorder as satisfaction with life and the ability to achieve goals irrespective of psychological difficulties has high value (Ritsner, 2007). Furthermore, impaired sleep has been implicated in the sustainment of decreased QoL in patients diagnosed with serious mental illness (Ong et al., 2020, Hofstetter et al., 2005b, Ritsner et al., 2004, Afonso et al., 2011). It is theorised that QoL is the outcome of two key factors: distress factors (e.g., psychopathology, negative life events and psychological distress) and protective factors (e.g., social relationship, leisure activities and medication). This distress/protection vulnerability model of QoL postulates that many aspects of life can be protective or distressing. However, QoL is perceived as low when distress factors outweigh protective factors (Ritsner and Awad, 2007, Ritsner et al., 2004). Sleep is a protective factor, however when impaired it can shift to become distressing and can contribute to poor QoL. Understanding the relationship between sleep and QoL in individuals who are experiencing sleep difficulties whilst *vulnerable* to developing mental health difficulties is an important line of enquiry, particularly when considering outcomes beyond clinical symptoms in UHR youth.

The systematic review in chapter 3 of this thesis describes several studies that have examined the cross-sectional associations between sleep disruptions (sleep quality, duration and circadian rhythm), psychotic symptoms and functioning in UHR youth. However, there are limited longitudinal studies (n=6) examining the relationship between sleep domains (duration, quality and timing of sleep) and symptoms, functioning and QoL in UHR youth. This sparsity of research may reflect the challenges identifying and recruiting UHR youth (Wilson et al., 2018a). It may also

mirror a broader issue relating to a lack of replication studies in this area, but also more widely across Psychology (Maxwell et al., 2015, Shrout and Rodgers, 2018). Discussions concerning false positives rates, transparency in research and low power to detect effects are particularly pertinent to the replication crisis (Diener and Biswas-Diener, 2016). Aside from methodological and statistical factors that influence replicability, there are also philosophical concepts that offer explanations for the replication crisis (e.g., objectivism in research (e.g., researcher bias) and universalism (e.g., universal laws governing studied phenomenon)) (Wiggins and Chrisopherson, 2019). Replicating research across conditions and using differing methods is at the core of credible science, knowledge production and advancing clinical practice and treatment (Tackett et al., 2019, Fusar-Poli et al., 2016a).

Therefore, the primary aims of this study are to replicate and extend existing literature through investigating:

i. Specific sleep disturbances (sleep duration, quality, chronotype and fatigue) at baseline and their prospective association with *positive psychotic symptom severity* and *UHR status* at 12 month follow up in an Australian help seeking sample.
ii. Specific sleep disturbances (sleep duration, quality, chronotype and fatigue) at baseline and their prospective association with *QoL* and/or *functioning* at 12 month follow up in an Australian help seeking sample.

The secondary aim of this study is to:

i. Replicate the analysis conducted in the Australian sample (as set out in the primary aims above) in a *UK help seeking sample* to investigate the prospective association between specific baseline sleep disturbances and *UHR status, psychotic symptom severity, functioning* and *QoL* at 6 month follow up.

Primary research question:

i. Are baseline sleep disturbances (sleep duration, quality, chronotype and fatigue) associated with UHR status, severity of psychotic symptoms, functioning or QoL at 12 month follow up in an *Australian* help seeking sample?

Secondary research question:

i. Are the findings from the primary research question replicable when examined in a UK sample (i.e. are baseline sleep disturbances (sleep duration, quality, chronotype and fatigue) associated with UHR status, severity of psychotic symptoms, functioning or QoL at 6 month follow up in an UK help seeking sample?

Hypotheses:

i. Australian and UK help seeking youth who meet *UHR criteria* at 6 and/or 12 month follow up will report poorer sleep quality, lower sleep quantity, persistent fatigue and delayed chronotype at baseline.
ii. Australian and UK help seeking youth reporting more severe *positive psychotic symptoms* at 6 and/or 12 month follow up will report poorer sleep quality, lower sleep quantity, persistent fatigue and delayed chronotype at baseline.
iii. Australian and UK help seeking youth reporting reduced *functioning* at 6 and/or 12 month follow up will report poorer sleep quality, lower sleep quantity, persistent fatigue and delayed chronotype at baseline.
iv. Australian and UK help seeking youth reporting poorer *QOL* at 6 and/or 12 month follow up will report poorer sleep quality, lower sleep quantity, persistent fatigue and delayed chronotype at baseline.

5.2 **METHOD**

5.2.2 Study design

Australian Transitions

The data presented in this thesis chapter is taken from The Transitions longitudinal cohort study involving young people seeking help for early mental health difficulties in Australia. This study received approval from The University of Melbourne and The University of Sydney Human Research Ethics Committees. The use of this data as part of this thesis was approved by the Transitions Principal Investigator team in November 2020.

UK Transitions

To address to secondary aims and hypothesis of this chapter, the data analysed and presented is taken from The Transitions longitudinal cohort study involving young people seeking help for early mental health difficulties in the Birmingham area of the UK. This study received approval from The University of Birmingham and The National Health Service Research Ethics Committees. The use of this data as part of this thesis was approved by the Transitions Principal Investigator team in November 2020.

5.2.3 Participants

Australian Transitions

Participants included youth aged 12 to 25 years, recruited between January 2011 and August 2012 from four Headspace clinical service centres in Australia (n=2 Melbourne centres and n=2 Sydney centres), which are designed to support young people facing psychological difficulties (Purcell et al., 2015a). To be eligible to take part participants were required to be English speaking to allow them to provide informed consent and complete the study assessments. The exclusion criteria included the absence of parental consent (for participants aged 12-14), intellectual disability (e.g., IQ <65) and non-English speakers which would have prevented informed consent and the completion of assessment.

UK Transitions

73 young people, aged 16-25 years, were involved in the UK Transitions study. Young people were recruited from specialised mental health services in the South Birmingham area (Birmingham Healthy Minds and Youth Space) and local advertisements, between August 2012 and August 2013. To meet the inclusion criteria for the study, young people needed to be help seeking for their mental health difficulties with no current diagnosis of psychotic disorder. The inclusion and exclusion criteria in the Australian Transitions study also applied. A total of 5 participants were excluded; n=2 withdrew from the study and n=3 excluded during the analysis due to severity and frequency of reported psychotic symptoms reaching threshold level at baseline.

5.2.4 Procedure

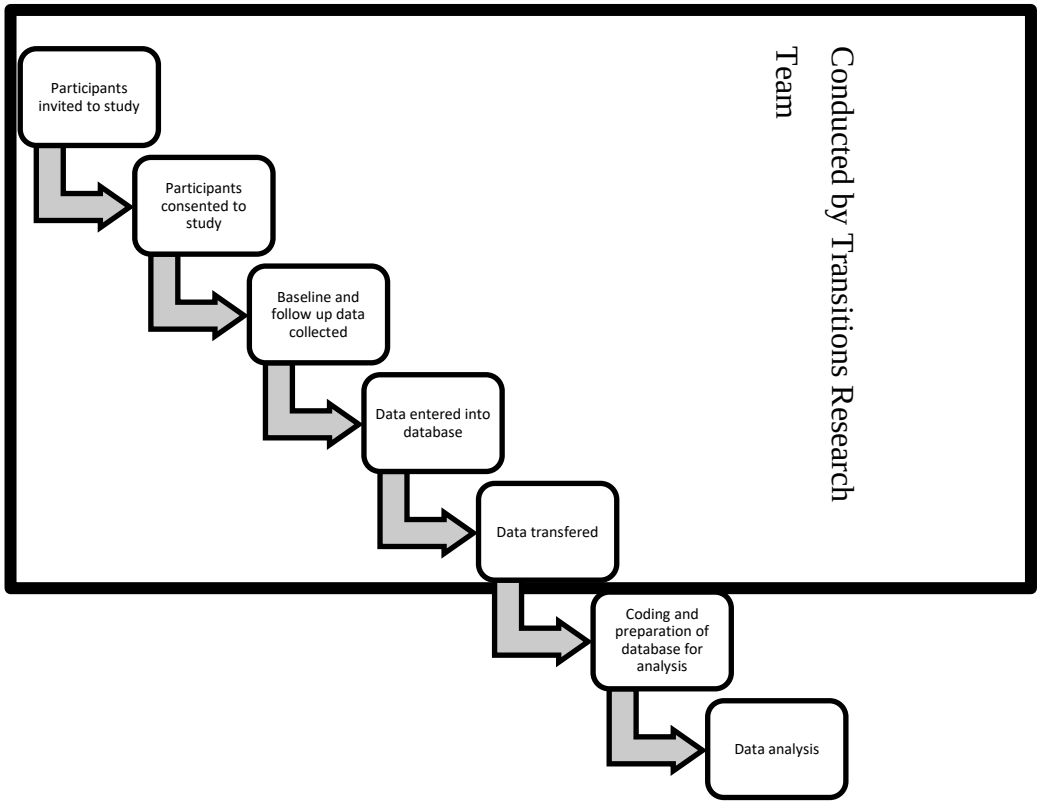
Australian Transitions

Participants receiving treatment, or on the waiting list for a clinical intervention, at Headspace were approached to take part in the study (see Figure 7). Following recruitment, Psychology graduate Research Assistants conducted clinical structured interviews in accordance with the study protocol (Purcell et al., 2015a). Self-report measures were then completed by participants using iPads or laptops. Participants were reimbursed with a $20 gift voucher for their involvement in the study (Purcell et al., 2015b).

UK Transitions

Participants engaged with Youthspace and Birmingham Healthy Minds were approached by their clinician with study information, or provided consent to be contacted by the research team. As part of their clinical care with Youthspace and Birmingham Healthy Minds, participants were in receipt of psychotropic medication and/or talking therapy (n=37 receiving antidepressant medication, n=4 receiving antipsychotic and or mood stabilising medication. N=38 were engaged in psychological therapy). Local advertisements in clinical services (primary care and secondary mental health services) were also displayed to share study details with individuals in the community (n=7). Following screening and recruitment, assessments were carried out at the University of Birmingham, in participant homes or via telephone where necessary, by trained researchers trained to degree level or above. Following baseline assessments, participants were invited to take part in 3 and 6 month follow up assessments which included repeating assessment measures (Heinze et al., 2018).

Figure 7. Flowchart of study activities



5.2.5 Measures

5.2.5.1 Psychotic symptoms

The Comprehensive Assessment of At Risk Mental State (CAARMS): The CAARMS is an extensively used instrument operationalizing the UHR criteria . This semi structured interview includes 27 items that assess positive symptoms (including disordered thought content, perceptual abnormalities and disorganised speech) in addition to conceptual disorganization, motor changes, concentration and attention, emotion and affect, subjectively impaired and impaired tolerance to stress (Yung *et al.*, 2005). It is used by trained mental health professionals internationally and can be administered repeatedly to assess changes in symptom over time (Fusar-Poli et al., 2016a). Each subscale assesses the intensity and frequency of psychotic symptoms on a scale of 0-6. Intensity and frequency scores from positive symptom subscales can be used to identify 3 groups: (i) those with attenuated psychotic symptoms with an intensity or frequency below threshold for clinical psychosis (ii) those with brief self-limited threshold frank psychotic symptoms (BLIPS) that spontaneously resolve within seven days and (iii) a family history of psychotic

disorder (constituting a genetic vulnerability) along with recent and significant decline in functioning. Scores to meet the three criteria vary across subscales, with higher intensity scores required on the perceptual abnormality scale compared to thought disorder subscales (as detailed in the paragraph below). Early studies reported an increased risk of psychotic illness in those who met the UHR criteria at 12 months, compared to non-psychotic help seeking youth, with a relative risk of 12.44 (95% CI = 1.5–103.41, p = 0.0025) (Yung et al., 2005a). The CAARMS has high predictive validity, good discriminant validity, excellent concurrent validity and good to excellent inter-rater reliability (Yung et al., 2005a, Raballo et al., 2011). When compared to a similar extensively used instrument operationalising UHR criteria (the Structured Interview for Psychosis-Risk Syndrome (SIPS)), the CAARMS has shown agreement in the identification of UHR participants (overall agreement 86%; kappa=0.78 95%; CI 0.684 to 0.878) (Fusar-Poli et al., 2016a).

This study defined UHR participants according to the CAARMS criteria (Schultze-Lutter et al., 2013, Yung et al., 2004). The UHR group in this study included participants that scored 3-5 in severity on the Unusual Thought Content *and/or* Non-Bizarre Ideas subscales *and/or* a score of 3-4 in intensity on the Perceptual Abnormality subscale *and/or* a rating as 4-5 on the Disorganised Speech scale *plus* a minimum frequency of once a month to twice a week (more than one hour per occasion) or 3 to 6 times a week (less than one hour per occasion several times a week). As reported by other studies, the functional decline criterion was not applied when assessing UHR status to ensure sufficient cases in each group (Schultze-Lutter et al., 2015). Participants rated as <3 in severity (or <4 on the perceptual abnormality scale) on CAARMS subscales were assigned to the non-UHR group. CAARMS positive psychotic symptom severity scores were operationalised as the sum of the global rating scale (0-6) and frequency of all four subscales (0-6), a method adopted in other research studies (Morrison et al., 2012).

5.2.5.2 Depression and anxiety

The Generalised Anxiety Disorder (GAD-7): The GAD-7 is a self-report seven item questionnaire used to assess anxiety throughout the last two weeks. Items are rated on a scale of 0-2, with total scores ranging between 0-21 to represent mild, moderate or severe anxiety based on a cut off score of 5, 10 or 15 respectively. This widely

used tool is validated for used in clinical and non-clinical populations with a sensitivity of 89% and specificity of 83% for generalised anxiety disorder (Williams, 2014).

The Quick Inventory of Depressive Symptomatology (QIDS) 16 item adolescent version: The QIDS[16] is a 16 item questionnaire evaluating the symptoms of nine domains of major depressive disorder derived from the DSM-IV experienced over the last seven days. Each question is assessed on a four point Likert scale with total scores ranging from 0-27. The instrument is validated in adolescent populations, demonstrating good reliability ($\alpha \geq 0.8$) (Bernstein et al., 2010).

The Kessler Psychological Distress Scale (K10): The K10 is a 10 item screening tool used in clinical and epidemiological research to assess psychological distress over the past 30 days. The frequency of experiencing statements on the questionnaire ('all of the time', 'most of the time', 'some of the time', 'a little of the time', 'none of the time') are rated on a scale of 1-5. A score out of 50 is derived to determine degree of distress, ranging from 'severe distress' to 'no distress'(Andrews and Slade, 2001). The K10 has been shown to be a sensitive screening tool for serious mental illness (Kessler et al., 2003), demonstrating consistent psychometric property and an ability to discriminate between clinical and non-clinical groups (Kessler et al., 2002).

5.2.5.3 Sleep

The Pittsburgh Sleep Quality Index (PSQI): The PSQI is an internationally used self-report measure of sleep quality (Buysse et al., 1991). The questionnaire is a 19 item measure with a sensitivity of 89.6% and specificity of 86.5% for recognising sleep disorders (cut off score: 5) (Buysse et al., 2008). This study included four sleep indices derived from the PSQI; duration, quality and daytime sleepiness and chronotype. Similar to previous studies (Glozier et al., 2014), sleep duration scores were curtailed (range 3-15 hours) to reduce the effect of outliers; chronotype was operationalised into normal sleepers (with a bedtime between 22:00 - 01:59) and delayed (bed time between 02:00 - 06:00); sleep efficiency was calculated according the PSQI scoring system as number of hours slept divided by hours in bed, multiplied by 100. Sleep quality was dichotomised as 'good' or 'bad' based on the responses 'very good', 'fairly good', 'fairly bad', 'very bad' to ensure adequate group sizes. These sleep domains were selected based on domains reported on in

previous studies presented in the systematic review (see chapter 3 of this thesis). A large number of these studies utilised the PSQI to assess these sleep difficulties, therefore this study will seek to replicate and compare findings that have been reported elsewhere.

5.2.5.4 Social and role functioning and QoL

The Social and Occupational Functioning Assessment Scale (SOFAS): The SOFAS is a well-used measure of global and current functioning. This tool is used to rate social and occupational functioning on a scale of 0 to 100 (Rybarczyk, 2011). Problems that are a direct result of physical or mental health problems are considered when rating on this scale.

The World Health Organisation Quality of Life assessment (WHOQOL-1): The use of one item taken from the WHOQOL-100 asking participants to provide a rating of their overall Quality of Life (QoL) is included in this study. Participants were asked to rate their QoL as very good, good, neither good nor poor, poor, very poor. Inclusion of one item from the WHOQOL-100 has been adopted in previous studies (Purcell et al., 2015a).

5.2.6 Data analysis

Data analysis was conducted using SPSS version 27. To capture participant characteristics at baseline, means and standard deviations were calculated for continuous normally distributed variables (and medians for non-normally distributed variables) and n's and percentages for categorical variables. All data was checked for parametric assumptions. To assess the normality of data histograms, Q-Q and P-P scatter graphs were generated and checked. For those variables that were not normally distributed, square root and log transformations were carried out. The outcome variables psychotic symptom severity and SOFAS scores were unsuccessfully transformed. Consequently, a bootstrapping (1000 samples) approach was adopted to enable several regression analyses to be conducted and to account for the non-normal distribution of the data (Field, 2013).

The regression models constructed were the same for both primary and secondary analyses. To reduce the risk of multicollinearity, the four sleep variables (sleep duration, quality, chronotype and daytime sleepiness) were included as predictors in

separate regression models. To examine whether sleep variables were prospectively associated with UHR status at 6 and 12 month follow up scores a series of stepwise logistic regression models were constructed. Sleep variables were entered into block one, followed by age, gender, education and employment status in block 2 and baseline QIDS, baseline K-10 and baseline GAD-7 scores in block 3.

To determine whether sleep duration, quality, chronotype and daytime sleepiness were prospectively associated with psychotic symptom severity and/or occupational and social functioning at 6 and 12 month follow up, hierarchical multiple regression models were developed including sleep variables in block one, followed by age, gender, education and employment status in block 2 and baseline QIDS, baseline K-10 and baseline GAD-7 scores in block 3.

Finally, to examine whether sleep domains were prospectively associated with QoL at 12 month follow up a series of multinomial regression analyses were performed including sleep variables in block one, followed by age, gender, education and employment status in block 2 and baseline QIDS, baseline K-10 and baseline GAD-7 scores in block 3.

5.3 **RESULTS**

The findings from the Australian sample are presented first, followed by a replication study involving the UK sample in the second half of the results section for this chapter.

5.4 **PRELIMINARY ANALYSIS**

5.4.2 Baseline characteristics of Australian sample

As described in table 11, the total sample included 415 participants (n=288, 69.4% female) with a mean age of 18.49 (SD 3.21). More than half of all participants were not in employment (59.8%), with the majority in education (71.8%) at baseline. The UHR and non-UHR group did not differ significantly on demographic variables. However, they did differ significantly on clinical variables (psychotic symptoms severity score, QIDS, K-10 and GAD-7), functioning (SOFAS) and QoL (WHO-QoL).

The average sleep duration for the sample was 7.48 hours, with just over half of all participants reporting good quality sleep (54.5%). Most participants reported a normal chronotype (88.0%) and none persistent daytime disturbances relating to sleep (< 3+ times per week) (85.1%).

Table 11 shows that the UHR group had a significantly lower sleep duration (UHR=7.08, non-UHR=7.68) and higher levels of sleep related persistent fatigue compared to the non-UHR group. Whilst the two groups did not differ significantly in relation to sleep quality and daytime sleepiness, more than half of the non-UHR group reported good sleep quality (59.2%) compared to the UHR group (44.4%). Furthermore, 10% of the UHR group compared to 15% of the non-UHR group reported a delayed chronotype.

TABLE 11. BASELINE DIFFERENCES BETWEEN THE AUSTRALIAN UHR AND NON-UHR GROUP

	Total sample n=415	**UHR n=133**	**non-UHR n=282**	**Statistics**
Demographics				
Age (M±SD)	18.49 (3.21)	18.36 (3.11)	18.55 (3.25)	t(413)=-0.57, p=0.56
Gender n (%)				
Male	127 (30.6)	41 (30.8)	86 (30.5)	$x^2(1)=0.05$, p=0.95
Female	288 (69.4)	92 (69.2)	196 (69.5)	
Employment[1] n (%)				
Not in employment	248 (59.8)	81 (60.9)	167 (59.2)	$x^2(1)=0.11$, p=0.74
In employment	167 (40.2)	52 (39.1)	115 (40.8)	
Education n (%)				
Not in education	117 (28.2)	37 (27.8)	80 (28.4)	$x^2(1)=0.01$, p=0.91
In education	298 (71.8)	96 (72.2)	202 (71.6)	
Clinical measures				
Psychotic symptoms (median)	13	20	10	U=7725.500, z=-9.687, p<0.001
QIDS (M±SD)[2]	10.09 (5.59)	11.78 (5.69)	9.29 (5.37)	t(413)=-4.33, p<0.001
K-10 (M±SD)[3]	28.71 (9.49)	31.45 (9.57)	27.41 (9.19)	t(412)=-4.12, p<0.001
GAD 7 (M±SD)[4]	9.68 (6.01)	11.53 (6.44)	8.80 (5.60)	t(412)=-4.10, p<0.001
Functioning and quality of life				
SOFAS (n, median)[5]	68.00	65.00	70.00	U=14372.00, z=-3.86, p<0.001
WHO-QoL n (%)				
Very poor	24 (5.8)	14 (10.6)	10 (3.6)	$x^2(4)=11.85$, p=0.01
Poor	81 (19.7)	32 (24.2)	49 (17.6)	
Neither poor nor good	142 (34.5)	43 (32.6)	99 (35.5)	
Good	133 (32.4)	35 (26.5)	99 (35.1)	
Very good	31 (7.5)	8 (6.1)	23 (8.2)	
Sleep				
Sleep duration (M±SD)	7.48 (2.09)	7.08 (2.10)	7.68 (2.06)	t(413)=2.79, p=0.006
Sleep quality n (%)				

Good	226 (54.5)	59 (44.4)	167 (59.2)	$x^2(1)=-8.04$, p=0.05
Bad	189 (45.5)	74 (55.6)	115 (40.8)	
Chronotype n (%)				
Normal	365 (88.0)	113 (85.0)	252 (89.4)	$x^2(1)=1.59$, p=0.20
Delayed	50 (12.0)	20 (15.0)	30 (10.6)	
Daytime sleepiness n (%)				
None persistent fatigue	353 (85.1)	101 (75.9)	252 (90.0)	$x^2(1)=13.50$, p<0.001
Persistent fatigue	60 (14.5)	32 (24.1)	28 (10.0)	

Notes. UHR = ultrahigh risk, M = mean, SD = standard deviation. [1]Fulltime and part time employment [2]QIDS range = 3-19. [3]K-10 range = 10-50. [4]GAD-7 range = 0-21. [5]SOFAS = 0-100.

Table 12 shows baseline information for participants included in the study compared to those that did not participate at 12 month follow up. The participating and non-participating groups differed significantly on demographic factors (gender, education status), depression, role and social functioning scores, quality of life, and sleep variables (sleep quality and chronotype). Therefore, the regression analyses that follow will control for demographic and clinical factors. Furthermore, the outcome variables (psychotic symptoms, UHR status, functioning, QoL) will be interpreted in light of the significant findings in Table 12.

5.4.3 Differences between the participating and none participating group

TABLE 12. DEMOGRAPHIC AND CLINICAL FACTORS FOR THE AUSTRALIAN PARTICIPATING AND NONE PARTICIPATING GROUP

	Participating group (n=415)	**None participating group (n=387)**	**Statistics**
Age (M±SD)	18.49 (3.21)	18.06 (3.24)	t(800)=-1.89, p=0.60
Gender n (%)			
Male	127 (30.6)	146 (37.7)	$x^2(1)=0.07$, p=0.03
Female	288 (69.4)	241 (62.3)	
Employment[1] n (%)			
Not in employment	248 (59.8)	229 (62.2)	$x^2(1)=0.03$, p=0.48
In employment	167 (40.2)	139 (37.8)	
Education n (%)			
Not in education	117 (28.2)	138 (37.5)	$x^2(1)=0.10$, p=0.01
In education	298 (71.8)	230 (62.5)	
QIDS[2] (M±SD)	10.09 (5.59)	10.45 (5.15)	t(779)=0.95, p=0.06
K-10[3] (M±SD)	28.71 (9.49)	29.49 (9.62)	t(774)= 1.13, p=0.26
GAD-7[4] (M±SD)	9.68 (6.01)	10.05 (5.96)	t(772)=0.87, p=0.39
SOFAS[5] (median)	68.00	62.00	U=67024.500, z=-3.785,p<0.001
WHO-QoL n (%)			
Very poor	24 (5.8)	35 (9.8)	$x^2(4)=0.11$, p=0.06
Poor	81 (19.7)	59 (16.5)	
Neither poor nor good	142 (34.5)	139 (38.9)	
Good	133 (32.4)	93 (26.1)	
Very good	31 (7.5)	31 (8.7)	

Sleep duration (M±SD)	7.49 (2.10)	7.28 (2.43)	t(734)=--1.30, p=0.19
Sleep quality n (%)	7.48 (2.09)		
Good	226 (54.5)	166 (46.2)	$x^2(1)$=0.08, p=0.02
Bad	189 (45.5)	193 (53.8)	
Chronotype n (%)			
Normal	365 (88.0)	222 (81.3)	$x^2(1)$=-0.09, p=0.01
Delayed	50 (12.0)	51 (18.7)	
Daytime sleepiness n (%)			
None persistent fatigue	353 (85.1)	317 (88.5)	$x^2(1)$=0.05, p=0.21
Persistent fatigue	60 (14.5)	41 (11.5)	

Notes. UHR = ultrahigh risk, M = mean, SD = standard deviation. [1]Fulltime and part time employment.[2] QIDS range = 3-19. [3]K-10 range = 10-50. [4]GAD-7 range = 0-21. [5]SOFAS = 0-100.

5.5 **PRIMARY ANALYSIS**

5.5.2 Sleep disturbances and UHR status in the Australian Transitions sample

To examine whether sleep domains were prospectively associated with UHR status at 12 month follow up, separate regression analyses were conducted. Three blocks were included in each analysis; block one included the sleep variable only, block two included the sleep variable in addition to demographic variables (age, gender, employment and educational status), block three included the sleep variable, demographic variables and clinical variables (K10, GAD-7 and QIDS scores).

5.5.2.1 Sleep duration and UHR status

To explore the longitudinal association between baseline sleep duration and UHR status at 12 months three logistic regression models were constructed. Model A, including sleep duration as the sole predictor variable was significant (x^2 (1, n=414) = 7.83, p=0.005), suggesting that it was able to discriminate between UHR and non UHR participants. The model explained 2.1% (Cox and Snell R square) and 2.9% (Nagelkerke R square) of the variance in UHR status and sleep duration was a significant contributor to the model (Beta=-0.15 Standard Error=0.57, p=0.01). Model B, containing sleep duration and demographic variables was not statistically significant (x^2 (5, n=414) = 8.70, p=0.12), although sleep duration was a significant contributor in this model (Beta=-0.15, Standard Error=0.06, p=0.01). However, the final full model (model C) was statistically significant, suggesting that it could distinguish between UHR and non UHR participants (x^2 (8, n=414) = 28.44, p<0.001), however sleep duration did not make a significant contribution to the overall model (Beta=-0.85 Standard Error=0.06, p=0.14). Therefore, sleep duration is shown to be a significant predictor variable for UHR status when included as a

single predictor, however when incorporating demographic plus clinical factors into the models sleep duration is no longer significant.

5.5.2.2 Sleep quality and UHR status

Sleep quality (dichotomised as good or poor) was included in a three step model to examine the association with UHR status at 12 month follow up. Model A (including sleep quality only) was significant (x^2 (1, n=414) = 7.87, p=0.005), however as a single predictor, sleep quality explained 1% (Cox and Snell R square) and 2.6% (Nagelkerke R square) of the variance in UHR status. The model correctly identified 67.9% of UHR cases and sleep quality was a significant predictor in the model (Beta=0.59, Standard Error=0.21, p=0.009). Model B including sleep quality and demographic factors was not statistically significant (x^2 (5, n=414) = 8.25, p=0.14), suggesting that the model did not distinguish between UHR and non UHR participants. Sleep quality was the only significant predictor in model B (Beta=0.60, Standard Error=0.22, p=0.007). Finally model C, including sleep quality, demographic and clinical factors, was statistically significant x^2 (8, n=414) = 26.26, p=0.001). However, the contribution of sleep quality to the model was not statistically significant (Beta= 0.13, Standard Error=0.25, p=0.60). These findings suggest that sleep quality is significantly associated with UHR status when included as a sole predictor in a regression model, however when adjusting for demographic and clinical factors the model/ contribution of sleep quality loses significance.

5.5.2.3 Chronotype and UHR Status

When examining the longitudinal association between baseline chronotype (normal or delayed) and UHR status at 12 month follow up model C, which included 8 independent variables (chronotype, age, sex, education status, employment status, K-10, GAD-7, QIDS scores), was significant x^2 (8, N=414) = 26.42, p=0.001, showing that the model was able to detect differences between UHR and non UHR participants. The model explained 6.2% (Cox and Snell R square) and 8.6% (Nagelkerke R square) of the variance in UHR status, correctly identifying 70% of cases. Chronotype was not a significant contributor to this bootstrapped model (Beta=0.22, Standard Error =0.35, p=0.52) or model A including chronotype only (Beta=0.39, Standard Error=0.32, p=0.21) or model B including chronotype and demographic variables (Beta=0.41, Standard Error=0.33, P=0.20). These results

suggest that chronotype is not significantly associated with later UHR status independently or when included as part of a model with demographic and clinical factors.

5.5.2.4 Daytime sleepiness and UHR status

To explore the association between daytime sleepiness (persistent vs non-persistent sleep related fatigue) in UHR status at 12 months a three step model was constructed. Model A including daytime sleepiness as a single predictor variable was statistically significant (x^2 (1, N=412) = 13.40, p<0.001), with daytime sleepiness found to be a statistically significant predictor variable (Beta=1.04, Standard Error =0.29, p=0.001). The model explained 3.2% (Cox and Snell R square) and 4.5% (Nagelkerke R square). Model B included daytime sleepiness and demographic factors (age, gender, employment and education status), revealing a statistically significant model (x^2 (5, N=412) = 14.12, p=0.02), with daytime sleepiness as the only statistically significant predictor in the model (Beta=1.05, Standard Error =0.29, p=0.001). The model explained 3.4% (Cox and Snell R square) and 4.7% (Nagelkerke R square). Finally model C, including daytime sleepiness, demographic and clinical variables was statistically significant (x^2 (8, N=412) = 31.78, p<0.001) with 69.2% accuracy when predicting UHR status. The model explained 7.4% (Cox and Snell R square) and 10.4% (Nagelkerke R square). Daytime sleepiness was a significant contributor in the final model (Beta=0.73, Standard Error =0.32, p=0.01). These results consistently show that when daytime sleepiness is included as a single predictor variable or included with demographic and clinical factors it is significantly associated with UHR status at 12 month follow up.

5.5.3 Sleep disturbances and positive symptom severity scores at 12 month follow up in the Australian Transitions sample

5.5.3.1 Sleep duration and psychotic symptom severity

The association between baseline sleep duration and psychotic symptom severity at 12 month follow up was explored in a linear regression analysis. Model A, comprising of sleep duration as a single predictor, explained less than 1% of the variance in positive symptom severity (R squared change = 0.003, *F* (1, 412) =1.04, p=0.31), model B including sleep plus demographic variables explained <1% of the variance in symptom severity at 12 months (R squared change = 0.007, *F* (5, 408)

=0.80, p=0.54) but model C with the addition of clinical variables (QIDS, K10 and GAD-7) explained 14% of the variance in psychotic symptom severity (R squared change = 0.14, *F* (8, 405)=8.80, p<0.001). Sleep duration was not a statistically significant contributor to models A (Beta=-0.22, Standard Error: 0.25, p=0.39), model B (Beta=-0.23, Standard Error: 0.26, p=0.39) or model C (Beta=-0.22, Standard Error: 0.24, p=0.38).

5.5.3.2 Sleep quality and psychotic symptom severity

Exploring the relationship between baseline sleep quality and psychotic symptom severity at 12 months revealed 3 significant models. Model A included sleep quality as a sole predictor variable, this model explained 3% of the variance in positive symptom severity (R squared change = 0.03, *F* (1, 412) =11.23, p=0.001). Model B included sleep quality and demographic variables (age, sex, educational and employment status) and explained <1% of the variance in positive symptom severity (R squared change = 0.006, *F* (5, 408) =2.74, p=0.02). Finally, the full model included sleep quality, demographic and clinical factors. This model explained 11% of the variance in psychotic symptom severity (R squared change = 0.11, *F* (8, 405) =8.70, p<0.001). Sleep quality was a statistically significant predictor in model A (Beta=3.01, Standard Error: 0.87, p=0.001) and model B (Beta=3.00, Standard Error: 0.87, p=0.001), however it did not contribute significantly to model C (Beta=-0.40, Standard Error: 0.92, p=0.68).

5.5.3.3 Chronotype and psychotic symptom severity

To assess the prospective association between chronotype and psychotic symptom severity at 12 month follow up three models were constructed. Chronotype was the only predictor in model A and explained 1% of the variance in positive symptoms severity (R squared change = 0.013). After entering demographic variables (sex, age, employment and educational status), the total variance explained by the model reduced to <1% (R squared change 0.007). Finally, when including clinical factors in addition to chronotype and demographic variables, the overall model explained 13% of the total variance, R squared change = 0.13, F (8, 405) = 8.97, p<0.001. Although chronotype was a significant contributor in model A (Beta=3.23, Standard Error: 1.44, p=0.02) and model B (Beta=3.23, Standard Error: 1.46, p=0.03), it was not a

statistically significant variable in the final model (Beta=1.93, Standard Error:1.34, p=0.16).

5.5.3.4 Daytime sleepiness and psychotic symptom severity

Finally, when examining the association between baseline daytime sleepiness and psychotic symptom severity at 12 month follow up, model A explained 4% of the variance in psychotic symptoms severity (R squared change = 0.04, F (1, 410) = 17.13, p<0.001). Model B including daytime sleepiness and demographic variables explained < 1% of the variance in psychotic symptom severity (R squared change = 0.006, F (5, 406) = 82.26, p=0.002). Finally the full adjusted model (model C) explained 11% of the variance in psychotic symptom severity at 12 month follow up (R squared change = 0.11, F (8, 403) = 73.36, p<0.001). Daytime sleepiness was a statistically significant predictor in model A (Beta=5.23, Standard Error: 1.42, p=0.02) and model B (Beta=5.17, Standard Error: 1.42, p=0.02), however it was only significant at trend level in model C (Beta=2.75, Standard Error: 1.43, p=0.06).

5.5.4 Sleep disturbances and Quality Of Life at 12 month follow up in the Australian Transitions sample

5.5.4.1 Sleep duration and QoL

Baseline sleep duration scores, demographic and clinical variables were entered as predictor variables in a model containing QoL status at 12 month follow up as the outcome. Results from the multinomial regression analysis revealed a significant model (x^2 (16, N=409) = 61.93, p<0.001) suggesting that the model was able to discriminate between participants reporting poor, neither poor nor good or good category for QoL. The model explained 14% (Cox and Snell R square) and 16% (Nagelkerke R square). Sleep duration was *not* a statistically significant predictor variable for the poor QoL category (Beta=-0.21, standard error = 0.71, p=0.77) or neither good nor poor QoL category (Beta=0.02, standard error = 0.06, p=0.70) when good QoL was included as the reference point. Unadjusted analysis including sleep duration as a single predictor variable showed poor model fit (x^2 (2, N=410) = 4.36, p=0.11) and sleep duration was not a significant contributor to poor (Beta=-0.14, standard error = 0.76, p=0.06) or the neither good/nor poor category (Beta=-0.03, standard error = 0.06, p=0.60), when good quality of life was the reference category.

5.5.4.2 Sleep quality and QoL

When exploring the prospective association between sleep quality and QoL at 12 month follow up, the final model including 8 variables (sleep quality, age, sex, employment, education, QIDS, K-10, GAD-7 scores) was significant: x^2 (16, N=409) = 61.71, p<0.001, explaining 15% (Cox and Snell) and 17% (Nagelkerke R square) of the variance in quality of life scores at 12 month follow up. Sleep quality was a statistically significant variable for the poor QoL category (Beta=0.71, standard error=0.34, p=0.04) but not the neither good nor bad QoL category (Beta=0.34, standard error=0.27, p=0.20) when good quality of life was the reference point. This suggests that sleep quality is associated with *poor* QoL at 12 month follow up. In the unadjusted analysis with sleep quality entered as the only predictor variable, the model was statistically significant x^2 (2, N=410) = 24.79, p<0.001, explaining 5% (Cox and Snell) and 6% (Nagelkerke R square) of the variance in quality of life scores. Bootstrapped analysis revealed sleep quality as a significant predictor for poor (Beta=1.28, standard error=0.27, p=0.001) and neither good nor poor QoL (Beta=0.73, standard error=0.24, p=0.001) in this model.

5.5.4.3 Chronotype and QoL

Chronotype was included with demographic and clinical variables in a multinomial regression analysis involving QoL status as the outcome. Findings revealed a significant model x^2 (16, N=409) = 61.60, p<0.001. The model explained 14% (Cox and Snell R square) and 16% (Nagelkerke R square) of the variance for quality of life. However, chronotype did not significantly contribute as a predictor variable for the poor QoL category (Beta=-0.07, standard error = 0.43, p=0.88) or neither good nor poor QoL category (Beta=-0.04, standard error = 0.37, p=0.92) when good QoL was included as the reference point. In the unadjusted analysis (chronotype as a single independent variable with no confounding variables entered) the model had a poor fit: x^2 (2, N=410) = 1.25, p=0.53. The model explained 3% (Cox and Snell) and 4% (Nagelkerke R square) of the variance in QoL scores. Chronotype was not a statistically significant contributor to the models poor QoL category (Beta=0.42, standard error = 0.39, p=0.28) or neither good nor poor QoL category (Beta=0.25, standard error = 0.35, p=0.49). These results show that chronotype is not a significant predictor variable for later QoL.

5.5.4.4 Daytime sleepiness and QoL

In the final set of analysis investigating QoL as the outcome, daytime sleepiness was included in a model with age, sex, education, employment status, QIDS, K-10 and GAD-7 scores. The overall model was statistically significant x^2 (16, N=407) = 73.24, p<0.001, explaining 16.5% (Cox and Snell R square) and 19% (Nagelkerke R square) of the variance for QoL. Persistent daytime sleepiness was a significant contributor to the model for both poor quality of life (Beta=-1.25, standard error = 0.43, p=0.002) and neither good nor poor quality of life (Beta=-0.97, standard error = 0.41, p=0.02), the reference category for this analysis was good quality of life. The unadjusted analysis including daytime sleepiness as the only predictor variable revealed similar findings (x^2 (2, N=408) = 24.68, p<0.001). When the reference category was good QoL, daytime sleepiness was significant to poor QoL (Beta=-1.70, standard error = 0.37, p=0.001) and neither good nor poor QoL (Beta=1.21, standard error = 0.36, p=0.02) at 12 month follow up.

5.5.5 Sleep disturbances and role and social functioning at 12 month follow up in the Australian Transitions sample

5.5.5.1 Sleep duration and functioning

When exploring the association between baseline sleep duration and SOFAs scores, model A explained 3% of the variance in role and social functioning (R squared change = 0.03, *F* (1, 412) = 2.19, p=0.14). Model B including sleep duration and demographic variables explained 8% of the variance in role and social functioning scores (R squared change = 0.08, *F* (5, 408) = 7.90, p<0.001). Finally the full adjusted model (model C) explained 16% of the variance in psychotic symptom severity at 12 month follow up (R squared change = 0.16, *F* (8, 405) = 11.04, p<0.001). Sleep duration was not a statistically significant predictor in model A (Beta=0.45, Standard Error: 0.34, p=0.18), model B (Beta=0.39, Standard Error: 0.33, p=0.23), or model C (Beta=-0.11, Standard Error: 0.30, p=0.70).

5.5.5.2 Sleep quality and functioning

Exploring the relationship between baseline sleep quality and role and social functioning at 12 months follow up revealed 3 significant models. Model A included sleep quality as a sole predictor variable, this model explained 3% of the variance in

positive symptom severity (R squared change = 0.03, *F* (1, 412) =11.84, p=0.001). Model B included sleep quality and demographic variables (age, sex, educational and employment status) and explained 10% of the variance in positive symptom severity (R squared change = 0.10, *F* (5, 408) =9.98, p<0.001). Finally, the full model included sleep quality, demographic and clinical factors. This model explained 16% of the variance in psychotic symptom severity (R squared change = 0.16, *F* (8, 405)=11.03, p<0.001). Sleep quality was a statistically significant predictor in model A (Beta=-4.39, Standard Error: 1.27, p=0.001) and model B (Beta=-4.15, Standard Error: 1.23, p=0.001), however it did not contribute significantly to model C (Beta=-0.43, Standard Error: 1.41, p=0.76).

5.5.5.3 Chronotype and functioning

The association between baseline chronotype and role and social functioning at 12 month follow up was explored in a linear regression analysis. Model A, comprising of chronotype as a single predictor, explained less than 3% of the variance in functioning (R squared change = 0.03, *F* (1, 412) =12.42, p<0.001), model B including chronotype plus demographic variables explained 10% of the variance for functioning at 12 months (R squared change = 0.10, *F* (5, 408) =10.23, p<0.001) and model C with the addition of clinical variables (QIDS, K10 and GAD-7) explained 18% of the variance in psychotic symptom severity (R squared change = 0.18, *F* (8, 405)=12.24, p<0.001). Chronotype was a statistically significant contributor to models A (Beta=-6.87, Standard Error: 1.92, p=0.001), model B (Beta=-6.64, Standard Error: 1.80, p=0.01) and model C (Beta=-5.19, Standard Error: 1.81, p=0.04). These results suggest that even when controlling for demographic and clinical variables, chronotype is an important predictor for future functioning levels.

5.5.5.4 Daytime sleepiness and functioning

Three models were constructed to examine the relationship between baseline daytime sleepiness scores and role and social functioning at 12 month follow up. When daytime sleepiness was included as the only predictor in model A, findings revealed that it explained 1% of the variance in role and social functioning (R squared change = 0.01). After entering demographic variables (sex, age, employment and educational status), the total variance explained by the model was 8% (R squared change 0.08). Finally, when including clinical factors in addition to daytime

sleepiness and demographic variables, the overall model explained 16% of the total variance, R squared change = 0.16, *F* (8, 403) = 11.06, p<0.001. Although daytime sleepiness was a significant contributor in model A (Beta=-4.11, Standard Error: 1.83, p=0.02) and model B (Beta=-3.42, Standard Error: 1.74, p=0.04) it was not a statistically significant in the final model (Beta=-0.43, Standard Error: 1.84, p=0.84).

5.6 SECONDARY ANALYSIS: UK TRANSITIONS REPLICATION STUDY

5.7 PRELIMINARY ANALYSIS

As described in table 13, the total UK sample included 52 participants (n=33, 66% female) with a mean age of 20.31 (SD 2.68). More than half of all participants were not in employment (69.2%), but were in education (59.6%) at baseline. The UHR and non-UHR group did not differ significantly on demographic variables. However, they did differ significantly on one clinical variable (K-10) in addition to functioning (SOFAS) and QoL (WHO-QoL) scores.

The average sleep duration for the sample was 7.90 hours (SD 2.86), with just over one third of participants reporting good quality sleep (38.5%). Most participants reported a normal chronotype (78.8%) and none persistent daytime disturbances relating to sleep (< 3+ times per week) (84.3%).

Table 13 shows that the UHR group did not differ significantly from the non UHR group on sleep duration (p=0.74), quality (p=0.68), chronotype (p=0.59), or daytime sleepiness (p=0.42).

TABLE 13. BASELINE DIFFERENCES BETWEEN UK TRANSITIONS UHR AND NON-UHR PARTICIPANTS

	Total sample N=52	**UHR N=20**	**non-UHR N=32**	**Statistics**
Demographics				
Age (M±SD)	20.31 (2.68)	21.0 (2.27)	19.88 (2.85)	t(50)= -1.49, p=0.14
Gender n (%)				
Male	17 (34.0)	4 (21.1)	13 (41.9)	$x^2(1)=0.21$, p=0.12
Female	33 (66.0)	15 (78.9)	18 (58.1)	
Employment[1] n (%)				
Not in employment	36 (69.2)	16 (80.0)	20 (62.5)	$x^2(1)=0.18$, p=0.17
In employment	16 (30.8)	4 (20.0)	12 (37.5)	
Education n (%)				
Not in education	21 (40.4)	9 (45.0)	12 (37.5)	$x^2(1)=0.07$, p=0.59

In education	31 (59.6)	11 (55.0)	20 (62.5)	
Clinical measures				
Psychotic symptoms (median)	23.00	24.00	20.00	U=11.00, z=-1.06, p=0.29
QIDS (M±SD)[2]	10.48 (3.72)	11.15 (3.80)	10.06 (3.66)	t(50)=-1.03, p=0.31
K-10 (M±SD)[3]	30.45 (7.75)	33.55 (6.77)	28.45 (7.78)	t(49)= -2.40, p=0.02
GAD 7 (M±SD)[4]	13.04 (5.42)	14.05 (5.38)	12.39 (5.43)	t(49)= -1.07, p=0.29
Functioning and quality of life				
SOFAS (n, median)[5]	66.00	56.50	69.00	U=175.00, z=-2.73, p=0.006
WHO-QoL n (%)				
Very poor	3 (5.8)	3 (15.0)	0 (0.0)	$x^2(4)=0.42$, p=0.02
Poor	14 (26.9)	4 (20.0)	10 (31.3)	
Neither poor nor good	20 (38.5)	7 (35.0)	13 (40.6)	
Good	11 (21.2)	6 (30.0)	5 (15.6)	
Very good	4 (7.7)	0 (0.0)	4 (12.5)	
Sleep				
Sleep duration (M±SD)	7.90 (2.86)	8.08 (2.85)	7.79 (2.91)	t(48)= -0.34, p=0.74
Sleep quality n (%)				
Good	20 (38.5)	7 (35.0)	13 (40.6)	$x^2(1)=-0.06$, p=0.68
Bad	32 (61.5)	13 (65.0)	19 (59.4)	
Chronotype n (%)				
Normal	41 (78.8)	15 (75.0)	26 (81.3)	$x^2(1)=0.07$, p=0.59
Delayed	11 (21.2)	5 (25.0)	6 (18.8)	
Daytime sleepiness n (%)				
None persistent fatigue	43 (84.3)	15 (78.9)	28 (87.5)	$x^2(1)=0.11$, p=0.42
Persistent fatigue	8 (15.7)	4 (21.1)	4 (12.5)	

Notes. UHR = ultrahigh risk, M = mean, SD = standard deviation. [1]Fulltime and part time employment [2]QIDS range = 3-19. [3]K-10 range = 10-50. [4]GAD-7 range = 0-21. [5]SOFAS = 0-100.

5.7.2 Differences between the UK Transitions participating and none participating group

Table 14 shows baseline information for participants included in the study compared to those that did not participate at 6 month follow up. The participating and non-participating groups did not differ significantly on demographic, clinical or sleep variables.

TABLE 14. DEMOGRAPHIC AND CLINICAL FACTORS FOR THE UK PARTICIPATING AND NONE PARTICIPATING GROUP

	Participating group (n=52)	**None participating group (n=16)**	**Statistics**
Age (M±SD)	20.31 (2.68)	19.88 (2.66)	t(66)=-0.57, p=0.57
Gender n (%)			
Male	17 (34.0)	3 (18.8)	$x^2(1)=0.14$, p=0.23
Female	33 (66.0)	13 (81.3)	
Employment[1] n (%)			

Not in employment	36 (69.2)	13 (81.3)	$x^2(1)=0.11$, p=0.34
In employment	16 (30.8)	3 (18.8)	
Education n (%)			
Not in education	21 (40.4)	9 (56.3)	$x^2(1)=0.14$, p=0.27
In education	31 (59.6)	7 (43.8)	
QIDS[2] (M±SD)	10.48	11.81	t(66)=1.12, p=0.26
K-10[3] (M±SD)	30.45	32.28	t(63)= 0.73, p=0.47
GAD-7[4] (M±SD)	13.03	12.38	t(65)=-0.43, p=0.67
SOFAS[5] (median)	66.00	61.00	U=339.500, z=-1.107p=0.27
WHO-QoL n (%)			
Very poor	3 (5.8)	3 (18.8)	$x^2(4)=0.21$, p=0.64
Poor	14 (26.9)	4 (25.0)	
Neither poor nor good	20 (38.5)	6 (37.5)	
Good	11 (21.2)	2 (12.5)	
Very good	4 (7.7)	1 (6.3)	
Sleep duration (M±SD)	7.90 (2.86)	7.07 (2.87)	t(64)=-1.01, p=0.32
Sleep quality n (%)			
Good	20 (38.5)	3 (18.8)	$x^2(1)=0.18$, p=0.13
Bad	32 (61.5)	13 (81.3)	
Chronotype n (%)			
Normal	41 (78.8)	13 (81.3)	$x^2(1)=-0.02$, p=0.83
Delayed	11 (21.2)	3 (18.8)	
Daytime sleepiness n (%)			
None persistent fatigue	43 (84.3)	14 (87.5)	$x^2(1)=0.04$, p=0.75
Persistent fatigue	8 (15.7)	2 (12.5)	

Notes. UHR = ultrahigh risk, M = mean, SD = standard deviation. [1]Fulltime and part time employment.[2] QIDS range = 3-19. [3]K-10 range = 10-50. [4]GAD-7 range = 0-21. [5]SOFAS = 0-100.

5.7.3 Prospective associations between sleep disturbances and UHR status, psychotic symptom severity, functioning and QoL in the UK Transitions sample

To replicate the findings reported in the primary analysis of this chapter (in the Australian cohort), several regression analyses were conducted to explore the association between sleep domains and UHR status, psychotic symptom severity, functioning and QoL at 6 month follow up in the UK transitions sample. Three blocks were included in each analysis; block one included the sleep variable only, block two included the sleep variable in addition to demographic variables (age, gender, employment and educational status), block three included the sleep variable, demographic variables and clinical variables (K10, GAD-7 and QIDS scores).

5.8 **PRIMARY ANALYSIS**

5.8.2 Sleep disturbances and UHR status in the UK Transitions sample

5.8.2.1 Sleep duration and UHR status

To investigate the prospective association between baseline sleep duration and UHR status at 6 months three logistic regression models were constructed. Model A, including sleep duration as the only predictor variable, was not significant (x^2 (1, n=46) = 0.89, p=0.34), suggesting that it was not able to effectively discriminate between UHR and non UHR participants. Sleep duration was not a significant contributor to the model (Beta=0.11 Standard Error=0.13, p=0.32). Model B, containing sleep duration and demographic variables was not statistically significant (x^2 (5, n=46) = 6.74, p=0.24), and sleep duration was not a significant contributor in this model (Beta=0.11, Standard Error=0.24, p=0.45). The final full model (model C) also failed to reach statistical significance, suggesting that it could not discriminate between UHR and non UHR participants (x^2 (8, n=46) = 9.48, p=0.30), and sleep duration did not make a significant contribution to the overall model (Beta=0.15, Standard Error=15.70, p=0.30).

5.8.2.2 Sleep quality and UHR status

The relationship between sleep quality (dichotomised as good or poor) and UHR status at 6 month follow up in the UK samples was explored. Model A (including sleep quality only) was not significant (x^2 (1, n=48) = 0.20, p=0.65), and its contribution to this unadjusted model also failed to reach statistical significance (Beta= -0.28, Standard Error=1.17, p=0.66). Model B including sleep quality and demographic factors was not statistically significant (x^2 (5, n=48) = 5.78 p=0.33), suggesting that the model did not distinguish between UHR and non UHR participants. Sleep quality was not a significant predictor in model B (Beta=-0.36, Standard Error=1.37, p=0.67). Finally model C, including sleep quality, demographic and clinical factors, was not statistically significant x^2 (8, n=48) = 8.72, p=0.37). The contribution of sleep quality to the model was not statistically significant (Beta= -0.20, Standard Error=52.23, p=0.85).

5.8.2.3 Chronotype and UHR status

When examining the prospective association between baseline chronotype (normal or delayed) and UHR status at 6 month follow up model C, which included 8 independent variables (chronotype, age, sex, education status, employment status, K-10, GAD-7, QIDS scores), was not significant x^2 (8, N=48) = 9.00, p=0.34). Chronotype was not a significant contributor to the final bootstrapped model (Beta=0.54, Standard Error =22.66, p=0.54) or model A including chronotype only (Beta=0.25, Standard Error=2.69, p=0.73) or model B including chronotype and demographic variables (Beta=0.80, Standard Error=3.87, P=0.31). These results suggest that chronotype is not significantly associated with UHR status independently or when included as part of a model with demographic and clinical factors in this UK sample.

5.8.2.4 Daytime sleepiness and UHR status

To explore the relationship between daytime sleepiness and UHR status at 6 month follow up, a three stepped model was constructed. Model A included daytime sleepiness as a single predictor variable was not statistically significant (x^2 (1, N=47) = 0.55, p=0.46), daytime sleepiness was not found to be a statistically significant predictor variable in this model (Beta=0.58, Standard Error =3.93, p=0.44). Model B included daytime sleepiness and demographic factors (age, gender, employment and education status), revealing a non- significant model (x^2 (5, N=47) = 5.73, p=0.33), with daytime sleepiness was not a significant predictor in the model (Beta=-0.10, Standard Error =4.09, p=0.88). Finally model C, including daytime sleepiness, demographic and clinical variables was not statistically significant (x^2 (8, N=47) = 9.71, p<0.29). Daytime sleepiness was not a significant contributor in the final model (Beta=-0.16, Standard Error =16.04, p=0.86).

5.8.3 Sleep disturbances and positive symptom severity scores in the UK Transitions sample

5.8.3.1 Sleep duration and positive symptom severity

To investigate the association between baseline sleep duration and psychotic symptom severity at 6 month follow up linear regression analysis was conducted. Model A, containing sleep duration as a single predictor, explained 3% of the variance in positive symptom severity (R squared change = 0.03, F (1, 44) =1.41,

p=0.24), model B including sleep plus demographic variables explained 14% of the variance in symptom severity at 6 months (R squared change = 0.14, F (5, 40) =1.64, p=0.17) but model C with the addition of clinical variables (QIDS, K10 and GAD-7) explained 24% of the variance in psychotic symptom severity (R squared change = 0.24, F (8, 37)=3.22, p<0.007). Sleep duration was not a statistically significant contributor to model A (Beta=0.58, Standard Error: 0.56, p=0.30), model B (Beta=0.32, Standard Error: 0.56, p=0.56) or model C (Beta=-0.56, Standard Error: 0.49, p=0.24).

5.8.3.2 Sleep quality and positive symptom severity

To assess the prospective association between sleep quality and psychotic symptom severity at 6 month follow up in the UK sample three models were constructed. Sleep quality was included as the only predictor in model A, explaining 6% of the variance in positive symptoms severity (R squared change=0.06). When entering demographic variables (sex, age, employment and educational status, the total variance explained by the model was 13% (R squared change 0.13), finally when including clinical factors in addition to sleep quality and demographic variables, the overall model explained 18% of the total variance, R squared change = 0.18, F (8, 39) = 2.91, p=0.01. Sleep quality was a significant contributor to model A (Beta=-4.30, Standard Error: 2.52, p=0.09) and but not model B (Beta=-4.14, Standard Error: 2.78, p=0.16) or in the final model (Beta=0.38, Standard Error: 3.2, p=0.90).

5.8.3.3 Chronotype and positive symptom severity

Exploring the relationship between baseline chronotype and psychotic symptom severity at 6 month follow up revealed a non-significant relationship between the two variables. Model A included chronotype as a sole predictor variable, this model explained 1% of the variance in positive symptom severity (R squared change = 0.01, *F* (1, 46) =0.51, p=0.48). Model B included sleep quality and demographic variables (age, sex, educational and employment status) and explained 15% of the variance in positive symptom severity (R squared change = 0.15, *F* (5, 42) =2.74, p=0.19). Finally, the full model included chronotype, demographic and clinical factors. This model explained 22% of the variance in psychotic symptom severity (R squared change = 0.22, *F* (8, 47) =2.91, p<0.01). Chronotype was not a statistically significant predictor in model A (Beta=2.31, Standard Error: 3.56, p=0.51), model B

(Beta=2.77, Standard Error: 3.46, p=0.41), or model C (Beta=0.26, Standard Error: 3.31, p=0.94).

5.8.3.4 Daytime sleepiness and positive symptom severity

Finally, when examining the association between baseline daytime sleepiness and psychotic symptom severity at 6 month follow up, model A explained <1% of the variance in psychotic symptoms severity (R squared change = 0.001, F (1, 45) = 0.02, p=0.88). Model B including daytime sleepiness and demographic variables explained a slightly higher 16% of the variance in psychotic symptom severity (R squared change = 0.16, F (5, 41) = 1.55, p=0.20). Finally the full adjusted model (model C) explained 22% of the variance in psychotic symptom severity at 6 month follow up (R squared change = 0.22, F (8, 38) = 2.95, p=0.01). Daytime sleepiness was not a statistically significant predictor in models A (Beta=0.53, Standard Error: 3.64, p=0.88) and model B (Beta=-3.57, Standard Error: 4.28, p=0.42) or in the fully adjusted model C (Beta=-2.87, Standard Error: 3.73, p=0.42).

5.8.4 Sleep disturbances and role and social functioning in the UK Transitions sample

5.8.4.1 Sleep duration and role and social functioning

When exploring the association between baseline sleep duration and 6 month follow up SOFAs scores, model A explained 0% of the variance in role and social functioning (R squared change = 0.00, *F* (1, 44) = 0.00, p=0.99). Model B including sleep duration and demographic variables explained 19% of the variance in role and social functioning scores (R squared change = 0.19, *F* (5, 40) = 1.94, p=0.11). Finally the full adjusted model (model C) explained 11% of the variance in psychotic symptom severity at 12 month follow up (R squared change = 0.11, *F* (8, 37) = 2.00, p=0.07). Sleep duration was not a statistically significant predictor in model A (Beta=0.02, Standard Error: 0.77, p=0.99), model B (Beta=0.28, Standard Error: 0.78, p=0.73), or model C (Beta=-0.21, Standard Error: 0.81, p=0.80).

5.8.4.2 Sleep quality and role and social functioning

Linear regression models were constructed to examine the relationship between baseline sleep quality and role and social functioning at 6 months follow up. Model A included sleep quality as a sole predictor variable, this model explained 4% of the

variance in positive symptom severity (R squared change = 0.04, *F* (1, 46) =2.07, p=0.16). Model B included sleep quality and demographic variables (age, sex, educational and employment status) and explained 17% of the variance in positive symptom severity (R squared change = 0.17, *F* (5, 42) =2.30, p=0.06). Finally, the full model included sleep quality, demographic and clinical factors. This model explained 7% of the variance in psychotic symptom severity (R squared change = 0.07, *F* (8, 39) =1.92, p=0.08). Sleep quality was not a statistically significant predictor in model A (Beta=7.03, Standard Error: 4.90, p=0.17) model B (Beta=6.63, Standard Error: 4.81, p=0.17), or model C (Beta=4.87, Standard Error: 6.36, p=0.43).

5.8.4.3 Daytime sleepiness and role and social functioning

Three models were constructed to examine the relationship between baseline daytime sleepiness scores and role and social functioning at 6 month follow up. When daytime sleepiness was included as the only predictor in model A, findings revealed that it explained 3% of the variance in role and social functioning (R squared change = 0.03). When entering demographic variables (sex, age, employment and educational status, the total variance explained by the model increased to 11% (R squared change 0.11), finally when including clinical factors in addition to daytime sleepiness and demographic variables, the overall model explained 8% of the total variance, R squared change = 0.08, *F* (8, 38) = 1.38, p=0.23. Daytime sleepiness was not a significant contributor to any of the three models (model A (Beta=-7.26, Standard Error: 4.43, p=0.10), or model B (Beta=-2.88, Standard Error: 5.54, p=0.61), model C (Beta=-0.81, Standard Error: 5.50, p=0.89).

5.8.4.4 Chronotype and role and social functioning

The association between baseline chronotype and role and social functioning at 6 month follow up was explored in a linear regression analysis. Model A, comprising of chronotype as a single predictor, explained <1% of the variance in functioning (R squared change = 0.009, *F* (1, 46) =0.40, p=0.53), model B including chronotype plus demographic variables explained 18% of the variance for functioning at 6 months (R squared change = 0.18, *F* (5, 42) =1.98, p=0.10) and model C with the addition of clinical variables (QIDS, K10 and GAD-7) explained 8% of the variance in psychotic symptom severity (R squared change = 0.08, *F* (8, 39)=1.80, p=0.10).

Chronotype was not a statistically significant contributor to any of the three (model A (Beta=-3.85, Standard Error: 6.38, p=0.53), model B (Beta=-4.28, Standard Error: 6.51, p=0.46) and model C (Beta=-1.71, Standard Error: 7.69, p=0.80). These results suggest that chronotype is not an important predictor variable when considering functional outcome of UK help seeking youth.

5.8.5 Sleep disturbances and Quality Of Life in the UK Transitions sample

Due to the small number of participants in the QoL groups at 6 month follow up (Poor QoL=7, neither good nor bad QoL=14, good/very good QoL=24) it was not possible to conduct a multinomial regression analysis using this data. The analysis would have been severely underpowered, therefore invalidating any results generated.

5.9 **DISCUSSION**

This study investigated the prospective associations between specific sleep domains (duration, quality, chronotype and daytime sleepiness) and UHR status, psychotic symptoms, functioning and QoL in a large Australian and UK help seeking sample of young people. Several key findings emerged from this study. Firstly, daytime sleepiness was found to be associated with UHR status, increased positive symptom severity one year later in the Australian sample. Secondly, there was a prospective association between daytime sleepiness and poor QoL, which has not been reported by previous research. Thirdly, a delayed chronotype was related to poorer role and social functioning at 12 month follow up. Fourth, after controlling for demographic and clinical variables and sleep duration were not significantly related to *any* of the study outcomes at 6 or 12 month follow ups. The results presented in this study support and extend previous cross-sectional studies reporting that sleep disturbances are associated with symptoms and functioning in UHR youth (see systematic review and meta-analysis in chapter 3 of this thesis). Furthermore, this study provides novel evidence to suggest that there is specificity pertaining to *which* sleep domains relate to symptoms, functioning and QoL in help seeking youth.

5.9.2 Sleep disturbances and UHR status

In support of hypothesis one, baseline daytime sleepiness was found to be associated with UHR status at 12 month follow up. This finding is aligned with previous research reporting that general sleep related difficulties assessed by the SIPS were significant predictor variables, within a larger model, predicting transition to psychosis (Ruhrmann et al., 2010a). Arguably, the results from this Transitions study provide additional evidence to support the inclusion of sleep related variables in future psychosis prediction models. It also extends existing research through demonstrating that there may be some specificity in the type and timing of sleep problems associated with psychosis risk status (i.e. daytime sleepiness rather than sleep duration, quality and chronotype which were not found to be significantly associated with UHR status at 6 or 12 month follow up). Sleep disturbances are recognised as a non-specific symptom preceding psychosis, demonstrated by sleep items included in well used screening tools for psychosis (e.g., SIPS). However, further exploration into the contribution of specific sleep disturbances in prediction models and screening for distinct sleep disruptions in assessment tools for psychosis would be a fruitful line of enquiry.

5.9.3 Sleep disturbances and positive psychotic symptom severity

In support of hypothesis 2, this study revealed a significant association between daytime sleepiness and increased psychotic symptom severity at 12 months, when accounting for clinical and demographic factors. These findings are consistent with research involving patients with psychotic illness experiencing sleep related fatigue (Waters et al., 2013). Waters et al. (2013) and colleagues revealed that daytime sleepiness did not always occur with measurable sleep disruptions (e.g., reduced sleep duration) and were consequently a reflection of sleep satisfaction. Furthermore, they theorised that impairments to brain regions such as the prefrontal cortex and angulate cingulate impact on processes including motor and executive control in addition to arousal and drive. Critically, these regions are implicated in both daytime sleepiness and psychiatric disorder and may explain the co-occurrence of the experiences (Sawant and Thakurdesai, 2018, Waters et al., 2013). The authors highlight daytime sleepiness as a key target for intervention in psychosis patients (Waters et al., 2013). The results presented in this Transitions chapter provide

evidence to indicate that daytime sleepiness should also be targeted in help seeking youth as this may improve the severity of later psychotic symptoms.

5.9.4 Sleep disturbances and role and social functioning

Consistent with previous research involving a subset of the Australian Transitions cohort (Glozier et al., 2014) and in support of hypothesis 3, the findings from this study show that a delayed sleep onset time (between 2am-6am) was related to poorer functioning at 12 month follow up, when controlling for demographic and clinical variables. This was the single sleep domain at baseline to be related to subsequent functioning in the Australian sample. It is unsurprising that biological rhythms that are out of sync with the environment will negatively impact on daytime activities and societal demands (Gariépy et al., 2019). Consequently, whilst youth may have a natural disposition to experience a delayed sleep phase, this could create fertile ground for later difficulties in those with a vulnerability to mental health problems. It is important to note that the findings from Glozier et al (2014) (Glozier et al., 2014) included a depression subgroup of the Australian Transitions sample. However, their findings along with those from this current study suggest that treatments that target the timing of sleep could be beneficial for UHR youth and more broadly all young people seeking health for low level mental health disturbances. This is important as providing interventions that will improve functioning as young people enter employment, leave education and gain increasing social independence is likely to be beneficial at an individual and societal level. Understanding the impact of the timing of sleep (or circadian rhythms) on functioning alongside sleep quality and quantity is a meaningful and nuance area to be explored by future research.

5.9.5 Sleep disturbances and QoL

The final area investigated in this study was the unexplored relationship between sleep disturbances and QoL. In support of hypothesis 4 and the distress/protection vulnerability model (Ritsner, 2007), both impaired sleep quality and persistent daytime sleepiness were found to be statistically significant predictor variables of poor QoL at 12 month follow up. It is an important finding of this study that it was not possible replicate this analysis in the UK sample due to the small number of participants in the QoL groups (Poor QoL=7, neither good nor bad QoL=14, good/very good QoL=24). Nonetheless, the novel findings from the Australian

sample align with recent research involving First Episode Psychosis patients reporting that PSQI measured sleep quality and fatigue was related to poorer WHO-QoL assessed QoL (Ong et al., 2020). Ong et al. (2020) proposition that poor sleep quality and daytime sleepiness negatively impacted on patients perceptions of life, achievements and desire for personal growth (Hofstetter et al., 2005b). The findings presented in this chapter support such research and suggest the presence of an underexplored relationship between sleep and quality of life which is detectable even before the First Episode of Psychosis. Therefore, the replication of these findings in longitudinal studies involving help seeking samples and subjective and objective QoL instruments would enable the mechanisms underlying poor sleep quality and daytime sleepiness in QoL to be better understood.

5.9.6 Future research considerations

The bidirectional relationship between sleep problems and psychotic symptoms, functioning and QoL is beyond the scope of this study but is nonetheless a key consideration. It may be that poor sleep is driven by psychotic symptoms, poor functioning or reduced QoL. The longitudinal design of the Transitions studies has enabled the exploration of the prospective association between sleep disturbances and later symptoms. However, future research should seek to extend this study by examining the role of earlier sleep disturbances, potentially those that pre-date symptoms, to better understand whether early sleep disturbances are a signal for poor outcomes including subclinical psychotic symptoms, poor functioning and impaired QoL. Furthermore, including a longer follow up period, greater than 12 months would be key, as findings from the UK Transitions sample including a 6 month follow up did not reveal significant associations. Consequently, earlier measurement of the exposure variable and longer follow up periods would allow adequate time for adverse outcomes to present and be measured.

This study included a single measurement for the independent and dependent variables. However, future research should seek to explore the cumulative effects of persistent sleep difficulties and risk of later difficulties over several time points to build a comprehensive picture of the relationships between sleep and subsequent problems.

The mechanisms that underlie sleep disturbances and psychotic symptoms have been explained in the literature by a neurodevelopmental diathesis stress model (Lunsford-Avery and A. Mittal, 2013) and a cognitive model (Freeman et al., 2012) which are multifaceted (see chapter 1 of this thesis for further discussion). These models suggest that the relationship between sleep and psychosis are not linear but involve mediating factors. Future research should seek to test such models to expand on our understanding of sleep disturbances and key outcomes in clinical and non-clinical groups.

5.9.7 Limitations

It is important to acknowledge the limitations of this study. Firstly, this study aimed to replicate the findings from the Australian Transitions study using the UK Transitions sample. However, the findings from the UK sample did not support or mirror the results presented in the primary analyses of this chapter. This may be a consequence of a substantially smaller sample size in the UK Transitions study and a 6 month rather than 12 month follow up period. It is therefore possible that the UK Transitions study was underpowered with insufficient time between data collection points to enable examination of potential effects. In addition to the methodological differences between the two samples, the lack of replication may also be a reflection of the demographic and clinical differences between the Australian and UK groups. For instance, the UK sample had a higher overall mean age and a higher percentage of participants not in employment or education. In relation to clinical factors, the UK sample had an overall higher median score for psychotic symptoms and mean QIDS, K-10, and GAD 7 score. Furthermore, the overall mean score for functioning was lower in the UK sample. These baseline between group differences were not compared statistically but might be important factors when considering why findings were not replicated in the UK sample. Despite the lack of replication in findings, there remains a need to examine the unique contributions of different types of sleep difficulties (such as duration, quality, chronotype and fatigue) on key outcomes in UK UHR youth, using valid and reliable sleep questionnaires. Secondly, the assumption of normality was violated and transformations failed to normalise the distribution of the data for SOFAS and psychotic symptom severity scores. Consequently, all regression analyses were performed using a bootstrapping method.

Whilst this is a recommended approach when equivalent non-parametric tests are not available (Field, 2013), it is important to recognise the limitations of this approach and to interpret the findings with caution. Thirdly, analyses were conducted with cases that included all data required for the specific analysis. This method to handling missing data is reported elsewhere in the literature (Seaman and White, 2013), but can result in restrictions to the number of overall participants included in the analyses (and differences in the n's across the various analysis conducted). Fourthly, the QIDs and K-10 measure both include questions assessing sleep disturbances. Whilst it is acknowledged that disruptions to sleep are an integral component of depression and distress in addition to being fundamental to UHR status, the inclusion of these questions may have confounded the analysis. Consequently, each set of analysis included a model without clinical factors (depression, distress and anxiety), to examine the relationship and contribution of sleep variables on the outcome of interest.

5.9.8 Conclusion

This study presents findings to show that UHR youth experience lower sleep duration, reduced sleep quality and increased daytime sleepiness compared to their non-UHR counterparts. Analysis of longitudinal data revealed daytime sleepiness to be associated with UHR status, increased positive symptom severity and reduced quality of life one year later. A delayed chronotype was related to poorer functioning and daytime sleepiness was associated with poor QoL at 12 month follow up. Sleep duration and quality were not significantly related to *any* of the study outcomes at 6 or 12 month follow ups. Therefore, it is arguable that specific baseline sleep difficulties may be an important consideration when developing treatment plans for youth seeking help for their mental health problems. Further research into tailored sleep treatments for this group of patients, which account for other subclinical symptoms, would be an important line of enquiry for future research. These findings support the concept of recognising and treating sleep difficulties independently of early symptoms in help seeking youth, rather than treating sleep as a secondary consequence of co-morbid mental health difficulties during this early stage.

Chapter 6. **PATIENT AND PUBLIC INVOLVEMENT**

6.1 **BACKGROUND**

There is accumulating evidence to suggest that there is a prospective association between sleep disturbances and Psychotic Experiences (PE) in clinical and non-clinical samples (see chapters 3- 5 of this thesis). Despite strong signals to indicate that sleep disturbances predate PE, it is not possible to draw definitive conclusions concerning the direction of causality due to the observational nature of existing studies (Davies et al., 2017).

To test causality, the Bradford Hill criteria proposes nine fundamental conditions that should be fulfilled (Fedak et al., 2015). The first criterion is 'strength of association', which suggests that large associations reported in research may be indicative of a causal relationship rather than attributable to bias or confounding variables. The strength of association can be determined by statistical significance, assessment of methodology and weight of the evidence in the context of other high quality research. Criterion two is 'consistency', highlighting a need to replicate findings across conditions and populations with consistent results. Criterion three is concerned with 'specificity', or the notion that causal relationships are more likely when the exposure is linked to a *specific* disease. Criterion four is 'temporality', which emphasises the importance of the exposure preceding the outcome. Designing studies to assess the temporal progression between exposure and outcome are essential to ascertaining causality. The fifth proposed criterion is 'biological gradient', which captures the importance of a dose response relationship between the exposure and outcome. Criterion six is concerned with 'biological plausibility' or the ability for existing biological or social models to explain the observed direct or indirect association. Criterion seven is 'coherence', which states that the cause and effect relationship should be sensible and in line with the broader literature and understanding of the area. The eighth criterion is 'experiment', which focuses on a need for experimental causation and manipulation to provide support for causal relationship. The final criterion is 'analogy', which is concerned with proposing and testing mechanisms of actions across a range of strong and weak evidence (Fedak et al., 2015) .

A number of the Bradford Hill criterion have been applied to assess the association between sleep disturbances and PE throughout this thesis. For instance chapter 4 (The ALSPAC chapter) examines the strength of association between early sleep disturbances and later PE; in addition to temporality and biological gradient through the inclusion of sleep disturbances in childhood and subsequent PE in adulthood. Chapter 5 (The Transitions Chapter) explores consistency through replicating analysis across two separate help seeking samples and tests the neurodevelopmental theory of schizophrenia (described in chapter 1) which links to the biological plausibility criterion. It is important to continue driving this area forward through research that tests the Bradford Hill Criteria to increase understanding concerning the direction of causality between sleep disturbances and PE.

To continue exploring the causal relationship between sleep disturbances and PE experimental studies are vital. There have been a small number of intervention studies on sleep and PE over the recent years (Reeve et al., 2018a, Freeman et al., 2017). One experimental study (Reeve et al., 2018a), randomised 68 non-clinical volunteers to one of two groups; a sleep loss condition (restricted to 4 hours over 3 nights) and a control condition (standard sleep). In this within subjects cross-over designed study, participants alternated between sleep conditions over a two week period, with a wash out period built into the weekends. Sleep was assessed objectively using actigraphy and PE measured using the specific psychotic experiences questionnaire. The authors reported a statistically significant increase psychotic symptoms (paranoia, hallucinations), cognitive impairment (cognitive disorganisation, working memory) and negative affect in the sleep loss condition. Furthermore, mediation analysis revealed negative affect to be a mediating factor in the relationship between sleep loss and increased PE. This study demonstrates that manipulating sleep produces changes in PE in a non-clinical sample using a robust research design. However, ethical considerations surrounding the use of sleep restriction techniques in clinical samples requires attention by future researchers. It may be more ethically sound and feasible to adopt alternative methods in clinical populations.

In a recent study involving a sleep intervention, Freeman et al. (2017) randomly assigned 3,755 students (across 26 UK universities) for receive online CBTi

(delivered via a web based platform called Sleepio) or treatment as usual. Sleep was evaluated using an 8-item scale (the Sleep Condition Indicator Scale); paranoia assessed using the Paranoid Thought Scale and hallucinations using the Specific Psychotic Experiences questionnaire. Finding revealed that 10 weeks of the CBTi intervention resulted in a reduction in insomnia, paranoia and hallucination scores. The authors highlighted the self-reporting rather than objective measurement of sleep disturbances to be a limitation of the study. Furthermore, the non-clinical nature of the sample limits the generalisability of the findings, therefore warranting replication in clinical groups.

As part of a pilot study, Bradley et al. (2018) offered an 8 session CBT intervention in a sample of 12 UHR patients experiencing sleep disturbances. The intervention targeted stimulus control, regulation of daily activities and circadian rhythm. The authors reported that acceptability of a sleep focussed intervention was high as indicated by completion rates of the 8 sessions (89%). Furthermore, there were significant improvements to sleep disturbances (measured by the insomnia severity index, PSQI and actigraphy and sleep diaries), with 6/11 patients reporting a reduction in insomnia levels to below clinical threshold. Furthermore, improvements in mood (assessed by the Depression, Anxiety and Stress Scale, The Warwick–Edinburgh Mental Well-being Scale) and PE (measured by the Green Paranoid Thoughts Scale and the Specific Psychotic Experiences Questionnaire) were recorded post intervention. This study did not adopt a randomised design with blinding of researchers and included a follow up period of one month. Therefore, future research building on this study would provide additional evidence to support our understanding how PE's change in response to altered sleep.

The studies described above demonstrate a shift in the literature, towards investigating the causal relationship between sleep disturbances and PE through a range of interventions and treatments. The pervasiveness and complexity of sleep disturbances and co-occurring PE requires that highly adaptable interventions are utilised (Waite and Sheaves, 2020, Sheaves et al., 2018, Barrett et al., 2020, Blake et al., 2017, Myers et al., 2011, Chiu et al., 2018). For instance, Cognitive Behavioural Therapy (CBT) for nightmares has been shown to be an effective intervention for patients diagnosed with non-affective psychotic disorder (Sheaves et al., 2015a). It

involves a collection of cognitive, behavioural and psychoeducational components to address perpetuating and maintenance factors contributing to nightmares (Taylor and Pruiksma, 2014, Sheaves et al., 2019). This intervention is tailored to the patients nightmares and incorporates Imagery Rescripting (IR) to enable participants to consider alternative outcomes to their nightmares. Imagery rehearsal is practiced between sessions and strategies to reduce arousal, negative thought content, fear associated with the nightmare and promotion of coping strategies are integrated into the sessions (e.g., grounding and relaxation techniques, adjusting sleeping) (Sheaves et al., 2019). CBTi is a similar intervention that targets symptoms of insomnia rather than nightmares (Waters et al., 2017). A recent study investigated the efficacy of CBT for insomnia (CBTi) to further understand the variability in patient outcome following intervention (Waters et al., 2020). Using Grade of Membership analysis this study revealed three profiles of responders to CBTi: (i) non-responders, (ii) partial responders and (iii) strong responders. Significant predictors of treatment response included severity of negative affect, psychotic symptom severity and higher doses of antipsychotic medication. This important research study highlights that whilst interventions for sleep disturbances can be effective, there are further factors beyond the efficacy of the intervention that influence treatment response (Waters et al., 2020).

Although the interventional studies described above provide encouraging findings, they also have several limitations which need to be addressed to move closer to understanding causality in the context of Psychosis. For instance, they examine sleep disturbances and PE in the context of non-clinical samples (or a small sample of UHR patients [n=12]); include short follow up periods (e.g., one month); involve subjective sleep assessments; and in the UHR sample there is an absence of randomisation which could introduce bias.

Therefore, this there is a need for further interventional studies which utilise findings from this thesis and the studies above to examine the direction of causality between sleep disturbances and PE as a next step in this area. Prior to assessing the effectiveness of a sleep intervention in a UHR sample, it is key to establish effective strategies for recruitment and the feasibility of assessing sleep using objective and self-reported measures in ARMS youth.

The use of patient and public involvement consultation groups are an efficacious approach to collecting the views and experiences of representative groups to inform research (Wilson et al., 2018b). The involvement of patients and the public in the co-design of research has increased significantly since changes to the UK national health research governance framework in 2005 (Wilson et al., 2018b). In healthcare, collaborating with patient groups to generate and execute research studies has enabled high quality and meaningful research to be developed and implemented into practice (Stewart and Liabo, 2012). The experiences of key stakeholders are often translated into research to contribute a wider set of ideas which inform the rationale, methods, interpretation or dissemination of research (Rashid et al., 2017). This is important as it bridges the gap between research and practice, through incorporating patient and public evaluations during knowledge production rather than after new practices and conventions are implemented (Gillard et al., 2012).

The real time experiences and insights of patient and public involvement (PPI) groups are most effective and impactful when those that would have been involved are carefully selected and the collaboration process is well planned (Rise et al., 2013). For instance, it is important that contributors have direct experience of the research area and there is a degree of diversity in the individuals involved to provide fair representation of patient views (Boivin et al., 2018). To access the expertise that these contributors bring, researchers should consider which stage(s) of the project PPI consultations will be held, what contribution they would like from PPI groups and how views will be gathered and incorporated (Crocker et al., 2017, Buck et al., 2014). Such considerations allow for meaningful rather than tokenistic involvement of patient and public groups (Andrews et al., 2015).

This study sought to establish the feasibility and acceptability of proposed recruitment methods and research design for a future feasibility study. It was not possible to gather this information through the systematic review and meta-analysis (see chapter 3) and so therefore was an important step in developing the study.

The PPI consultation had three key aims:

1) To identify effective strategies for recruiting ARMS participants

2) To ascertain key methods for keeping participant engaged throughout the duration of the study
3) To establish the feasibility of the proposed methods for collecting sleep data

6.2 **METHODS**

6.2.2 Participants

Participants included 9 young people (7 female and 2 male) aged between 12-21 years old, from the NIHR young person's advisory group and members of the mental health group in Staffordshire. All participants had first-hand experiences of utilising secondary mental health services for a range of mental health conditions including schizophrenia and bipolar disorder.

6.2.3 Setting

The session was held at the Learning centre at the University of Birmingham on 7th July 2018 for one hour.

6.2.4 Method

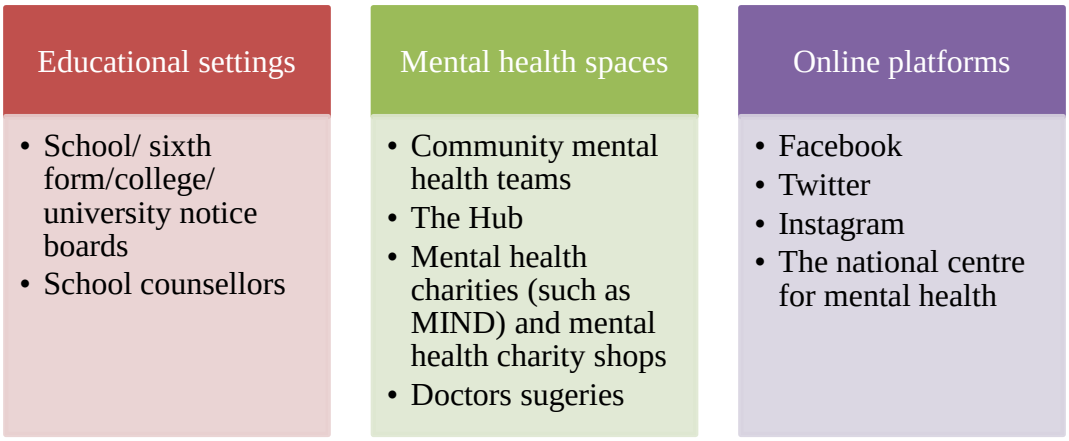
A short introduction of the study and aims of the session was provided by the PhD student in the form of a 10 minute PowerPoint presentation. Participants were then presented with seven questions presented in an interactive discussion format, accompanied by a hard copy of questions distributed among participants for individuals that were more comfortable writing down their answers rather than verbalising them in a group setting. An actigraph was also shown to participants for demonstration purposes. Each question was discussed for approximately 10 minutes or until saturation was achieved.

6.3 **RESULTS**

6.3.2 Recruitment

Participants were asked 'how do you think we could find young people to take part in this study'? A range of suggestions were provided (see figure 1).

Figure 1. Participants suggestions for spaces to display study posters



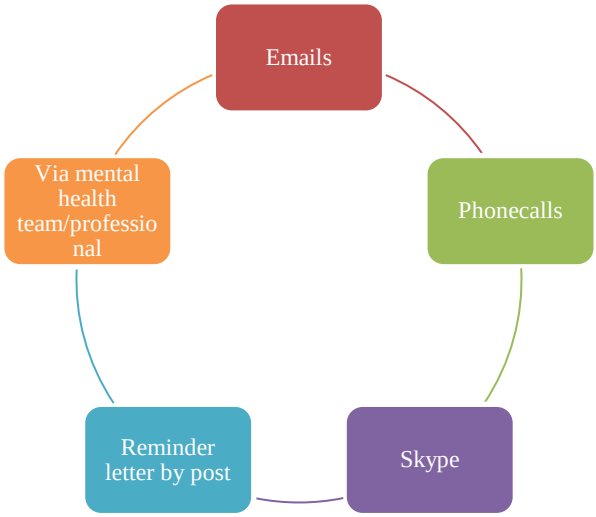
There was a group consensus that displaying posters including study details in a wide range of settings attract potential ARMS patients. The group suggested that involving healthcare professionals in the identification of young people would be a key strategy. Individuals described differences in the demographics using different online platforms (e.g., there are less young people (e.g., age 16-21) using Facebook so twitter may be more suitable for attracting younger people under 21. But Facebook may be useful for those 21+) as an important consideration. The PPI group queried the possibility of approaching patients diagnosed with a psychotic illness to explore whether they also have a family member that could be 'at risk'. The group also recommended displaying the posters for controls in different spaces, to maximise recruitment chances.

6.3.3 Participant engagement

The second question discussed during the PPI session was 'how can we keep in touch with participants over the six months that they are involved in the study?'. The group suggested utilising a combination contact methods (see figure 2) which are agreed with each participant during the first assessment appointment. Confirming appointments dates via email following the first assessment and reminder emails or text messages one week prior to the follow up assessments were proposed as prompts to support with engagement of participants. The group highlighted that phone calls can be difficult for many patients and can provoke anxieties, particularly when contact is made from an unknown number. Consequently, it was suggested that 'a text or call should be an option rather than prescribed'. For participants struggling with their mental health symptoms at follow up assessments, the option of collecting

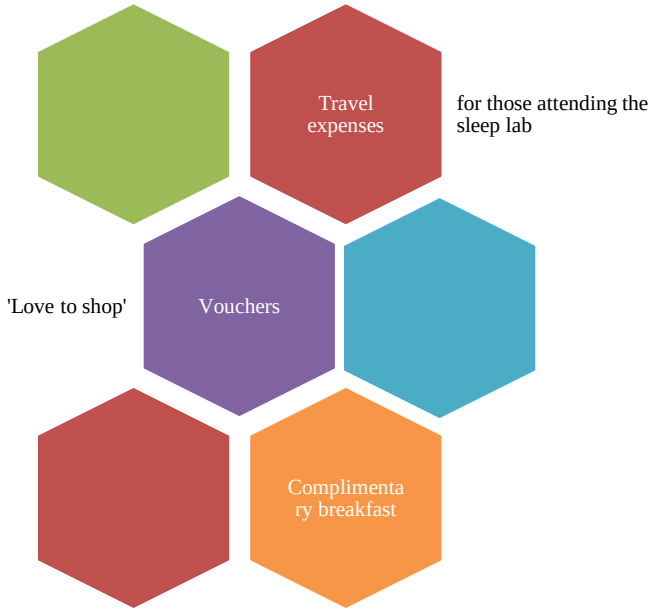
data via skype/telephone could be considered to prevent participants being lost at follow up.

Figure 2. Staying in contact with participants



The third question asked to the group was 'What kind of incentives would be fair for participants that become involved?'. A spectrum of responses was provided for this question, ranging from suggestions that there should be no incentives offered due to contribution that would be made through the research to others with similar experiences. It was agreed that participants who consented to the PSG arm of the study should be compensated in the form of travel expenses, complimentary breakfast and potentially £10-£20 in money or vouchers. One member of the group suggested that this is particularly important for those who may have caring or employment commitments. The group debated the timing of when vouchers or money should be offered to participants, with some suggesting that providing vouchers at the final follow up assessment may be unethical. One member of the PPI group stated that 'it is important to have incentives as lots of participation is involved. Not massive [amounts of money] though- it's not needed as shouldn't be hard to recruit'.

Figure 3. Incentives for participants involved



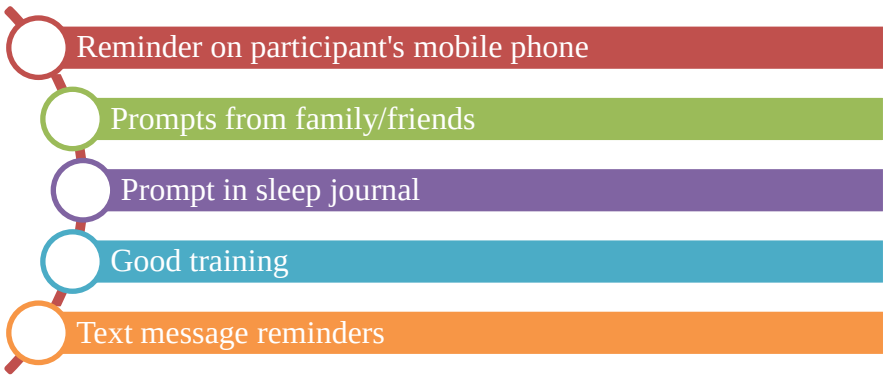
6.3.4 Assessing sleep disturbances

The PPI group were asked ‘do you think that young people will wear the wrist watches for 7 days’? 8/9 members of the group stated that they would wear the actigraph for 7 consecutive days. The device was likened to watches and/or Fitbit which are commonly worn overnight. It was also agreed that individuals who consent to the study will understand that wearing the actigraph is a requirements of the study and should therefore agree to this. One person described a preference for not wearing any device on his wrist at night. Therefore, the question of whether the actigraph could be worn on the ankle, whether the straps could be changed to make it more comfortable and whether the actigraph’s are water resistant were relevant questions asked by the group.

The event button on actigraphs provide an important marker on the data to indicate the wake up time and sleep onset time of participants. The group discussed the question of *how* to remind young people to press the events button. The responses included offering to remind participants through daily text messages; encouraging participants to set reminders on their mobile phones to ‘press the button’; suggesting that family/friends that they may live with prompt where possible; or including a question on the sleep journal to remind participants would be useful. The PPI group agreed that thorough initial training surrounding how to use the actigraph and the significance of the event button for data interpretation would also be essential. The

group described the sedative effects of mental health medications and how mental health symptoms can impact on memory. This could result in participants forgetting to press the events button and consequently should be accounted for during data analysis.

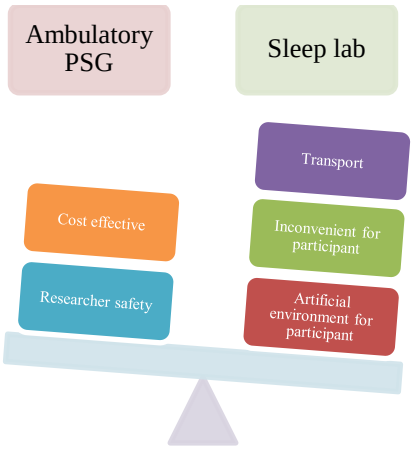
Figure 4. Prompting participants to press the actigraph event button



The option of offering participants ambulatory PSG monitoring was discussed as an alternative to overnight monitoring at the sleep laboratory. The PPI group suggested that both options should be discussed explicitly with participants prior to consenting to the research. The group gave thoughtful consideration to the positives and negatives of both options, describing home monitoring as more cost effective for the researcher due to the lack of travel expenses to be reimbursed to participants. However, the safety of the researcher lone working would be a concern, particularly if applying the sensors in the patients home during unsociable hours.

For the participant, attending for overnight monitoring may require more time and effort but may be an 'interesting' experience. Participants may struggle to sleep outside of their home in a 'strange environment' and so may prefer being at home. Travel considerations are also important to consider due to limited public transport connections to the University of Warwick and may influence the demographics of participants willing to take part in this arm of the study (e.g., those that live in a closer proximity of the University may be more willing to consent and travel to the sleep lab). Mental health symptoms were also highlighted as a potential barrier to participants travelling to the sleep laboratory.

Figure 5. Cost-benefit of ambulatory vs sleep lab PSG monitoring



To gauge the acceptability of the planned study, the PPI group were asked whether they would take part in the proposed research. There was a general consensus across the group that they would take part and requested for posters to be shared with the PPI group following ethical approvals. One participant commented that they would take part as 'it's an interesting topic and control participants may have an interest in their own sleep patterns. It's good to be part of something that may make a difference'.

6.3.5 Additional feedback

The group provided feedback on the study beyond questions asked as part of the focus group. These suggestions included avoiding the word psychosis on recruitment posters as this can be stigmatizing and may exclude those that are not familiar with the term psychosis. One suggestion was that it would be acceptable to list symptoms rather than to use the term 'psychosis'.

The group expressed that the planned study could raise issues about awareness of the at risk mental state. It was suggested that individuals seeking help for their mental health problems may not know that they are at risk of developing a mental health problem or that they are 'at risk' for psychosis. The PPI group proposed that the study could tell people more about psychosis and what symptoms present before diagnosis or perhaps could signpost to health professionals and resources to access further information.

6.4 **DISCUSSION**

Nine young people from the NIHR youth advisory board provided their expert opinions on the feasibility and acceptability of a study seeking to examine the prospective association of sleep quality and quantity in ARMS youth. Several important areas of consideration were discussed during the focus group to increase recruitment, engagement and to recognise the contribution of participants that would take part in this study. This collaborative process of engaging young people in the development of research is critical to producing research that is impactful and acceptable to those that will become involved.

The process of identifying an established group of young people with lived experiences of mental health difficulties to participate in this focus group was challenging. Whilst there are several groups across the Midlands area including carers and older adults, there were barriers to finding a suitable PPI group due to demographic of members in the groups, costs and time/date availability of set meeting sessions. The moral and pragmatic need to consult with a PPI group is often unstructured and riddled with complexities whilst seeking to balance meaningful and effective patient and public involvement (Forbat et al., 2009, Bagley et al., 2016). Furthermore, ethical considerations relating to the topic and language used with children and young people require significant consideration (Mitchell et al., 2019). Therefore, understandably research has called for adaptable infrastructure to support with guiding the collaboration with PPI contributors in research (Garfield et al., 2015) as well as the implementation of a diverse use of models (e.g., involvement on trial committees, discrete specified activities) (South et al., 2016, Howe, 2018).

The discussions exploring recruitment strategies highlighted a need for intensive, diverse and dynamic approaches to identifying eligible participants to be invited to the study. This is a well-recognised strategy within research involving ARMS patients (Fusar-Poli et al., 2016b). For instance, research investigating the effectiveness of two recruitment strategies among ARMS patients (a screening method in secondary mental health services and a population referred to an early psychosis clinic) revealed that screening identified a three-fold higher detection rate compared to the referral method (Rietdijk et al., 2012). This study emphasizes the variations in recruitment strategy success and perhaps a need for a layered approach

to recruitment where resources permit. It also underlines the importance of specialist early psychosis clinics in research, particularly in engaging young people that are likely to transition to psychosis rather than experiencing transitory symptoms (Minichino et al., 2019).

The PPI group expressed that a flexible and sensitive approach should be taken to engaging participant in the study following recruitment. This included inviting participants to express how they wish to be contacts to reduce the numbers of participants lost at follow-up. Predictors of disengagement of ARMS patients from longitudinal research include stage of study, frequency of invitations, participation burden and severe negative symptoms; demonstrating that drop-out rates are multifaceted (Leanza et al., 2020). However, ensuring that participant requests are accommodated where possible may be important in increasing engagement in research.

Assessing the acceptability and feasibility of sleep disturbances using actigraphy and polysomnography was an important focus of the PPI group session. The demands of measuring sleep using objective measurements were considered, with the group suggesting that there would be significant costs to the patient for overnight PSG monitoring at The University of Warwick. This finding was unsurprising, particularly when considering the lack of studies involving ARMS patients undertaking PSG (Gonçalves et al., 2016). Furthermore, there are a limited number of studies involving actigraphy in ARMS samples despite the findings that actigraphy is an inexpensive and sensitive method of assessment in ARMS youth (Lunsford-Avery et al., 2015). Therefore, this PPI consultation provides evidence to indicate that objective assessments of sleep may be considered burdensome to some individuals but that this should be balanced with a need to further knowledge of sleep quality and quantity in at risk groups.

The process of engaging with an expert group to shape a future feasibility study provided an important opportunity to think critically about the interface between scientific knowledge and patient experience in producing rigorous, patient centred, representative and well informed research (Realpe and Wallace, 2010).

Chapter 7. **DISCUSSION**

7.1 **SUMMARY OF FINDINGS**

The findings presented in this thesis suggest that there is a prospective association between sleep disturbances and Psychotic Experiences (PE) across clinical and non-clinical groups. In the general population, sleep disturbances may appear early as part of a normal developmental trajectory, however those that persist appear to be related to persistent PE in adulthood. In help seeking youth and Ultra High Risk (UHR) patients, sleep difficulties are shown to be associated with poorer outcomes including severity of PE, reduced QoL and functioning.

This thesis aimed to explore the relationship between sleep disturbances and PE across time and populations. Specifically, it examined the timing, specificity and persistence of sleep disturbances and their prospective association with PE along the psychosis continuum. Several key findings emerged from the studies presented, including (i) UHR and help seeking youth reported reduced sleep quality, quantity and circadian rhythm dysfunction which were associated with symptoms, poor functioning and reduced QoL *and* (ii) difficulties initiating and maintaining sleep, in addition to parasomnias, during childhood and adolescence were associated with the occurrence and persistence of PE in early adulthood. These findings are important as they suggest that sleep disturbances are not simply a consequence of psychotic illness or medication effects, but they may contribute the development and severity of psychotic illness. Equally, they are not necessarily non-specific symptoms that emerge prior to the onset of psychotic disorder. Instead, there is some specificity in relation to which types of sleep problems relate to increased PE and therefore risk for psychosis. There is strong evidence presented in this thesis to suggest that the relationship between sleep disturbances and PE is maintained over time and populations.

7.2 **STRENGTHS AND LIMITATIONS**

This thesis has the following strengths: (i) it robustly summarises existing evidence surrounding sleep disturbances and risk for psychosis using a narrative and meta-analytic approach, providing timely evidence to suggest that there are differences in how specific sleep disturbances (e.g., wake after sleep onset, sleep duration) relate to

PE (see chapter 3); (ii) it provides novel evidence on sleep disturbances and PE assessed across *multiple* time points, using well-validated measures, to build an understanding of the role of *persistent* early sleep disturbances and PE that continue into adulthood (see chapter 4); and (iii) it demonstrates that sleep disturbances are related to not only PE but other key but under-investigated outcomes (namely functioning and QoL) in youth seeking help for early mental health difficulties.

However, it is important to point out key limitations of this thesis. Firstly, chapter 3 includes a range of studies that differ in their approaches to assessing sleep disturbances (e.g., actigraphy, polysomnography, PSQI), limiting the number of studies in the final meta-analysis. This may reflect the early stages of this research area; with a lack of agreement on how to measure sleep in UHR youth and a need to standardise the way sleep is assessed and reported in clinical samples. Secondly, the studies presented in chapters 4 and 5 were observational in their design and did not manipulate sleep and then assess changes to PE. This means that it is not possible to draw conclusions on the direction of causality. Consequently, chapter 6 of this thesis presents the findings from a patient and public consultation which can be used to inform future interventional studies to continue to drive forward knowledge in this area. Finally, sleep disturbances described in chapters 3-5 of this thesis were self-reported rather than objectively measured. This has implications for two reasons: firstly, self-reported sleep may be subject to reporting biases (by both parents and children) and secondly, if there are biological or physiological markers of sleep (e.g., abnormal sleep spindles) linked to the pathophysiology of Psychosis, these have not been measured or explored but may be a fundamental mechanism underlying the relationship. Therefore, the feasibility of assessing sleep using actigraphy and polysomnography in future intervention studies is explored in chapter 6.

7.3 **CLINICAL IMPLICATIONS**

Research has shown that clinicians in mental health teams often assess sleep problems informally, with no treatment offered or basic sleep hygiene and/or pharmacology rather than recommended treatments such as CBTi or Imagery Rescripting for individuals with difficulties such as insomnia or nightmares (O'Sullivan et al., 2015, Rehman et al., 2017, Committee et al., 2010). Sleep problems are often seen as secondary or corollary to the psychiatric symptoms and

therefore not given adequate focus despite being a central complaint for many young people (Rehman et al., 2017). Treatment for sleep problems are often limited by service level challenges (such as lack of time and training), patient factors (including lifestyle) and environmental issues (e.g., inpatient settings). Given the effectiveness of psychological treatments such as Cognitive Behavioural Therapy for Insomnia (Bradley et al., 2018) and the impact of sleep disturbances on psychopathology and functioning, there is a strong need to recognise and treat sleep disturbance using effective and inexpensive interventions, early in the course of mental illness (Harvey et al., 2011).

7.4 **NEXT STEPS**

A feasibility study based on the findings from the PPI consultation would be an important next step in this area to establish the causal role of sleep disturbances in the development and progression of PE over time. A study manipulating sleep as the exposure and measuring the resulting changes in PE as an outcome in a controlled trial design would provide further evidence to understand the relationship between these variables. Such an ambitious study would be informed by the findings from chapters 3-5 of this thesis and would be based on several key methodological considerations. Firstly, future trials should aim to recruit UHR youth as they will be experiencing persistent psychotic symptoms which increase their risk of psychotic disorder. Identifying and recruiting this population is likely to be challenging due to multiple factors related to patient's characteristics (e.g., delays in seeking help, limited family support, lack of clarity regarding referral pathways) and service level features (e.g., limited designated services available for UHR youth). Therefore, a layered approach to identifying and recruiting participants is proposed; whereby patients would be identified through primary and secondary health services, community settings and social media advertisements. Engaging psychiatric community teams and healthcare professionals would also be fundamental to the process of recruiting sufficient participants to the study.

The size of the sample and follow up period are critical considerations as demonstrated in the Transitions study chapter of this thesis (i.e., it is possible that the UK Transitions study was underpowered with insufficient time between data collection points to enable examination of potential associations). The trial would

adopt a longitudinal design with follow up assessments conducted three monthly, following the initial intervention, for 12 months. UHR patients are likely to be experiencing distressing mental health difficulties which drive their help seeking behaviour. Consequently, engaging in research may not be priority or practical for many and this may contribute to high attrition rates. The trial would therefore require researchers to work closely with mental health clinicians to stay informed with changes to patient mental health status and suitability to remain involved in the trial. In addition, scheduling assessments in advance and creating reminders for participants, collecting next of kin details and agreeing suitable locations for data collection are practical approaches to maintaining contact with participants throughout the study. Hybrid models involving a blend of face to face and/or virtual psychiatric care may be a new way of working across healthcare going forward (Dave et al., 2020, Giacco et al., 2017). Consequently, remaining in touch with participants through digital sources may be an additional approach to support recruitment and engagement in future studies in this area.

Future research should utilise an evidence-based intervention to manipulate sleep in UHR youth. CBTi has been shown to be effective in non-clinical groups experiencing PE and in clinical groups with psychotic symptoms (Taylor and Pruiksma, 2014, Waters et al., 2017, Waters et al., 2020, Chiu et al., 2018). Randomly allocating participants to receive an evidence based intervention or treatment as usual and then assessing sleep using objective and self-report measures would be key. There are a range of challenges associated with the reliability and validity of self-reported (e.g., inaccuracies in the reporting of sleep duration, subjectivity associated with sleep quality perceptions) and objective sleep assessments (i.e., the accuracy and sensitivity of actigraphs; the validity of polysomnography readings due to the participant being in a new or unknown environment). Consequently, a cross-validation study should be considered in future studies to compare the data derived from actigraphs and PSG recordings. Furthermore, several researchers trained and skilled would be involved in the analysis of the data to reduce bias that may arise during analysis and interpretation of data.

Unlike the Transitions study, future research should aim to include multiple measurements of the exposure and outcome variable. This would enable exploration of the cumulative effects of persistent sleep difficulties on later PE over several time points to build a comprehensive picture of the relationships between the two experiences.

7.5 **RESEARCH CONSIDERATIONS**

The findings from this thesis have important implications for future research. Firstly, there is significant variability in the measures used to assess sleep disturbances and psychotic symptoms across clinical and non-clinical groups, impacting on reported prevalence rates and comparability of findings between studies. Future research should seek to establish gold-standard tools, particularly for use in UHR youth, as this may aid recognition of risk factors and early symptoms. For instance, the National Institute of Mental Health initiative to improve cognition in Schizophrenia led to the development of a battery of assessments that are used globally to assess cognitive domains and consequently improve psychological and pharmacological treatment research (Marder et al., 2004). A similar research agenda would support in enhancing and standardising assessment and treatment of sleep difficulties and disorders in psychosis. Secondly, it is evident that the relationship between sleep disturbances and PE is complex and the mechanisms and mediating factors between these experiences are yet to be fully understood. This thesis conducted exploratory path analysis involving anxiety and depression as mediating factors in a general population sample. Future research should seek to extend these early investigations through complex statistical modelling to examine the contribution of social, emotional and biological factors that may underlie and mediate the dynamic relationship between sleep and PE. Finally, replicating research is at the core of credible science, knowledge production and advancing clinical practice and treatment. Future research should seek to replicate and extend the findings presented in this thesis through examining the relationship between sleep and PE across other clinical groups experiencing psychotic experiences (e.g., those with affective psychosis) and examining a range of other psychotic experiences (e.g., negative symptoms) to continue to drive forward knowledge in this area.

7.6 **CONCLUSION**

Sleep disturbances and PE present widely throughout the developmental period in healthy populations, representing normal phenomenon that usually spontaneously resolve without care or intervention. In healthy populations, those sleep disturbances that persist past the childhood and adolescent phase are associated with later psychotic experiences, which may increase risk of psychotic illness. In youth seeking help for their mental health difficulties, impairments to sleep are linked to poor outcomes and are therefore an important clinical need to be considered. Whilst there are indications that there is some specificity in relation to which sleep problems may be problematic, further interventional studies are needed to understand the potential causal pathways underlying these co-occuring experiences.

APPENDIX 1: EXAMPLE SEARCH TERMS

Risk terms	Prodrom* OR risk OR "ultra high risk" OR "at risk mental state" OR "clinical high risk" OR "early intervention" OR prepsychotic
Psychosis terms	Schizophren* OR Schizotyp* OR psychosis OR psychotic OR hallucinat* OR delus*
Sleep terms	Sleep OR sleep quality OR REM sleep OR non REM sleep OR sleep wake cycle OR sleep spindle OR sleep stage OR sleep deprivation OR sleep time OR slow wave sleep OR sleep pattern OR sleep disorder OR sleep parameters OR dream OR nightmare OR parasomnia OR insomnia OR circadian OR chronotype OR polysomnogra* OR actigraph* OR ambulatory monitoring

APPENDIX 2. SLEEP QUESTIONS

Sleep difficulty	**Question**	**Childs age**	**Response**
Sleep difficulties score	Item is the sum of several variables assessing : refusal to go to bed, waking very early/ after a few hours of sleep, difficulty going to sleep, experienced nightmares, getting up after being put to bed, night time awakening	42 months	0=Not suspected 1=Suspected 2=Definitely present
Sleep difficulties	"In past year has your child regularly had difficulty going to sleep?"	1.6y, 2.5y, 3.5y, 4.75y, 5.75y	Yes, did not worry parent Yes, worried parent a bit Yes worried parent greatly No did not happen
Night awakening	"*In the past year, has your child regularly woken in the night?*"	1.6y, 2.5y, 3.5y, 4.75y, 5.75y	Yes, did not worry parent Yes, worried parent a bit Yes worried parent greatly No did not happen
Nightmares	"*In the past year, has your child regularly had nightmares?*"	1.6y, 2.5y, 3.5y, 4.75y, 5.75y	Yes, did not worry parent Yes, worried parent a bit Yes worried parent greatly No did not happen

Nightmares	"*Since your 12th birthday have you had any dreams that woke you up*? *Were they frightening*? Did you feel sweaty, did your heart race or did you breathe very fast or have a dry mouth? When did the dream happen? Was it at the start of the night or towards the morning? How often would you say that you have these types of dreams (nightmares)? Thinking back to the last 6 months"	12 years	0= not suspected 1= Suspected 2=Definitely present
Sleep walking	"*Has anyone ever told you, since you were 12 that you got out of bed and walked around while you were fast asleep?* How often would you say that this happens? Thinking back to the last 6 months"	12 years	0= Not suspected 1=Suspected 2=Definitely present
Night terrors	"Has any one ever told you, since you were 12, that you scream out at night, sit up in bed, seem to fight or wrestle with unseen creatures or shout at them in your sleep? Describe" "Do you remember what you were thinking or dreaming? Did your parents or others ever wake you? How did you feel? Have you ever injured yourself in your sleep when having these night terrors? When does this usually happen at night? Was it at the start of the night or towards the morning? How often would you say that this happens? Thinking back to the last 6 months."	12 years	0=Not suspected 1=Suspected 2=Definitely present

APPENDIX 3. DATA COLLECTED THROUGHOUT THE STUDY

			Pregnancy	Birth	6months	18 months	24months	30months	3.5years	4years	5years	6years	7years	8years	9years	10years	11years	12years	18years	24years
Variable	**Measure**	**Questionnaire**																		
Sex	Parent reported			x																
Ethnicity	Parent reported			x																
Mothers educational level	Parent reported		x																	
Childhood emotional difficulties	Parent reported								x											
Preschool night awakenings	Parent reported					x		x	x	x	x									
Preschool sleep difficulties	Parent reported					x		x	x	x	x									
Preschool nightmares	Parent reported					x		x	x	x	x									
Adolescent nightmares	Child reported																	x		
Adolescent night terrors	Child reported																	x		
Adolescent sleep walking	Child reported																	x		
IQ	Child reported	WISC												x						
Depression	Parent reported	SMFQ													x		x			
Anxiety	Parent and teacher repo	DAWBA														x				
Any psychiatric diagnosis	Parent and teacher repo	DAWBA											x							
Child abuse	Parent reported	The upsetting events questionnaires						x	x	x	x	x								
Psychotic experiences	Child reported	PLIKSI																	x	x

REFERENCES

ADDINGTON, J., CORNBLATT, B. A., CADENHEAD, K. S., CANNON, T. D., MCGLASHAN, T. H., PERKINS, D. O., SEIDMAN, L. J., TSUANG, M. T., WALKER, E. F. & WOODS, S. W. 2011. At clinical high risk for psychosis: outcome for nonconverters. *American Journal of Psychiatry,* 168**,** 800-805.

ADDINGTON, J., MCGREGOR, L., MARULANDA, D. & RAEDLER, T. 2013. Recruitment strategies for the detection of individuals at clinical high risk of developing psychosis. *Epidemiology and psychiatric sciences,* 22**,** 181-185.

ADDINGTON, J., VAN MASTRIGT, S. & ADDINGTON, D. 2004. Duration of untreated psychosis: impact on 2-year outcome. *Psychological medicine,* 34**,** 277-284.

AFONSO, P., BRISSOS, S., FIGUEIRA, M. L. & PAIVA, T. 2011. Schizophrenia patients with predominantly positive symptoms have more disturbed sleep–wake cycles measured by actigraphy. *Psychiatry Research,* 189**,** 62-66.

ALDERMAN, T., ADDINGTON, J., BEARDEN, C., CANNON, T. D., CORNBLATT, B. A., MCGLASHAN, T. H., PERKINS, D. O., SEIDMAN, L. J., TSUANG, M. T. & WALKER, E. F. 2015. Negative symptoms and impaired social functioning predict later psychosis in L atino youth at clinical high risk in the N orth A merican prodromal longitudinal studies consortium. *Early intervention in psychiatry,* 9**,** 467-475.

ALSPAC. 2020. *Search for variables collected in the ALSPAC study* [Online]. Available: http://variables.alspac.bris.ac.uk/?_ga=2.245381124.1898193879.1619110145-2000693536.1617376759 [Accessed].

ANCOLI-ISRAEL, S., COLE, R., ALESSI, C., CHAMBERS, M., MOORCROFT, W. & POLLAK, C. P. 2003. The role of actigraphy in the study of sleep and circadian rhythms. *Sleep,* 26**,** 342-392.

ANDERSON, K. N. & BRADLEY, A. J. 2013. Sleep disturbance in mental health problems and neurodegenerative disease. *J Nature science of sleep,* 5**,** 61.

ANDREASEN, N. C. & OLSEN, S. 1982. Negative v positive schizophrenia: Definition and validation. *Archives of general psychiatry,* 39**,** 789-794.

ANDREWS, G. & SLADE, T. 2001. Interpreting scores on the Kessler psychological distress scale (K10). *Australian and New Zealand journal of public health,* 25**,** 494-497.

ANDREWS, L. M., ALLEN, H., SHEPPARD, Z. A., BAYLIS, G. & WAINWRIGHT, T. W. 2015. More than just ticking a box… how patient and public involvement improved the research design and funding application for a project to evaluate a cycling intervention for hip osteoarthritis. *Research Involvement and Engagement,* 1**,** 13.

ARBUCKLE, J. L. 2011. IBM SPSS Amos 20 user's guide. *Amos Development Corporation, SPSS Inc.*

ARCINIEGAS, D. B. 2015. Psychosis. *Continuum: Lifelong Learning in Neurology,* 21**,** 715.

ATKINSON, R. & FLINT, J. 2001. Accessing hidden and hard-to-reach populations: Snowball research strategies. *Social research update,* 33**,** 1-4.

AUGEDAL, A. W., HANSEN, K. S., KRONHAUG, C. R., HARVEY, A. G. & PALLESEN, S. 2013. Randomized controlled trials of psychological and pharmacological treatments for nightmares: a meta-analysis. *Sleep Medicine Reviews,* 17**,** 143-152.

BAGLEY, H. J., SHORT, H., HARMAN, N. L., HICKEY, H. R., GAMBLE, C. L., WOOLFALL, K., YOUNG, B. & WILLIAMSON, P. R. 2016. A patient and public involvement (PPI) toolkit for meaningful and flexible involvement in clinical trials–a work in progress. *Research involvement and engagement,* 2**,** 1-14.

BARCLAY, N. L. & GREGORY, A. M. 2013. Sleep in childhood and adolescence: age-specific sleep characteristics, common sleep disturbances and associated difficulties. *The neurobiology of childhood***,** 337-365.

BARRETT, E. A., AMINOFF, S. R., SIMONSEN, C. & ROMM, K. L. 2020. Opening the curtains for better sleep in psychotic disorders-considerations for improving sleep treatment. *Comprehensive Psychiatry,* 103**,** 152207.

BARRETT, E. A., SUNDET, K., FAERDEN, A., AGARTZ, I., BRATLIEN, U., ROMM, K. L., MORK, E., ROSSBERG, J. I., STEEN, N. E. & ANDREASSEN, O. A. 2010. Suicidality in first episode psychosis is associated with insight and negative beliefs about psychosis. *Schizophrenia Research,* 123**,** 257-262.

BEBBINGTON, P., RAI, D., STRYDOM, A., BRUGHA., MCMANUS,S., MORGAN, Z. 2014. Psychotic disorder. *Adult Psychiatic Morbidity Survey*.

BEBBINGTON, P. E., BHUGRA, D., BRUGHA, T., SINGLETON, N., FARRELL, M., JENKINS, R., LEWIS, G. & MELTZER, H. 2004. Psychosis, victimisation and childhood disadvantage: evidence from the second British National Survey of Psychiatric Morbidity. *The British Journal of Psychiatry,* 185**,** 220-226.

BEEBE, D. W. 2011. Cognitive, behavioral, and functional consequences of inadequate sleep in children and adolescents. *Pediatric Clinics,* 58**,** 649-665.

BELL, R. Q. 1992. Multiple-risk cohorts and segmenting risk as solutions to the problem of false positives in risk for the major psychoses. *Psychiatry,* 55**,** 370-381.

BERNSTEIN, I. H., RUSH, A. J., TRIVEDI, M. H., HUGHES, C. W., MACLEOD, L., WITTE, B. P., JAIN, S., MAYES, T. L. & EMSLIE, G. J. 2010. Psychometric properties of the Quick Inventory of Depressive Symptomatology in adolescents. *International journal of methods in psychiatric research,* 19**,** 185-194.

BIRCHWOOD, M., TODD, P. & JACKSON, C. 1998. Early intervention in psychosis: the critical period hypothesis. *The British journal of psychiatry,* 172**,** 53-59.

BLAKE, M. J., SNOEP, L., RANITI, M., SCHWARTZ, O., WALOSZEK, J. M., SIMMONS, J. G., MURRAY, G., BLAKE, L., LANDAU, E. R. & DAHL, R. E. 2017. A cognitive-behavioral and mindfulness-based group sleep intervention improves behavior problems in at-risk adolescents by improving perceived sleep quality. *Behaviour research and therapy,* 99**,** 147-156.

BLANCHARD, J. J., ANDREA, A., ORTH, R. D., SAVAGE, C. & BENNETT, M. E. 2020a. Sleep Disturbance and Sleep-Related Impairment in Psychotic Disorders Are Related to Both Positive and Negative Symptoms. *Psychiatry Research***,** 112857.

BLANCHARD, J. J., ANDREA, A., ORTH, R. D., SAVAGE, C. & BENNETT, M. E. 2020b. Sleep disturbance and sleep-related impairment in psychotic disorders are related to both positive and negative symptoms. *Psychiatry Research,* 286**,** 112857.

BLOOD, M. L., SACK, R. L., PERCY, D. C. & PEN, J. C. 1997. A comparison of sleep detection by wrist actigraphy, behavioral response, and polysomnography. *Sleep,* 20**,** 388-395.

BOIVIN, A., RICHARDS, T., FORSYTHE, L., GRÉGOIRE, A., L'ESPÉRANCE, A., ABELSON, J. & CARMAN, K. L. 2018. Evaluating patient and public involvement in research. British Medical Journal Publishing Group.

BORBÉLY, A. A. 1982. A two process model of sleep regulation. *Hum neurobiol,* 1**,** 195-204.

BORBÉLY, A. A., DAAN, S., WIRZ-JUSTICE, A. & DEBOER, T. 2016. The two-process model of sleep regulation: a reappraisal. *Journal of sleep research,* 25**,** 131-143.

BOURGIN, J., TEBEKA, S., MALLET, J., MAZER, N., DUBERTRET, C. & LE STRAT, Y. 2020. Prevalence and correlates of psychotic-like experiences in the general population. *Schizophrenia research,* 215**,** 371-377.

BOYD, A., GOLDING, J., MACLEOD, J., LAWLOR, D. A., FRASER, A., HENDERSON, J., MOLLOY, L., NESS, A., RING, S. & DAVEY SMITH, G. 2013. Cohort profile: the 'children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. *International journal of epidemiology,* 42**,** 111-127.

BRADLEY, J., FREEMAN, D., CHADWICK, E., HARVEY, A. G., MULLINS, B., JOHNS, L., SHEAVES, B., LENNOX, B., BROOME, M. & WAITE, F. 2018. Treating sleep problems in young people at ultra-high risk of psychosis: a feasibility case series. *Behavioural and cognitive psychotherapy,* 46**,** 276-291.

BREDEROO, S. G., DE BOER, J. N., DE VRIES, J., LINSZEN, M. M. & SOMMER, I. E. 2021. Fragmented sleep relates to hallucinations across perceptual modalities in the general population. *Scientific Reports,* 11**,** 1-9.

BROOME, M. R., WOOLLEY, J. B., TABRAHAM, P., JOHNS, L. C., BRAMON, E., MURRAY, G. K., PARIANTE, C., MCGUIRE, P. K. & MURRAY, R. M. 2005. What causes the onset of psychosis? *Schizophrenia research,* 79**,** 23-34.

BUCK, D., GAMBLE, C., DUDLEY, L., PRESTON, J., HANLEY, B., WILLIAMSON, P. R., YOUNG, B. & GROUP, E. P. A. 2014. From plans to actions in patient and public involvement: qualitative study of documented plans and the accounts of researchers and patients sampled from a cohort of clinical trials. *BMJ open,* 4.

BUYSSE, D. J., ANGST, J., GAMMA, A., AJDACIC, V., EICH, D. & RÖSSLER, W. 2008. Prevalence, course, and comorbidity of insomnia and depression in young adults. *Sleep,* 31**,** 473-480.

BUYSSE, D. J., REYNOLDS, C. F., MONK, T. H., BERMAN, S. R. & KUPFER, D. J. 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry res,* 28**,** 193-213.

BUYSSE, D. J., REYNOLDS III, C. F., MONK, T. H., HOCH, C. C., YEAGER, A. L. & KUPFER, D. J. 1991. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep,* 14**,** 331-338.

BUYSSE, D. J., YU, L., MOUL, D. E., GERMAIN, A., STOVER, A., DODDS, N. E., JOHNSTON, K. L., SHABLESKY-CADE, M. A. & PILKONIS, P. A. 2010. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep,* 33**,** 781-792.

CANNON, T. D. & MEDNICK, S. A. 1993. The schizophrenia high-risk project in Copenhagen: three decades of progress. *Acta Psychiatrica Scandinavica,* 87**,** 33-47.

CAPPUCCIO, F., MILLER, M. A. & LOCKLEY, S. W. 2010. *Sleep, health, and society: From aetiology to public health*, Oxford University Press.

CARRIÓN, R. E., MCLAUGHLIN, D., GOLDBERG, T. E., AUTHER, A. M., OLSEN, R. H., OLVET, D. M., CORRELL, C. U. & CORNBLATT, B. A. 2013. Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA psychiatry,* 70**,** 1133-1142.

CARSKADON, M. A. 2002. *Adolescent sleep patterns: Biological, social, and psychological influences*, Cambridge University Press.

CARSKADON, M. A. 2011. Sleep in adolescents: the perfect storm. *Pediatric Clinics,* 58**,** 637-647.

CARSKADON, M. A. & BARKER, D. H. 2020. Editorial Perspective: Adolescents' fragile sleep—shining light on a time of risk to mental health. *Journal of Child Psychology and Psychiatry*.

CASCIO, N. L., SABA, R., HAUSER, M., VERNAL, D. L., AL-JADIRI, A., BORENSTEIN, Y., SHERIDAN, E. M., KISHIMOTO, T., ARMANDO, M. & VICARI, S. 2016. Attenuated psychotic and basic symptom characteristics in adolescents with ultra-high risk criteria for psychosis, other non-psychotic psychiatric disorders and early-onset psychosis. *European child & adolescent psychiatry,* 25**,** 1091-1102.

CASTILLEJOS, M., MARTÍN-PÉREZ, C. & MORENO-KÜSTNER, B. 2018. A systematic review and meta-analysis of the incidence of psychotic disorders: the distribution of rates and the influence of gender, urbanicity, immigration and socio-economic level. *Psychological medicine,* 48**,** 2101-2115.

CASTRO, J., ZANINI, M., GONÇALVES, B. D. S. B., COELHO, F. M. S., BRESSAN, R., BITTENCOURT, L., GADELHA, A., BRIETZKE, E. & TUFIK, S. 2015. Circadian rest–activity rhythm in individuals at risk for psychosis and bipolar disorder. *Schizophrenia Research,* 168**,** 50-55.

CHAPMAN, H. C., VISSER, K. F., MITTAL, V. A., GIBB, B. E., COLES, M. E. & STRAUSS, G. P. 2020. Emotion regulation across the psychosis continuum. *Development and psychopathology,* 32**,** 219-227.

CHIU, V. W., REE, M., JANCA, A., IYYALOL, R., DRAGOVIC, M. & WATERS, F. 2018. Sleep profiles and CBT-I response in schizophrenia and related psychoses. *Psychiatry research,* 268**,** 279-287.

CHIU, V. W., REE, M., JANCA, A. & WATERS, F. 2016. Sleep in schizophrenia: exploring subjective experiences of sleep problems, and implications for treatment. *Psychiatric Quarterly,* 87**,** 633-648.

CLARKE, L., CHISHOLM, K., CAPPUCCIO, F. P., TANG, N. K., MILLER, M. A., ELAHI, F. & THOMPSON, A. D. 2020. Sleep disturbances and the At Risk Mental State: A systematic review and meta-analysis. *Schizophrenia Research,* 227**,** 81-91.

COHRS, S. 2008. Sleep disturbances in patients with schizophrenia. *J CNS drugs,* 22**,** 939-962.

COLLIP, D., WIGMAN, J. T., MYIN-GERMEYS, I., JACOBS, N., DEROM, C., THIERY, E., WICHERS, M. & VAN OS, J. 2013. From epidemiology to daily life: linking daily life stress reactivity to persistence of psychotic experiences in a longitudinal general population study. *PloS one,* 8**,** e62688.

COMMITTEE, S. O. P., AURORA, R. N., ZAK, R. S., AUERBACH, S. H., CASEY, K. R., CHOWDHURI, S., KARIPPOT, A., MAGANTI, R. K., RAMAR, K. & KRISTO, D. A. 2010. Best practice guide for the treatment of nightmare disorder in adults. *Journal of clinical sleep medicine,* 6**,** 389-401.

CONLEY, S., KNIES, A., BATTEN, J., ASH, G., MINER, B., HWANG, Y., JEON, S. & REDEKER, N. S. 2019. Agreement between actigraphic and polysomnographic measures of sleep in adults with and without chronic conditions: a systematic review and meta-analysis. *Sleep medicine reviews,* 46**,** 151-160.

CORNBLATT, B., LENCZ, T. & OBUCHOWSKI, M. 2002. The schizophrenia prodrome: treatment and high-risk perspectives. *Schizophrenia research,* 54**,** 177-186.

CORNBLATT, B. A., AUTHER, A. M., NIENDAM, T., SMITH, C. W., ZINBERG, J., BEARDEN, C. E. & CANNON, T. D. 2007. Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. *Schizophrenia bulletin,* 33**,** 688-702.

COSGRAVE, J., HAINES, R., VAN HEUGTEN-VAN DER KLOET, D., PURPLE, R., PORCHERET, K., FOSTER, R. & WULFF, K. 2018. The interaction between subclinical psychotic experiences, insomnia and objective measures of sleep. *Schizophrenia research,* 193**,** 204-208.

COSGRAVE, J., PURPLE, R. J., HAINES, R., PORCHERET, K., VAN HEUGTEN-VAN DER KLOET, D., JOHNS, L., ALEXANDER, I., GOODWIN, G. M., FOSTER, R. G. & WULFF, K. 2021. Do environmental risk factors for the development of psychosis distribute differently across dimensionally assessed psychotic experiences? *Translational Psychiatry,* 11**,** 1-13.

COTTER, J., DRAKE, R. J., BUCCI, S., FIRTH, J., EDGE, D. & YUNG, A. R. 2014. What drives poor functioning in the at-risk mental state? A systematic review. *Schizophrenia research,* 159**,** 267-277.

COUGNARD, A., MARCELIS, M., MYIN-GERMEYS, I., DE GRAAF, R., VOLLEBERGH, W., KRABBENDAM, L., LIEB, R., WITTCHEN, H.-U., HENQUET, C. & SPAUWEN, J. 2007. Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. *Psychological medicine,* 37**,** 513.

CROCKER, J. C., BOYLAN, A. M., BOSTOCK, J. & LOCOCK, L. 2017. Is it worth it? Patient and public views on the impact of their involvement in health research and its assessment: a UK-based qualitative interview study. *Health Expectations,* 20**,** 519-528.

D'AMBROSIO, C. & REDLINE, S. 2014. Sleep across the lifespan. *Impact of sleep and sleep disturbances on obesity and cancer***,** 1-23.

DANEAULT, J.-G. & STIP, E. 2013. Genealogy of instruments for prodrome evaluation of psychosis. *Frontiers in psychiatry,* 4**,** 25.

DAVE, S., ABRAHAM, S., RAMKISSON, R., MATHEIKEN, S., PILLAI, A. S., REZA, H., BAMRAH, J. & TRACY, D. K. 2020. Digital psychiatry and COVID-19: the Big Bang effect for the NHS? *BJPsych bulletin***,** 1-5.

DAVIES, G., HADDOCK, G., YUNG, A. R., MULLIGAN, L. D. & KYLE, S. D. 2017. A systematic review of the nature and correlates of sleep disturbance in early psychosis. *Sleep Medicine Reviews,* 31**,** 25-38.

DE PABLO, G. S., CATALAN, A. & FUSAR-POLI, P. 2020. Clinical validity of DSM-5 attenuated psychosis syndrome: advances in diagnosis, prognosis, and treatment. *Jama Psychiatry,* 77**,** 311-320.

DEVINE, E. B., HAKIM, Z. & GREEN, J. 2005. A systematic review of patient-reported outcome instruments measuring sleep dysfunction in adults. *Pharmacoeconomics,* 23**,** 889-912.

DEVYLDER, J. E., LEHMANN, M. & CHEN, F.-P. 2015. Social and clinical correlates of the persistence of psychotic experiences in the general population. *Schizophrenia research,* 169**,** 286-291.

DIENER, E. & BISWAS-DIENER, R. 2016. *The replication crisis in psychology*, Noba Textbook Series: Psychology.

DOMINGUEZ, M., WICHERS, M., LIEB, R., WITTCHEN, H.-U. & VAN OS, J. 2011. Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. *Schizophrenia bulletin,* 37**,** 84-93.

DOWNS, S. H. & BLACK, N. 1998. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology,* 52**,** 377-384.

DUDLEY, R., TAYLOR, P., WICKHAM, S. & HUTTON, P. 2016. Psychosis, delusions and the "jumping to conclusions" reasoning bias: a systematic review and meta-analysis. *Schizophrenia bulletin,* 42**,** 652-665.

EBEL, H., GROSS, G., KLOSTERKÖTTER, J. & HUBER, G. 1989. Basic symptoms in schizophrenic and affective psychoses. *Psychopathology,* 22**,** 224-232.

ERED, A., COOPER, S. & ELLMAN, L. M. 2018. Sleep quality, psychological symptoms, and psychotic-like experiences. *Journal of psychiatric research,* 98**,** 95-98.

ERLENMEYER-KIMLING, L., SQUIRES-WHEELER, E., ADAMO, U. H., BASSETT, A. S., CORNBLATT, B. A., KESTENBAUM, C. J., ROCK, D., ROBERTS, S. A. & GOTTESMAN, I. I. 1995. The New York High-Risk Project: psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow-up. *Archives of general psychiatry,* 52**,** 857-865.

FAULKNER, S. M. & SIDEY-GIBBONS, C. 2019. Use of the Pittsburgh Sleep Quality Index (PSQI) in people with schizophrenia spectrum disorders: a mixed methods study. *Frontiers in psychiatry,* 10**,** 284.

FEDAK, K. M., BERNAL, A., CAPSHAW, Z. A. & GROSS, S. 2015. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerging themes in epidemiology,* 12**,** 1-9.

FERRARELLI, F., HUBER, R., PETERSON, M. J., MASSIMINI, M., MURPHY, M., RIEDNER, B. A., WATSON, A., BRIA, P. & TONONI, G. 2007. Reduced sleep spindle activity in schizophrenia patients. *American Journal of Psychiatry,* 164**,** 483-492.

FIELD, A. 2013. *Discovering statistics using IBM SPSS statistics*, Sage.

FISHER, H., CASPI, A., POULTON, R., MEIER, M., HOUTS, R., HARRINGTON, H., ARSENEAULT, L. & MOFFITT, T. 2013a. Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: a birth cohort study. *Psychological medicine,* 43**,** 2077.

FISHER, H. L., LEREYA, S. T., THOMPSON, A., LEWIS, G., ZAMMIT, S. & WOLKE, D. 2014. Childhood parasomnias and psychotic experiences at age 12 years in a United Kingdom birth cohort. *Sleep,* 37**,** 475-482.

FISHER, H. L., SCHREIER, A., ZAMMIT, S., MAUGHAN, B., MUNAFÒ, M. R., LEWIS, G. & WOLKE, D. 2013b. Pathways between childhood victimization and psychosis-like symptoms in the ALSPAC birth cohort. *Schizophrenia bulletin,* 39**,** 1045-1055.

FOLEY, D. L. & MORLEY, K. I. 2011. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. *Archives of general psychiatry,* 68**,** 609-616.

FONSECA-PEDRERO, E., SANTAREN-ROSELL, M., LEMOS-GIRÁLDEZ, S., PAINO, M., SIERRA-BAIGRIE, S. & MUNIZ, J. 2011. Psychotic-like experiences in the adolescent general population. *Actas espanolas de psiquiatria,* 39**,** 155-162.

FORBAT, L., HUBBARD, G. & KEARNEY, N. 2009. Patient and public involvement: models and muddles. *Journal of clinical nursing,* 18**,** 2547-2554.

FREEMAN, D. 2006. Delusions in the nonclinical population. *Current psychiatry reports,* 8**,** 191-204.

FREEMAN, D., SHEAVES, B., GOODWIN, G. M., YU, L.-M., NICKLESS, A., HARRISON, P. J., EMSLEY, R., LUIK, A. I., FOSTER, R. G. & WADEKAR, V. 2017. The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. *The Lancet Psychiatry,* 4**,** 749-758.

FREEMAN, D., STAHL, D., MCMANUS, S., MELTZER, H., BRUGHA, T., WILES, N. & BEBBINGTON, P. 2012. Insomnia, worry, anxiety and depression as predictors of the occurrence and persistence of paranoid thinking. *Social psychiatry and psychiatric epidemiology,* 47**,** 1195-1203.

FREEMAN, D., WAITE, F., STARTUP, H., MYERS, E., LISTER, R., MCINERNEY, J., HARVEY, A. G., GEDDES, J., ZAIWALLA, Z. & LUENGO-FERNANDEZ, R. 2015. Efficacy of cognitive behavioural therapy for sleep improvement in patients with persistent delusions and hallucinations (BEST): a prospective, assessor-blind, randomised controlled pilot trial. *The Lancet Psychiatry,* 2**,** 975-983.

FRIEDEMANN, C., HENEGHAN, C., MAHTANI, K., THOMPSON, M., PERERA, R. & WARD, A. M. 2012. Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis. *Bmj,* 345.

FRISTAD, M. A., WELLER, R. A. & WELLER, E. B. 1995. The Mania Rating Scale (MRS): further reliability and validity studies with children. *Annals of clinical psychiatry,* 7**,** 127-132.

FUSAR-POLI, P., BONOLDI, I., YUNG, A. R., BORGWARDT, S., KEMPTON, M. J., VALMAGGIA, L., BARALE, F., CAVERZASI, E. & MCGUIRE, P. 2012. Predicting

psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Archives of general psychiatry,* 69**,** 220-229.

FUSAR-POLI, P., BORGWARDT, S., BECHDOLF, A., ADDINGTON, J., RIECHER-RÖSSLER, A., SCHULTZE-LUTTER, F., KESHAVAN, M., WOOD, S., RUHRMANN, S. & SEIDMAN, L. J. 2013. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA psychiatry,* 70**,** 107-120.

FUSAR-POLI, P., CAPPUCCIATI, M., RUTIGLIANO, G., LEE, T., BEVERLY, Q., BONOLDI, I., LELLI, J., KAAR, S., GAGO, E. & ROCCHETTI, M. 2016a. Towards a standard psychometric diagnostic interview for subjects at ultra high risk of psychosis: CAARMS versus SIPS. *Psychiatry journal,* 2016.

FUSAR-POLI, P., ROCCHETTI, M., SARDELLA, A., AVILA, A., BRANDIZZI, M., CAVERZASI, E., POLITI, P., RUHRMANN, S. & MCGUIRE, P. 2015. Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis. *The British Journal of Psychiatry,* 207**,** 198-206.

FUSAR-POLI, P., RUTIGLIANO, G., STAHL, D., DAVIES, C., DE MICHELI, A., RAMELLA-CRAVARO, V., BONOLDI, I. & MCGUIRE, P. 2017. Long-term validity of the At Risk Mental State (ARMS) for predicting psychotic and non-psychotic mental disorders. *European Psychiatry,* 42**,** 49-54.

FUSAR-POLI, P., SCHULTZE-LUTTER, F., CAPPUCCIATI, M., RUTIGLIANO, G., BONOLDI, I., STAHL, D., BORGWARDT, S., RIECHER-RÖSSLER, A., ADDINGTON, J. & PERKINS, D. O. 2016b. The dark side of the moon: meta-analytical impact of recruitment strategies on risk enrichment in the clinical high risk state for psychosis. *Schizophrenia bulletin,* 42**,** 732-743.

GAEBEL, W. & ZIELASEK, J. 2015. Focus on psychosis. *Dialogues in clinical neuroscience,* 17**,** 9.

GALLAND, B. C., TAYLOR, B. J., ELDER, D. E. & HERBISON, P. 2012. Normal sleep patterns in infants and children: a systematic review of observational studies. *Sleep medicine reviews,* 16**,** 213-222.

GARBARINO, S. 2020. Sleep Disorders across the Lifespan: A Different Perspective. Multidisciplinary Digital Publishing Institute.

GARFIELD, S., JHEETA, S., JACKLIN, A., BISCHLER, A., NORTON, C. & FRANKLIN, B. D. 2015. Patient and public involvement in data collection for health services research: a descriptive study. *Research Involvement and Engagement,* 1**,** 8.

GARIÉPY, G., RIEHM, K. E., WHITEHEAD, R. D., DORÉ, I. & ELGAR, F. J. 2019. Teenage night owls or early birds? Chronotype and the mental health of adolescents. *Journal of sleep research,* 28**,** e12723.

GIACCO, D., AMERING, M., BIRD, V., CRAIG, T., DUCCI, G., GALLINAT, J., GILLARD, S. G., GREACEN, T., HADRIDGE, P. & JOHNSON, S. 2017. Scenarios for the future of mental health care: a social perspective. *The Lancet Psychiatry,* 4**,** 257-260.

GILLARD, S., SIMONS, L., TURNER, K., LUCOCK, M. & EDWARDS, C. 2012. Patient and public involvement in the coproduction of knowledge: reflection on the analysis of qualitative data in a mental health study. *Qualitative Health Research,* 22**,** 1126-1137.

GLOZIER, N., O'DEA, B., MCGORRY, P. D., PANTELIS, C., AMMINGER, G. P., HERMENS, D. F., PURCELL, R., SCOTT, E. & HICKIE, I. B. 2014. Delayed sleep onset in depressed young people. *BMC psychiatry,* 14**,** 33.

GOINES, K. B., LOPILATO, A. M., ADDINGTON, J., BEARDEN, C. E., CADENHEAD, K. S., CANNON, T. D., CORNBLATT, B. A., MATHALON, D. H., MCGLASHAN, T. H. & PERKINS, D. O. 2019. Sleep problems and attenuated psychotic symptoms in youth at clinical high-risk for psychosis. *Psychiatry research,* 282**,** 112492.

GOLDING, J. 1989. European longitudinal study of pregnancy and childhood (ELSPAC). *Paediatr Perinat Epidemiol,* 3**,** 460-469.

GOLDING, J., PEMBREY, M. & JONES, R. 2001. ALSPAC--the Avon Longitudinal Study of Parents and Children. I. Study methodology. *Paediatric and perinatal epidemiology,* 15**,** 74-87.

GOLDNER, E. M., HSU, L., WARAICH, P. & SOMERS, J. M. 2002. Prevalence and incidence studies of schizophrenic disorders: a systematic review of the literature. *The Canadian Journal of Psychiatry,* 47**,** 833-843.

GONÇALVES, B., CASTRO, J., ZANINI, M. A., BITTENCOURT, L., GADELHA, A., CUNHA, G. R., COELHO, F. M., TUFIK, S., BRESSAN, R. A. & BRIETZKE, E. 2016. Circadian rhythm disturbances and conversion to psychosis in ultra high-risk youth. *Brazilian Journal of Psychiatry,* 38**,** 178-179.

GOODMAN, A., HEIERVANG, E., COLLISHAW, S. & GOODMAN, R. 2011. The 'DAWBA bands' as an ordered-categorical measure of child mental health: description and validation in British and Norwegian samples. *Social psychiatry and psychiatric epidemiology,* 46**,** 521-532.

GOODMAN, R., FORD, T., RICHARDS, H., GATWARD, R. & MELTZER, H. 2000. The development and well-being assessment: Description and initial validation of an integrated assessment of child and adolescent psychopathology. *Journal of child psychology and psychiatry,* 41**,** 645-655.

GOTTESMAN, I. I. & ERLENMEYER-KIMLING, L. 2001. Family and twin strategies as a head start in defining prodromes and endophenotypes for hypothetical early-interventions in schizophrenia. *Schizophrenia research,* 51**,** 93-102.

GREGORY, A. M. & SADEH, A. 2012. Sleep, emotional and behavioral difficulties in children and adolescents. *Sleep medicine reviews,* 16**,** 129-136.

GRIVEL, M. M., LEONG, W., MASUCCI, M. D., ALTSCHULER, R. A., ARNDT, L. Y., REDMAN, S. L., YANG, L. H., BRUCATO, G. & GIRGIS, R. R. 2018. Impact of lifetime traumatic experiences on suicidality and likelihood of conversion in a cohort of individuals at clinical high-risk for psychosis. *Schizophrenia research,* 195**,** 549-553.

GROUP, W. 1998. Development of the World Health Organization WHOQOL-BREF quality of life assessment. *Psychological medicine,* 28**,** 551-558.

GULOKSUZ, S., PRIES, L. K., TEN HAVE, M., DE GRAAF, R., VAN DORSSELAER, S., KLINGENBERG, B., BAK, M., LIN, B. D., VAN EIJK, K. R. & DELESPAUL, P. 2020. Association of preceding psychosis risk states and non-psychotic mental disorders with incidence of clinical psychosis in the general population: a prospective study in the NEMESIS-2 cohort. *World Psychiatry,* 19**,** 199-205.

HAMILTON, M. 1959. Hamilton anxiety rating scale (HAM-A). *J Med,* 61**,** 81-82.

HARTLEY, H. O. 1958. Maximum likelihood estimation from incomplete data. *Biometrics,* 14**,** 174-194.

HARVEY, A. G., MURRAY, G., CHANDLER, R. A. & SOEHNER, A. 2011. Sleep disturbance as transdiagnostic: consideration of neurobiological mechanisms. *Clinical psychology review,* 31**,** 225-235.

HEINSSEN, R. K., CUTHBERT, B. N., BREILING, J., COLPE, L. J. & DOLAN-SEWELL, R. 2003. Overcoming barriers to research in early serious mental illness: issues for future collaboration. *Schizophrenia Bulletin,* 29**,** 737-745.

HEINZE, K., LIN, A., NELSON, B., RENIERS, R. L., UPTHEGROVE, R., CLARKE, L., ROCHE, A., LOWRIE, A. & WOOD, S. J. 2018. The impact of psychotic experiences in the early stages of mental health problems in young people. *BMC psychiatry,* 18**,** 214.

HIGGINS, J. P. & ALTMAN, D. G. 2008. Assessing risk of bias in included studies. *Cochrane handbook for systematic reviews of interventions: Cochrane book series***,** 187-241.

HODGEKINS, J., FRENCH, P., BIRCHWOOD, M., MUGFORD, M., CHRISTOPHER, R., MARSHALL, M., EVERARD, L., LESTER, H., JONES, P. & AMOS, T. 2015. Comparing time use in individuals at different stages of psychosis and a non-clinical comparison group. *Schizophrenia Research,* 161**,** 188-193.

HOFSTETTER, J. R., LYSAKER, P. H. & MAYEDA, A. R. 2005a. Quality of sleep in patients with schizophrenia is associated with quality of life and coping. *BMC psychiatry,* 5**,** 13.

HOFSTETTER, J. R., LYSAKER, P. H. & MAYEDA, A. R. 2005b. Quality of sleep in patients with schizophrenia is associated with quality of life and coping. *BMC psychiatry,* 5**,** 1-5.

HOLTZMAN, C., TROTMAN, H., GOULDING, S., RYAN, A., MACDONALD, A., SHAPIRO, D., BRASFIELD, J. & WALKER, E. 2013. Stress and neurodevelopmental processes in the emergence of psychosis. *Neuroscience,* 249**,** 172-191.

HORNE, J. 1988. *Why we sleep*, Oxford University Press Oxford.

HORNE, J. A. & ÖSTBERG, O. 1976. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International journal of chronobiology*.

HORWOOD, J., SALVI, G., THOMAS, K., DUFFY, L., GUNNELL, D., HOLLIS, C., LEWIS, G., MENEZES, P., THOMPSON, A. & WOLKE, D. 2008. IQ and non-clinical psychotic symptoms in 12-year-olds: results from the ALSPAC birth cohort. *The British Journal of Psychiatry,* 193**,** 185-191.

HOWE, A. 2018. Principles of patient and public involvement in primary care research, applied to mental health research. A keynote paper from the EGPRN Autumn Conference 2017 in Dublin. *European Journal of General Practice,* 24**,** 167-170.

HOWES, O. D. & MURRAY, R. M. 2014. Schizophrenia: an integrated sociodevelopmental-cognitive model. *The Lancet,* 383**,** 1677-1687.

JACOBS, R., AYLOTT, L., DARE, C., DORAN, T., GILBODY, S., GODDARD, M., GRAVELLE, H., GUTACKER, N., KASTERIDIS, P. & KENDRICK, T. 2020. The association between primary care quality and health-care use, costs and outcomes for people with serious mental illness: a retrospective observational study.

JAFARI, B. & MOHSENIN, V. 2010. Polysomnography. *Clinics in chest medicine,* 31**,** 287-297.

JARVIS, G. E. 2007. The social causes of psychosis in North American psychiatry: a review of a disappearing literature. *The Canadian Journal of Psychiatry,* 52**,** 287-294.

JEPPESEN, P., CLEMMENSEN, L., MUNKHOLM, A., RIMVALL, M. K., RASK, C. U., JØRGENSEN, T., LARSEN, J. T., PETERSEN, L., VAN OS, J. & SKOVGAARD, A. M. 2015. Psychotic experiences co-occur with sleep problems, negative affect and mental disorders in preadolescence. *Journal of Child Psychology and Psychiatry,* 56**,** 558-565.

JI, X. & LIU, J. 2016. Subjective sleep measures for adolescents: a systematic review. *Child: care, health and development,* 42**,** 825-839.

JUTAI, J. W., STRONG, J. G. & RUSSELL-MINDA, E. 2009. Effectiveness of assistive technologies for low vision rehabilitation: A systematic review. *Journal of Visual Impairment & Blindness,* 103**,** 210-222.

KASKIE, R. E., GRAZIANO, B. & FERRARELLI, F. 2017a. Schizophrenia and sleep disorders: links, risks, and management challenges. *Nature and science of sleep,* 9**,** 227.

KASKIE, R. E., GRAZIANO, B. & FERRARELLI, F. 2017b. Schizophrenia and sleep disorders: links, risks, and management challenges. *Nature and Science of Sleep,* 9**,** 227-239.

KAYMAZ, N., DRUKKER, M., LIEB, R., WITTCHEN, H.-U., WERBELOFF, N., WEISER, M., LATASTER, T. & VAN OS, J. 2012. Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results. *Psychological medicine,* 42**,** 2239-2253.

KELLEHER, I., KEELEY, H., CORCORAN, P., LYNCH, F., FITZPATRICK, C., DEVLIN, N., MOLLOY, C., RODDY, S., CLARKE, M. C. & HARLEY, M. 2012. Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *The British Journal of Psychiatry,* 201**,** 26-32.

KESHAVAN, M. S., MONTROSE, D. M., MIEWALD, J. M. & JINDAL, R. D. 2011. Sleep correlates of cognition in early course psychotic disorders. *Schizophrenia research,* 131**,** 231-234.

KESSLER, R. C., ANDREWS, G., COLPE, L. J., HIRIPI, E., MROCZEK, D. K., NORMAND, S.-L., WALTERS, E. E. & ZASLAVSKY, A. M. 2002. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychological medicine,* 32**,** 959-976.

KESSLER, R. C., BARKER, P. R., COLPE, L. J., EPSTEIN, J. F., GFROERER, J. C., HIRIPI, E., HOWES, M. J., NORMAND, S.-L. T., MANDERSCHEID, R. W. & WALTERS, E. E. 2003. Screening for serious mental illness in the general population. *Archives of general psychiatry,* 60**,** 184-189.

KINNER, S. A., ALATI, R., NAJMAN, J. M. & WILLIAMS, G. M. 2007. Do paternal arrest and imprisonment lead to child behaviour problems and substance use? A longitudinal analysis. *Journal of Child Psychology and Psychiatry,* 48**,** 1148-1156.

KıRLı, U., BINBAY, T., DRUKKER, M., ELBI, H., KAYAHAN, B., GÖKÇELLI, D. K., ÖZKıNAY, F., ONAY, H., ALPTEKIN, K. & VAN OS, J. 2019. DSM outcomes of psychotic experiences and associated risk factors: 6-year follow-up study in a community-based sample. *Psychol Med.,* 49**,** 1346-1356.

KNESEVICH, J., BIGGS, J., CLAYTON, P. & ZIEGLER, V. 1977. Validity of the Hamilton Rating Scale for depression. *The British Journal of Psychiatry,* 131**,** 49-52.

KOOPMAN-VERHOEFF, M. E., BOLHUIS, K., CECIL, C. A., KOCEVSKA, D., HUDZIAK, J. J., HILLEGERS, M. H., MILEVA-SEITZ, V. R., REISS, I. K., DUIJTS, L. & VERHULST, F. 2019. During day and night: Childhood psychotic experiences and objective and subjective sleep problems. *Schizophrenia research,* 206**,** 127-134.

KOUNALI, D., ZAMMIT, S., WILES, N., SULLIVAN, S., CANNON, M., STOCHL, J., JONES, P., MAHEDY, L., GAGE, S. & HERON, J. 2014. Common versus psychopathology-specific risk factors for psychotic experiences and depression during adolescence. *Psychological medicine,* 44**,** 2557-2566.

KRYSTAL, A. D. & EDINGER, J. D. 2008. Measuring sleep quality. *Sleep medicine,* 9**,** S10-S17.

KUSHIDA, C. A., CHANG, A., GADKARY, C., GUILLEMINAULT, C., CARRILLO, O. & DEMENT, W. C. 2001. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. *Sleep medicine,* 2**,** 389-396.

LAI, M.-C., KASSEE, C., BESNEY, R., BONATO, S., HULL, L., MANDY, W., SZATMARI, P. & AMEIS, S. H. 2019. Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *The Lancet Psychiatry,* 6**,** 819-829.

LANKHORST, N. E., BIERMA-ZEINSTRA, S. M. & VAN MIDDELKOOP, M. 2012. Risk factors for patellofemoral pain syndrome: a systematic review. *journal of orthopaedic & sports physical therapy,* 42**,** 81-94.

LASKEMOEN, J. F., SIMONSEN, C., BÜCHMANN, C., BARRETT, E. A., BJELLA, T., LAGERBERG, T. V., VEDAL, T. J., ANDREASSEN, O. A., MELLE, I. & AAS, M. J. C. P. 2019. Sleep disturbances in schizophrenia spectrum and bipolar disorders–a transdiagnostic perspective. 91**,** 6-12.

LAURENS, K., HOBBS, M., SUNDERLAND, M., GREEN, M. & MOULD, G. 2012. Psychotic-like experiences in a community sample of 8000 children aged 9 to 11 years: an item response theory analysis. *Psychological medicine,* 42**,** 1495-1506.

LEANZA, L., STUDERUS, E., MACKINTOSH, A. J., BECK, K., SEILER, L., ANDREOU, C. & RIECHER-RÖSSLER, A. 2020. Predictors of study drop-out and service disengagement in patients at clinical high risk for psychosis. *Social psychiatry and psychiatric epidemiology,* 55**,** 539-548.

LEDERMAN, O., ROSENBAUM, S., MALONEY, C., CURTIS, J. & WARD, P. B. 2017. Modifiable cardiometabolic risk factors in youth with at-risk mental states: A cross-sectional pilot study. *Psychiatry research,* 257**,** 424-430.

LEE, K. W., CHAN, K. W., CHANG, W. C., LEE, E. H. M., HUI, C. L. M. & CHEN, E. Y. H. 2016. A systematic review on definitions and assessments of psychotic-like experiences. *Early intervention in psychiatry,* 10**,** 3-16.

LEE, S. J., KIM, K. R., LEE, S. Y. & AN, S. K. 2017. Impaired social and role function in ultra-high risk for psychosis and first-episode schizophrenia: its relations with negative symptoms. *Psychiatry investigation,* 14**,** 539.

LEREYA, S. T., WINSPER, C., TANG, N. K. & WOLKE, D. 2017. Sleep problems in childhood and borderline personality disorder symptoms in early adolescence. *Journal of abnormal child psychology,* 45**,** 193-206.

LESTER, H., MARSHALL, M., JONES, P., FOWLER, D., AMOS, T., KHAN, N. & BIRCHWOOD, M. 2011. Views of young people in early intervention services for first-episode psychosis in England. *Psychiatric Services,* 62**,** 882-887.

LIDDLE, P. F. 1987. The symptoms of chronic schizophrenia: a re-examination of the positive-negative dichotomy. *The British Journal of Psychiatry,* 151**,** 145-151.

LIEMBURG, E., CASTELEIN, S., STEWART, R., VAN DER GAAG, M., ALEMAN, A., KNEGTERING, H., RISK, G. & INVESTIGATORS, O. O. P. 2013. Two subdomains of negative symptoms in psychotic disorders: established and confirmed in two large cohorts. *Journal of psychiatric research,* 47**,** 718-725.

LIN, A., WOOD, S., NELSON, B., BREWER, W., SPILIOTACOPOULOS, D., BRUXNER, A., BROUSSARD, C., PANTELIS, C. & YUNG, A. 2011. Neurocognitive predictors of functional outcome two to 13 years after identification as ultra-high risk for psychosis. *Schizophrenia research,* 132**,** 1-7.

LIN, A., WOOD, S. J., NELSON, B., BEAVAN, A., MCGORRY, P. & YUNG, A. R. 2015. Outcomes of nontransitioned cases in a sample at ultra-high risk for psychosis. *American Journal of Psychiatry,* 172**,** 249-258.

LINDGREN, M., MANNINEN, M., KALSKA, H., MUSTONEN, U., LAAJASALO, T., MOILANEN, K., HUTTUNEN, M. O., CANNON, T. D., SUVISAARI, J. & THERMAN, S. 2017. Suicidality, self-harm and psychotic-like symptoms in a general adolescent psychiatric sample. *Early intervention in psychiatry,* 11**,** 113-122.

LINSCOTT, R. & VAN OS, J. 2013. An Updated and Conservative Systematic Review and Meta-Analysis of Epidemiological Evidence on Psychotic Experiences in Children and Adults: On the Pathway From Proneness to Persistence to Dimensional Expression Across Mental Disorders. *Psychological medicine,* 43**,** 1133-1149.

LITTLEWOOD, D., KYLE, S., PRATT, D., PETERS, S. & GOODING, P. 2017. Examining the role of psychological factors in the relationship between sleep problems and suicide. *Clinical psychology review,* 54**,** 1-16.

LOBBESTAEL, J., LEURGANS, M. & ARNTZ, A. 2011. Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I disorders (SCID I) and Axis II disorders (SCID II). *Clinical psychology psychotherapy,* 18**,** 75-79.

LONGDEN, E. & READ, J. 2016. Social adversity in the etiology of psychosis: A review of the evidence. *American Journal of Psychotherapy,* 70**,** 5-33.

LÜDTKE, T., PFUHL, G., MORITZ, S., RÜEGG, N. L., BERGER, T. & WESTERMANN, S. 2021. Sleep problems and worrying precede psychotic symptoms during an online intervention for psychosis. *British journal of clinical psychology,* 60**,** 48-67.

LUNSFORD-AVERY, J. R., DEAN, D. J. & MITTAL, V. A. 2017a. Self-reported sleep disturbances associated with procedural learning impairment in adolescents at ultra-high risk for psychosis. *Schizophrenia Research,* 190**,** 160-163.

LUNSFORD-AVERY, J. R., GONCALVES, B. D. B., BRIETZKE, E., BRESSAN, R. A., GADELHA, A., AUERBACH, R. P. & MITTAL, V. A. 2017b. Adolescents at clinical-high risk for psychosis: Circadian rhythm disturbances predict worsened prognosis at 1-year follow-up. *Schizophrenia Research,* 189**,** 37-42.

LUNSFORD-AVERY, J. R., GONÇALVES, B. D. S. B., BRIETZKE, E., BRESSAN, R. A., GADELHA, A., AUERBACH, R. P. & MITTAL, V. A. 2017c. Adolescents at clinical-high risk for psychosis: circadian rhythm disturbances predict worsened prognosis at 1-year follow-up. *Schizophrenia research,* 189**,** 37-42.

LUNSFORD-AVERY, J. R., LEBOURGEOIS, M. K., GUPTA, T. & MITTAL, V. A. 2015. Actigraphic-measured sleep disturbance predicts increased positive symptoms in adolescents at ultra high-risk for psychosis: a longitudinal study. *Schizophrenia research,* 164**,** 15-20.

LUNSFORD-AVERY, J. R. & MITTAL, V. A. 2013. Sleep dysfunction prior to the onset of schizophrenia: A review and neurodevelopmental diathesis–stress conceptualization. *Clinical Psychology: Science and Practice,* 20**,** 291-320.

LUNSFORD-AVERY, J. R., ORR, J. M., GUPTA, T., PELLETIER-BALDELLI, A., DEAN, D. J., WATTS, A. K. S., BERNARD, J., MILLMAN, Z. B. & MITTAL, V. A. 2013. Sleep dysfunction and thalamic abnormalities in adolescents at ultra high-risk for psychosis. *Schizophrenia Research,* 151**,** 148-153.

LUNSFORD-AVERY, J. R. & A. MITTAL, V. 2013. Sleep dysfunction prior to the onset of schizophrenia: a review and neurodevelopmental diathesis–stress conceptualization. *Clinical Psychology: Science and Practice,* 20**,** 291-320.

MAIER, W., BULLER, R., PHILIPP, M. & HEUSER, I. 1988. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. *Journal of affective disorders,* 14**,** 61-68.

MALHI, G. S. & BELL, E. 2019. Make News: Attenuated psychosis syndrome–a premature speculation? *Australian & New Zealand Journal of Psychiatry,* 53**,** 1028-1032.

MANOACH, D. S., DEMANUELE, C., WAMSLEY, E. J., VANGEL, M., MONTROSE, D. M., MIEWALD, J., KUPFER, D., BUYSSE, D., STICKGOLD, R. & KESHAVAN, M. S. 2014. Sleep spindle deficits in antipsychotic-naïve early course schizophrenia and in non-psychotic first-degree relatives. *Frontiers in Human Neuroscience.,* 8**,** 762.

MANOACH, D. S., PAN, J. Q., PURCELL, S. M. & STICKGOLD, R. 2016. Reduced sleep spindles in schizophrenia: a treatable endophenotype that links risk genes to impaired cognition? *Biological psychiatry,* 80**,** 599-608.

MANSOURNIA, M. A. & ALTMAN, D. G. 2016. Inverse probability weighting. *Bmj,* 352.

MARDER, S. R., FENTON, W. & YOUENS, K. 2004. Schizophrenia, IX: cognition in schizophrenia—the MATRICS initiative. *American Journal of Psychiatry,* 161**,** 25-25.

MARINO, M., LI, Y., RUESCHMAN, M. N., WINKELMAN, J. W., ELLENBOGEN, J., SOLET, J. M., DULIN, H., BERKMAN, L. F. & BUXTON, O. M. 2013. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. *Sleep,* 36**,** 1747-1755.

MARSHALL, M., LEWIS, S., LOCKWOOD, A., DRAKE, R., JONES, P. & CROUDACE, T. 2005. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Archives of general psychiatry,* 62**,** 975-983.

MASON, O., STARTUP, M., HALPIN, S., SCHALL, U., CONRAD, A. & CARR, V. J. S. R. 2004. Risk factors for transition to first episode psychosis among individuals with 'at-risk mental states'. 71**,** 227-237.

MAXWELL, S. E., LAU, M. Y. & HOWARD, G. S. 2015. Is psychology suffering from a replication crisis? What does "failure to replicate" really mean? *American Psychologist,* 70**,** 487.

MCGLASHAN, T. H. 2005. Early detection and intervention in psychosis: an ethical paradigm shift. *The British Journal of Psychiatry,* 187**,** s113-s115.

MCGORRY, P. D., YUNG, A. R. & PHILLIPS, L. J. 2003. The "close-in" or ultra high-risk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. *Schizophrenia bulletin,* 29**,** 771-790.

MCGRATH, J., SAHA, S., CHANT, D. & WELHAM, J. 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic reviews,* 30**,** 67-76.

MCGRATH, J. J., SAHA, S., AL-HAMZAWI, A. O., ALONSO, J., ANDRADE, L., BORGES, G., BROMET, E. J., OAKLEY BROWNE, M., BRUFFAERTS, R. & CALDAS DE ALMEIDA, J. M. 2016. Age of onset and lifetime projected risk of psychotic experiences: cross-national data from the World Mental Health Survey. *Schizophrenia bulletin,* 42**,** 933-941.

MEDICINE, A. A. O. S. 2005. International classification of sleep disorders. *Diagnostic and coding manual***,** 51-55.

MENG, H., SCHIMMELMANN, B. G., KOCH, E., BAILEY, B., PARZER, P., GÜNTER, M., MOHLER, B., KUNZ, N., SCHULTE-MARKWORT, M. & FELDER, W. 2009. Basic symptoms in the general population and in psychotic and non-psychotic psychiatric adolescents. *Schizophrenia Research,* 111**,** 32-38.

MEZICK, E. J., MATTHEWS, K. A., HALL, M., STROLLO JR, P. J., BUYSSE, D. J., KAMARCK, T. W., OWENS, J. F. & REIS, S. E. 2008. Influence of race and socioeconomic status on sleep: Pittsburgh Sleep SCORE project. *Psychosomatic medicine,* 70**,** 410.

MICHELS, F., SCHILLING, C., RAUSCH, F., EIFLER, S., ZINK, M., MEYER-LINDENBERG, A. & SCHREDL, M. 2014. Nightmare frequency in schizophrenic patients, healthy relatives of schizophrenic patients, patients at high risk states for psychosis, and healthy controls. *International Journal of Dream Research,* 7**,** 9-13.

MILLER, T. J., MCGLASHAN, T., ROSEN, J., CADENHEAD, K., VENTURA, J., MCFARLANE, W., PERKINS, D., PEARLSON, G. & WOODS, S. 2003a. Interview for prodromal syndromes and the scale of prodromal symptoms: Predictive validity, interrater reliability, and training to reliability. *Schizophr Bull,* 29**,** 703-15.

MILLER, T. J., ZIPURSKY, R. B., PERKINS, D., ADDINGTON, J., WOODS, S. W., HAWKINS, K. A., HOFFMAN, R., PREDA, A., EPSTEIN, I., ADDINGTON, D., LINDBORG, S., MARQUEZ, E., TOHEN, M., BREIER, A. & MCGLASHAN, T. H. 2003b. The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. II. Baseline characteristics of the "prodromal" sample. *Schizophrenia Research,* 61**,** 19-30.

MINDELL, J. & BARRETT, K. 2002. Nightmares and anxiety in elementary-aged children: is there a relationship? *Child: care, health and development,* 28**,** 317-322.

MINICHINO, A., RUTIGLIANO, G., MERLINO, S., DAVIES, C., OLIVER, D., DE MICHELI, A., PATEL, R., MCGUIRE, P. & FUSAR-POLI, P. 2019. Unmet needs in patients with brief psychotic disorders: Too ill for clinical high risk services and not ill enough for first episode services. *European Psychiatry,* 57**,** 26-32.

MITCHELL, S. J., SLOWTHER, A.-M., COAD, J., AKHTAR, S., HYDE, E., KHAN, D. & DALE, J. 2019. Ethics and patient and public involvement with children and young people. *Archives of Disease in Childhood-Education and Practice,* 104**,** 195-200.

MOLLAYEVA, T., THURAIRAJAH, P., BURTON, K., MOLLAYEVA, S., SHAPIRO, C. M. & COLANTONIO, A. 2016. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. *Sleep medicine reviews,* 25**,** 52-73.

MORALES-MUÑOZ, I., BROOME, M. R. & MARWAHA, S. 2020. Association of parent-reported sleep problems in early childhood with psychotic and borderline personality disorder symptoms in adolescence. *JAMA psychiatry,* 77**,** 1256-1265.

MORENO-KÜSTNER, B., MARTIN, C. & PASTOR, L. 2018. Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. *PloS one,* 13**,** e0195687.

MORRISON, A. P. 2001. The interpretation of intrusions in psychosis: an integrative cognitive approach to hallucinations and delusions. *Behavioural and cognitive psychotherapy,* 29**,** 257-276.

MORRISON, A. P., FRENCH, P., STEWART, S. L., BIRCHWOOD, M., FOWLER, D., GUMLEY, A. I., JONES, P. B., BENTALL, R. P., LEWIS, S. W. & MURRAY, G. K. 2012. Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. *Bmj,* 344**,** e2233.

MYERS, E., STARTUP, H. & FREEMAN, D. 2011. Cognitive behavioural treatment of insomnia in individuals with persistent persecutory delusions: a pilot trial. *Journal of behavior therapy and experimental psychiatry,* 42**,** 330-336.

MYLONAS, D., TOCCI, C., COON, W. G., BARAN, B., KOHNKE, E. J., ZHU, L., VANGEL, M. G., STICKGOLD, R. & MANOACH, D. S. 2019. Naps reliably estimate nocturnal sleep spindle density in health and schizophrenia. *Journal of Sleep Research***,** e12968.

NELSON, B., FUSAR-POLI, P. & R YUNG, A. 2012a. Can we detect psychotic-like experiences in the general population? *Current pharmaceutical design,* 18**,** 376-385.

NELSON, B., THOMPSON, A. & YUNG, A. R. 2012b. Basic self-disturbance predicts psychosis onset in the ultra high risk for psychosis "prodromal" population. *Schizophrenia bulletin,* 38**,** 1277-1287.

NELSON, B., YUEN, H. P., WOOD, S. J., LIN, A., SPILIOTACOPOULOS, D., BRUXNER, A., BROUSSARD, C., SIMMONS, M., FOLEY, D. L. & BREWER, W. J. 2013. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study. *JAMA psychiatry,* 70**,** 793-802.

NEWBURY, J., ARSENEAULT, L., CASPI, A., MOFFITT, T. E., ODGERS, C. L. & FISHER, H. L. 2018. Cumulative effects of neighborhood social adversity and personal crime victimization on adolescent psychotic experiences. *Schizophrenia bulletin,* 44**,** 348-358.

NIEMI, L. T., SUVISAARI, J. M., TUULIO-HENRIKSSON, A. & LÖNNQVIST, J. K. 2003. Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. *Schizophrenia research,* 60**,** 239-258.

O'SULLIVAN, M., RAHIM, M. & HALL, C. 2015. The prevalence and management of poor sleep quality in a secondary care mental health population. *Journal of Clinical Sleep Medicine,* 11**,** 111-116.

OH, H., YANG, L. H., ANGLIN, D. M. & DEVYLDER, J. E. 2014. Perceived discrimination and psychotic experiences across multiple ethnic groups in the United States. *Schizophrenia research,* 157**,** 259-265.

OHAYON, M. M. 1997. Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing insomnia related to mental disorders from sleep disorders. *Journal of psychiatric research,* 31**,** 333-346.

OHAYON, M. M., CARSKADON, M. A., GUILLEMINAULT, C. & VITIELLO, M. V. 2004. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep,* 27**,** 1255-1273.

ONG, W. J., TAN, X. W., SHAHWAN, S., SATGHARE, P., CETTY, L., NG, B. T., TANG, C., VERMA, S., CHONG, S. A. & SUBRAMANIAM, M. 2020. Association between sleep quality and domains of quality of life amongst patients with first episode psychosis. *Health and Quality of Life Outcomes,* 18**,** 1-9.

PAN, J.-X. & FANG, K.-T. 2002. Maximum likelihood estimation. *Growth curve models and statistical diagnostics*. Springer.

PATEL, N. P., GRANDNER, M. A., XIE, D., BRANAS, C. C. & GOONERATNE, N. 2010. " Sleep disparity" in the population: poor sleep quality is strongly associated with poverty and ethnicity. *BMC Public Health,* 10**,** 1-11.

PAUS, T., KESHAVAN, M. & GIEDD, J. N. 2008. Why do many psychiatric disorders emerge during adolescence? *Nature reviews neuroscience,* 9**,** 947-957.

PERÄLÄ, J., SUVISAARI, J., SAARNI, S. I., KUOPPASALMI, K., ISOMETSÄ, E., PIRKOLA, S., PARTONEN, T., TUULIO-HENRIKSSON, A., HINTIKKA, J. & KIESEPPÄ, T. 2007. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of general psychiatry,* 64**,** 19-28.

PERKINS, D. O., GU, H., BOTEVA, K. & LIEBERMAN, J. A. 2005. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *American journal of psychiatry,* 162**,** 1785-1804.

PHILLIPS, L. J., MCGORRY, P. D., YUNG, A. R., MCGLASHAN, T. H., CORNBLATT, B. & KLOSTERKÖTTER, J. 2005. Prepsychotic phase of schizophrenia and related disorders: recent progress and future opportunities. *The British Journal of Psychiatry,* 187**,** s33-s44.

POE, S.-L., BRUCATO, G., BRUNO, N., ARNDT, L. Y., BEN-DAVID, S., GILL, K. E., COLIBAZZI, T., KANTROWITZ, J. T., CORCORAN, C. M. & GIRGIS, R. R. 2017. Sleep disturbances in individuals at clinical high risk for psychosis. *Psychiatry research,* 249**,** 240-243.

POPAY, J., ROBERTS, H., SOWDEN, A., PETTICREW, M., ARAI, L., RODGERS, M., BRITTEN, N., ROEN, K. & DUFFY, S. 2006. Guidance on the conduct of narrative synthesis in systematic reviews. *A product from the ESRC methods programme Version,* 1**,** b92.

POTUZAK, M., RAVICHANDRAN, C., LEWANDOWSKI, K. E., ONGÜR, D. & COHEN, B. M. 2012. Categorical vs dimensional classifications of psychotic disorders. *Comprehensive psychiatry,* 53**,** 1118-1129.

POULIN, J., DAOUST, A.-M., FOREST, G., STIP, E. & GODBOUT, R. 2003. Sleep architecture and its clinical correlates in first episode and neuroleptic-naive patients with schizophrenia. *Schizophrenia Research,* 62**,** 147-153.

POULIN, J., STIP, E. & GODBOUT, R. 2008. REM sleep EEG spectral analysis in patients with first-episode schizophrenia. *Journal of psychiatric research,* 42**,** 1086-1093.

POULTON, R., CASPI, A., MOFFITT, T. E., CANNON, M., MURRAY, R. & HARRINGTON, H. 2000. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Archives of general psychiatry,* 57**,** 1053-1058.

POWERS, A. R., ADDINGTON, J., PERKINS, D. O., BEARDEN, C. E., CADENHEAD, K. S., CANNON, T. D., CORNBLATT, B. A., MATHALON, D. H., SEIDMAN, L. J. & TSUANG, M. T. 2020. Duration of the psychosis prodrome. *Schizophrenia research,* 216**,** 443-449.

PURCELL, R., JORM, A., HICKIE, I., YUNG, A., PANTELIS, C., AMMINGER, G., GLOZIER, N., KILLACKEY, E., PHILLIPS, L. & WOOD, S. 2015a. T ransitions S tudy of predictors of illness progression in young people with mental ill health: study methodology. *Early Intervention in Psychiatry,* 9**,** 38-47.

PURCELL, R., JORM, A. F., HICKIE, I. B., YUNG, A. R., PANTELIS, C., AMMINGER, G. P., GLOZIER, N., KILLACKEY, E., PHILLIPS, L. J. & WOOD, S. J. 2015b. Demographic and clinical characteristics of young people seeking help at youth mental health services: baseline findings of the T ransitions S tudy. *Early Intervention in Psychiatry,* 9**,** 487-497.

RABALLO, A., NELSON, B., THOMPSON, A. & YUNG, A. 2011. The comprehensive assessment of at-risk mental states: from mapping the onset to mapping the structure. *Schizophrenia research,* 127**,** 107-114.

RAPADO-CASTRO, M., MCGORRY, P. D., YUNG, A., CALVO, A. & NELSON, B. 2015. Sources of clinical distress in young people at ultra high risk of psychosis. *Schizophrenia research,* 165**,** 15-21.

RASHID, A., THOMAS, V., SHAW, T. & LENG, G. 2017. Patient and public involvement in the development of healthcare guidance: an overview of current methods and future challenges. *The Patient-Patient-Centered Outcomes Research,* 10**,** 277-282.

REALPE, A. & WALLACE, L. M. 2010. What is co-production. *London: The Health Foundation***,** 1-1.

REEVE, S., EMSLEY, R., SHEAVES, B. & FREEMAN, D. 2018a. Disrupting sleep: the effects of sleep loss on psychotic experiences tested in an experimental study with mediation analysis. *Schizophrenia bulletin,* 44**,** 662-671.

REEVE, S., NICKLESS, A., SHEAVES, B. & FREEMAN, D. 2018b. Insomnia, negative affect, and psychotic experiences: Modelling pathways over time in a clinical observational study. *Psychiatry research,* 269**,** 673-680.

REEVE, S., NICKLESS, A., SHEAVES, B., HODGEKINS, J., STEWART, S., GUMLEY, A., FOWLER, D., MORRISON, A. & FREEMAN, D. J. S. R. 2018c. Sleep duration and psychotic experiences in patients at risk of psychosis: A secondary analysis of the EDIE-2 trial.

REEVE, S., SHEAVES, B. & FREEMAN, D. 2015. The role of sleep dysfunction in the occurrence of delusions and hallucinations: A systematic review. *Clinical Psychology Review,* 42**,** 96-115.

REEVE, S., SHEAVES, B. & FREEMAN, D. 2018d. Sleep disorders in early psychosis: incidence, severity, and association with clinical symptoms. *Schizophrenia bulletin,* 45**,** 287-295.

REEVE, S., SHEAVES, B. & FREEMAN, D. 2019. Sleep disorders in early psychosis: incidence, severity, and association with clinical symptoms. *Schizophrenia bulletin,* 45**,** 287-295.

REHMAN, A., WAITE, F., SHEAVES, B., BIELLO, S., FREEMAN, D. & GUMLEY, A. 2017. Clinician perceptions of sleep problems, and their treatment, in patients with non-affective psychosis. *Psychosis,* 9**,** 129-139.

REK, S., SHEAVES, B. & FREEMAN, D. 2017. Nightmares in the general population: identifying potential causal factors. *Social psychiatry and psychiatric epidemiology,* 52**,** 1123-1133.

RIETDIJK, J., KLAASSEN, R., ISING, H., DRAGT, S., NIEMAN, D., VAN DE KAMP, J., CUIJPERS, P., LINSZEN, D. & VAN DER GAAG, M. 2012. Detection of people at risk of developing a first psychosis: comparison of two recruitment strategies. *Acta Psychiatrica Scandinavica,* 126**,** 21-30.

RISE, M. B., SOLBJØR, M., LARA, M. C., WESTERLUND, H., GRIMSTAD, H. & STEINSBEKK, A. 2013. Same description, different values. How service users and providers define patient and public involvement in health care. *Health Expectations,* 16**,** 266-276.

RITSNER, M., KURS, R., PONIZOVSKY, A. & HADJEZ, J. 2004. Perceived quality of life in schizophrenia: relationships to sleep quality. *Quality of Life Research,* 13**,** 783-791.

RITSNER, M. S. 2007. The distress/protection vulnerability model of quality of life impairment syndrome. *Quality of life impairment in schizophrenia, mood and anxiety disorders*. Springer.

RITSNER, M. S. & AWAD, A. G. 2007. *Quality of life impairment in schizophrenia, mood and anxiety disorders*, Springer.

ROBUSTELLI, B. L., NEWBERRY, R. E., WHISMAN, M. A. & MITTAL, V. A. 2017. Social relationships in young adults at ultra high risk for psychosis. *Psychiatry research,* 247**,** 345-351.

ROUSSEAU, A. & BELLEVILLE, G. 2018. The mechanisms of action underlying the efficacy of psychological nightmare treatments: A systematic review and thematic analysis of discussed hypotheses. *Sleep medicine reviews,* 39**,** 122-133.

ROWLAND, L. M. & WICKWIRE, E. M. 2018. A Wake-up Call: Assess and Treat Sleep Disorders in Early Psychosis. *Schizophrenia bulletin*.

RUHRMANN, S., PARUCH, J., BECHDOLF, A., PUKROP, R., WAGNER, M., BERNING, J., SCHULTZE-LUTTER, F., JANSSEN, B., GAEBEL, W. & MÖLLER, H. J. 2008. Reduced subjective quality of life in persons at risk for psychosis. *Acta Psychiatrica Scandinavica,* 117**,** 357-368.

RUHRMANN, S., SCHULTZE-LUTTER, F., SALOKANGAS, R. K., HEINIMAA, M., LINSZEN, D., DINGEMANS, P., BIRCHWOOD, M., PATTERSON, P., JUCKEL, G. & HEINZ, A. 2010a. Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Archives of general psychiatry,* 67**,** 241-251.

RUHRMANN, S., SCHULTZE-LUTTER, F., SALOKANGAS, R. K. R., HEINIMAA, M., LINSZEN, D., DINGEMANS, P., BIRCHWOOD, M., PATTERSON, P., JUCKEL, G., HEINZ, A., MORRISON, A., LEWIS, S., GRAF VON REVENTLOW, H. & KLOSTERKOTTER, J. 2010b. Prediction of psychosis in adolescents and young adults at

high risk: Results from the prospective European prediction of psychosis study. *Archives of General Psychiatry,* 67**,** 241-251.

RYBARCZYK, B. 2011. Social and occupational functioning assessment scale (SOFAS). *LXIII, encyclopedia of clinical neuropsychology,* 1**,** 2313.

SADEH, A. 2015. Iii. Sleep assessment methods. *Monographs of the Society for Research in Child Development,* 80**,** 33-48.

SADEH, A., DAHL, R. E., SHAHAR, G. & ROSENBLAT-STEIN, S. 2009. Sleep and the transition to adolescence: a longitudinal study. *Sleep,* 32**,** 1602-1609.

SAGAYADEVAN, V., LEE, S. P., ONG, C., ABDIN, E., CHONG, S. A. & SUBRAMANIAM, M. 2018. Quality of life across mental disorders in psychiatric outpatients. *Ann Acad Med Singapore,* 47**,** 243-252.

SAGNA, A., GALLO, J. J. & PONTONE, G. M. 2014. Systematic review of factors associated with depression and anxiety disorders among older adults with Parkinson's disease. *Parkinsonism & related disorders,* 20**,** 708-715.

SAMIOTAKIS, G., KOLLIAS, C., LAZARATOU, H., ANAGNOSTOPOULOS, D. & KONTAXAKIS, V. 2017. Attenuated psychosis syndrome: A new diagnostic category for further study in DSM-5. *Psychiatrike= Psychiatriki,* 28**,** 120-130.

SANGLA, A. & KANDASAMY, Y. 2021. Effects of prematurity on long-term renal health: A systematic review. *BMJ open,* 11**,** e047770.

SAWANT, N. S. & THAKURDESAI, A. 2018. Case report: Sleep deprivation presenting as acute psychosis. *Indian Journal of Case Reports***,** 142-143.

SCHERMELLEH-ENGEL, K., MOOSBRUGGER, H. & MÜLLER, H. 2003. Evaluating the fit of structural equation models: Tests of significance and descriptive goodness-of-fit measures. *Methods of psychological research online,* 8**,** 23-74.

SCHIFFMAN, J. & T CARPENTER, W. 2015. Attenuated psychosis syndrome: benefits of explicit recognition. *Shanghai archives of psychiatry,* 27**,** 48.

SCHULTZE-LUTTER, F. 2009. Subjective symptoms of schizophrenia in research and the clinic: the basic symptom concept. *Schizophrenia bulletin,* 35**,** 5-8.

SCHULTZE-LUTTER, F., KLOSTERKÖTTER, J., PICKER, H., STEINMEYER, E.-M. & RUHRMANN, S. 2007. Predicting first-episode psychosis by basic symptom criteria. *Clin neuropsychiatry,* 4**,** 11-22.

SCHULTZE-LUTTER, F., MICHEL, C., SCHMIDT, S. J., SCHIMMELMANN, B., MARIC, N., SALOKANGAS, R., RIECHER-RÖSSLER, A., VAN DER GAAG, M., NORDENTOFT, M. & RABALLO, A. 2015. EPA guidance on the early detection of clinical high risk states of psychoses. *European Psychiatry,* 30**,** 405-416.

SCHULTZE-LUTTER, F., RUHRMANN, S. & KLOSTERKÖTTER, J. 2006. Can schizophrenia be predicted phenomenologically. *Evolving psychosis. Different stages, different treatments***,** 104-123.

SCHULTZE-LUTTER, F., SCHIMMELMANN, B. G., RUHRMANN, S. & MICHEL, C. 2013. 'A rose is a rose is a rose', but at-risk criteria differ. *Psychopathology,* 46**,** 75-87.

SCOTT, H., LACK, L. & LOVATO, N. 2020. A systematic review of the accuracy of sleep wearable devices for estimating sleep onset. *Sleep medicine reviews,* 49**,** 101227.

SCOTT, J., WELHAM, J., MARTIN, G., BOR, W., NAJMAN, J., O'CALLAGHAN, M., WILLIAMS, G., AIRD, R. & MCGRATH, J. 2008. Demographic correlates of psychotic-like experiences in young Australian adults. *Acta Psychiatrica Scandinavica,* 118**,** 230-237.

SEAMAN, S. R. & WHITE, I. R. 2013. Review of inverse probability weighting for dealing with missing data. *Statistical methods in medical research,* 22**,** 278-295.

SEOW, L. S. E., VERMA, S. K., MOK, Y. M., KUMAR, S., CHANG, S., SATGHARE, P., HOMBALI, A., VAINGANKAR, J., CHONG, S. A. & SUBRAMANIAM, M. 2018. Evaluating DSM-5 insomnia disorder and the treatment of sleep problems in a psychiatric population. *Journal of Clinical Sleep Medicine,* 14**,** 237-244.

SHAH, J., MIZRAHI, R. & MCKENZIE, K. 2011. The four dimensions: a model for the social aetiology of psychosis. *The British Journal of Psychiatry,* 199**,** 11-14.

SHARAFKHANEH, A., GIRAY, N., RICHARDSON, P., YOUNG, T. & HIRSHKOWITZ, M. 2005. Association of psychiatric disorders and sleep apnea in a large cohort. *Sleep,* 28**,** 1405-1411.

SHEAVES, B., HOLMES, E. A., REK, S., TAYLOR, K. M., NICKLESS, A., WAITE, F., GERMAIN, A., ESPIE, C. A., HARRISON, P. J. & FOSTER, R. 2019. Cognitive behavioural therapy for nightmares for patients with persecutory delusions (nites): an assessor-blind, pilot randomized controlled trial. *The Canadian Journal of Psychiatry,* 64**,** 686-696.

SHEAVES, B., ISHAM, L., BRADLEY, J., ESPIE, C., BARRERA, A., WAITE, F., HARVEY, A. G., ATTARD, C. & FREEMAN, D. 2018. Adapted CBT to stabilize sleep on psychiatric wards: a transdiagnostic treatment approach. *Behavioural and cognitive psychotherapy,* 46**,** 661-675.

SHEAVES, B., ONWUMERE, J., KEEN, N. & KUIPERS, E. 2015a. Treating your worst nightmare: a case-series of imagery rehearsal therapy for nightmares in individuals experiencing psychotic symptoms. *The Cognitive Behaviour Therapist,* 8.

SHEAVES, B., ONWUMERE, J., KEEN, N., STAHL, D. & KUIPERS, E. 2015b. Nightmares in patients with psychosis: the relation with sleep, psychotic, affective, and cognitive symptoms. *The Canadian Journal of Psychiatry,* 60**,** 354-361.

SHIMIZU, M., ZERINGUE, M. M., ERATH, S. A., HINNANT, J. B. & EL-SHEIKH, M. 2021. Trajectories of sleep problems in childhood: associations with mental health in adolescence. *Sleep,* 44**,** 190.

SHROUT, P. E. & RODGERS, J. L. 2018. Psychology, science, and knowledge construction: Broadening perspectives from the replication crisis. *Annual review of psychology,* 69**,** 487-510.

SIEGEL, J. M. 2003. Why we sleep. *Scientific American,* 289**,** 92-97.

SIMON, A. E., GRÄDEL, M., CATTAPAN-LUDEWIG, K., GRUBER, K., BALLINARI, P., ROTH, B. & UMBRICHT, D. 2012. Cognitive functioning in at-risk mental states for psychosis and 2-year clinical outcome. *Schizophrenia research,* 142**,** 108-115.

SINGH, S. P., MOHAN, M. & GIACCO, D. 2021. Psychosocial interventions for people with a first episode psychosis: between tradition and innovation. *Current Opinion in Psychiatry,* 5**,** 460-466.

SOUTH, A., HANLEY, B., GAFOS, M., CROMARTY, B., STEPHENS, R., STURGEON, K., SCOTT, K., CRAGG, W. J., TWEED, C. D. & TEERA, J. 2016. Models and impact of patient and public involvement in studies carried out by the Medical Research Council Clinical Trials Unit at University College London: findings from ten case studies. *Trials,* 17**,** 376.

SPITZER, R. L., WILLIAMS, J. B., GIBBON, M. & FIRST, M. B. 1992. The structured clinical interview for DSM-III-R (SCID): I: history, rationale, and description. *Archives of general psychiatry,* 49**,** 624-629.

STEPHANE, M., STARKSTEIN, S. & PAHISSA, J. 2014. Psychosis in general medical and neurological conditions. *The Assessment of Psychosis.* Routledge.

STEWART, R. & LIABO, K. 2012. Involvement in research without compromising research quality. *Journal of health services research & policy,* 17**,** 248-251.

STOWKOWY, J., BRUMMITT, K., BONNEVILLE, D., GOLDSTEIN, B. I., WANG, J., KENNEDY, S. H., BRAY, S., LEBEL, C., MACQUEEN, G. & ADDINGTON, J. 2020. Sleep disturbances in youth at-risk for serious mental illness. *Early Intervention in Psychiatry,* 14**,** 373-378.

STRAUSS, G. P., BARTOLOMEO, L. A. & HARVEY, P. D. 2021. Avolition as the core negative symptom in schizophrenia: relevance to pharmacological treatment development. *npj Schizophrenia,* 7**,** 1-6.

STRAUSS, J. S., CARPENTER, W. T. & BARTKO, J. J. 1974. Speculations on the processes that underlie schizophrenic symptoms and signs: III. *Schizophrenia Bulletin,* 1**,** 61.

SULLIVAN, S. A., KOUNALI, D., CANNON, M., DAVID, A. S., FLETCHER, P. C., HOLMANS, P., JONES, H., JONES, P. B., LINDEN, D. E. & LEWIS, G. 2020. A population-based cohort study examining the incidence and impact of psychotic experiences from childhood to adulthood, and prediction of psychotic disorder. *American Journal of Psychiatry,* 177**,** 308-317.

SYKES, L. A. Y., FERRARA, M., ADDINGTON, J., BEARDEN, C. E., CADENHEAD, K. S., CANNON, T. D., CORNBLATT, B. A., PERKINS, D. O., MATHALON, D. H. & SEIDMAN, L. J. 2020. Predictive validity of conversion from the clinical high risk syndrome to frank psychosis. *Schizophrenia research,* 216**,** 184-191.

TACKETT, J. L., BRANDES, C. M., KING, K. M. & MARKON, K. E. 2019. Psychology's replication crisis and clinical psychological science. *Annual review of clinical psychology,* 15**,** 579-604.

TAN, H. & ANG, Y. 2001. First-episode psychosis in the military: a comparative study of prodromal symptoms. *Australian & New Zealand Journal of Psychiatry,* 35**,** 512-519.

TAYLOR, D. J. & PRUIKSMA, K. E. 2014. Cognitive and behavioural therapy for insomnia (CBT-I) in psychiatric populations: a systematic review. *International review of psychiatry,* 26**,** 205-213.

TAYLOR, M. J., GREGORY, A. M., FREEMAN, D. & RONALD, A. 2015. Do sleep disturbances and psychotic-like experiences in adolescence share genetic and environmental influences? *Journal of Abnormal Psychology,* 124**,** 674.

TELZER, E. H., GOLDENBERG, D., FULIGNI, A. J., LIEBERMAN, M. D. & GÁLVAN, A. 2015. Sleep variability in adolescence is associated with altered brain development. *Developmental cognitive neuroscience,* 14**,** 16-22.

THABREW, H., STASIAK, K., BAVIN, L. M., FRAMPTON, C. & MERRY, S. 2018. Validation of the mood and feelings questionnaire (mfq) and short mood and feelings questionnaire (smfq) in new zealand help-seeking adolescents. *International Journal of Methods in Psychiatric Research,* 27**,** e1610.

THOMAS, A. B. 2001. Evolution of diagnostic criteria in psychoses. *Dialogues in clinical neuroscience,* 3**,** 257.

THOMPSON, A., LEREYA, S., LEWIS, G., ZAMMIT, S., FISHER, H. & WOLKE, D. 2015. Childhood sleep disturbance and risk of psychotic experiences at 18: UK birth cohort. *The British Journal of Psychiatry,* 207**,** 23-29.

TOUCHETTE, É., PETIT, D., PAQUET, J., BOIVIN, M., JAPEL, C., TREMBLAY, R. E. & MONTPLAISIR, J. Y. 2005. Factors associated with fragmented sleep at night across early childhood. *Archives of pediatrics & adolescent medicine,* 159**,** 242-249.

TROTTA, A., MURRAY, R. & FISHER, H. 2015. The impact of childhood adversity on the persistence of psychotic symptoms: a systematic review and meta-analysis. *Psychological medicine,* 45**,** 2481.

TSO, I. F., TAYLOR, S. F., GROVE, T. B., NIENDAM, T., ADELSHEIM, S., AUTHER, A., CORNBLATT, B., CARTER, C. S., CALKINS, R. & RAGLAND, J. D. 2017. Factor analysis of the Scale of Prodromal Symptoms: data from the Early Detection and Intervention for the Prevention of Psychosis Program. *Early intervention in psychiatry,* 11**,** 14-22.

TSUANG, M. T., VAN OS, J., TANDON, R., BARCH, D. M., BUSTILLO, J., GAEBEL, W., GUR, R. E., HECKERS, S., MALASPINA, D. & OWEN, M. J. 2013. Attenuated psychosis syndrome in DSM-5. *Schizophrenia research,* 150**,** 31-35.

UNTERRASSNER, L., WYSS, T. A., WOTRUBA, D., AJDACIC-GROSS, V., HAKER, H. & RÖSSLER, W. 2017. Psychotic-like experiences at the healthy end of the psychosis continuum. *Frontiers in psychology,* 8**,** 775.

VAN DER GAAG, M., HOFFMAN, T., REMIJSEN, M., HIJMAN, R., DE HAAN, L., VAN MEIJEL, B., VAN HARTEN, P. N., VALMAGGIA, L., DE HERT, M. & CUIJPERS, A. 2006. The five-factor model of the Positive and Negative Syndrome Scale II: a ten-fold cross-validation of a revised model. *Schizophrenia research,* 85**,** 280-287.

VAN HEES, V. T., SABIA, S., JONES, S. E., WOOD, A. R., ANDERSON, K. N., KIVIMÄKI, M., FRAYLING, T. M., PACK, A. I., BUCAN, M. & TRENELL, M. 2018. Estimating sleep parameters using an accelerometer without sleep diary. *Scientific reports,* 8**,** 1-11.

VAN OS, J., GILVARRY, C., BALE, R., VAN HORN, E., TATTAN, T. & WHITE, I. 1999. A comparison of the utility of dimensional and categorical representations of psychosis. *Psychological medicine,* 29**,** 595-606.

VAN OS, J., LINSCOTT, R. J., MYIN-GERMEYS, I., DELESPAUL, P. & KRABBENDAM, L. 2009. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological medicine,* 39**,** 179.

VAN VEELEN, N. M. & SOMMER, I. E. 2014. Psychosis in Psychiatric Disorders. *The Assessment of Psychosis*. Routledge.

VELTHORST, E., NELSON, B., WILTINK, S., DE HAAN, L., WOOD, S. J., LIN, A. & YUNG, A. R. 2013. Transition to first episode psychosis in ultra high risk populations: does baseline functioning hold the key? *Schizophrenia research,* 143**,** 132-137.

WAITE, F. & SHEAVES, B. 2020. Better sleep: evidence-based interventions. *A Clinical Introduction to Psychosis*. Academic Press.

WAITE, F., SHEAVES, B., ISHAM, L., REEVE, S. & FREEMAN, D. 2019. Sleep and schizophrenia: From epiphenomenon to treatable causal target. *Schizophrenia Research*.

WALKER, M. 2017. *Why we sleep: Unlocking the power of sleep and dreams*, Simon and Schuster.

WAMSLEY, E. J., TUCKER, M. A., SHINN, A. K., ONO, K. E., MCKINLEY, S. K., ELY, A. V., GOFF, D. C., STICKGOLD, R. & MANOACH, D. S. 2012. Reduced sleep spindles and spindle coherence in schizophrenia: mechanisms of impaired memory consolidation? *Biological psychiatry,* 71**,** 154-161.

WARNER, R. 2005. Problems with early and very early intervention in psychosis. *The British Journal of Psychiatry,* 187**,** s104-s107.

WATERS, F., BLOM, J., JARDRI, R., HUGDAHL, K. & SOMMER, I. 2018. Auditory hallucinations, not necessarily a hallmark of psychotic disorder. *Psychological medicine,* 48**,** 529-536.

WATERS, F., CHIU, V. W., DRAGOVIC, M. & REE, M. 2020. Different patterns of treatment response to Cognitive-Behavioural Therapy for Insomnia (CBT-I) in psychosis. *Schizophrenia research,* 221**,** 57-62.

WATERS, F., NAIK, N. & ROCK, D. 2013. Sleep, fatigue, and functional health in psychotic patients. *Schizophrenia research and treatment,* 2013.

WATERS, F., REE, M. J. & CHIU, V. 2017. *Delivering CBT for insomnia in psychosis: a clinical guide*, Routledge.

WERBELOFF, N., DRUKKER, M., DOHRENWEND, B. P., LEVAV, I., YOFFE, R., VAN OS, J., DAVIDSON, M. & WEISER, M. 2012. Self-reported attenuated psychotic symptoms as forerunners of severe mental disorders later in life. *Archives of general psychiatry,* 69**,** 467-475.

WHINNERY, J., JACKSON, N., RATTANAUMPAWAN, P. & GRANDNER, M. A. 2014. Short and long sleep duration associated with race/ethnicity, sociodemographics, and socioeconomic position. *Sleep,* 37**,** 601-611.

WIGGINS, B. J. & CHRISOPHERSON, C. D. 2019. The replication crisis in psychology: An overview for theoretical and philosophical psychology. *Journal of Theoretical and Philosophical Psychology,* 39**,** 202.

WIGMAN, J. T., VAN WINKEL, R., JACOBS, N., WICHERS, M., DEROM, C., THIERY, E., VOLLEBERGH, W. A. & VAN OS, J. 2011. A twin study of genetic and environmental determinants of abnormal persistence of psychotic experiences in young adulthood. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics,* 156**,** 546-552.

WILLIAMS, N. 2014. The GAD-7 questionnaire. *Occupational Medicine,* 64**,** 224-224.

WILSON, J., CLARKE, T., LOWER, R., UGOCHUKWU, U., MAXWELL, S., HODGEKINS, J., WHEELER, K., GOFF, A., MACK, R. & HORNE, R. 2018a. Creating an innovative youth

mental health service in the United Kingdom: the Norfolk Youth Service. *Early intervention in psychiatry,* 12**,** 740-746.

WILSON, P., MATHIE, E., POLAND, F., KEENAN, J., HOWE, A., MUNDAY, D., KENDALL, S., COWE, M., STANISZEWSKA, S. & GOODMAN, C. 2018b. How embedded is public involvement in mainstream health research in England a decade after policy implementation? A realist evaluation. *Journal of health services research & policy,* 23**,** 98-106.

WINSPER, C., BILGIN, A. & WOLKE, D. 2020. Associations between infant and toddler regulatory problems, childhood co-developing internalising and externalising trajectories, and adolescent depression, psychotic and borderline personality disorder symptoms. *Journal of Child Psychology and Psychiatry,* 61**,** 182-194.

WOOLGER, C. 2001. Wechsler intelligence scale for children-(WISC-III). *Understanding psychological assessment*. Springer.

WULFF, K., DIJK, D.-J., MIDDLETON, B., FOSTER, R. G. & JOYCE, E. M. 2012. Sleep and circadian rhythm disruption in schizophrenia. *The British Journal of Psychiatry,* 200**,** 308-316.

YATES, N. J. 2016. Schizophrenia: the role of sleep and circadian rhythms in regulating dopamine and psychosis. *Reviews in the Neurosciences,* 27**,** 669-687.

YOUNGSTROM, E. A., KMETT DANIELSON, C., FINDLING, R. L., GRACIOUS, B. L. & CALABRESE, J. R. 2002. Factor structure of the Young Mania Rating Scale for use with youths ages 5 to 17 years. *Journal of Clinical Child and Adolescent Psychology,* 31**,** 567-572.

YUNG, A., PHILLIPS, L. & MCGORRY, P. D. 2004. *Treating schizophrenia in the prodromal phase*, Taylor & Francis London.

YUNG, A., YUEN, H., PHILLIPS, L., FRANCEY, S. & MCGORRY, P. 2003. Mapping the onset of psychosis: the comprehensive assessment of at risk mental states (CAARMS). *Schizophrenia Research,* 1**,** 30-31.

YUNG, A. R., BUCKBY, J. A., COTTON, S. M., COSGRAVE, E. M., KILLACKEY, E. J., STANFORD, C., GODFREY, K. & MCGORRY, P. D. 2006. Psychotic-like experiences in nonpsychotic help-seekers: associations with distress, depression, and disability. *Schizophrenia bulletin,* 32**,** 352-359.

YUNG, A. R. & MCGORRY, P. D. 1996a. The initial prodrome in psychosis: descriptive and qualitative aspects. *Australian New Zealand Journal of Psychiatry,* 30**,** 587-599.

YUNG, A. R. & MCGORRY, P. D. 1996b. The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophrenia bulletin,* 22**,** 353-370.

YUNG, A. R., PAN YUEN, H., MCGORRY, P. D., PHILLIPS, L. J., KELLY, D., DELL'OLIO, M., FRANCEY, S. M., COSGRAVE, E. M. & KILLACKEY, E. 2005a. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Australian New Zealand Journal of Psychiatry*

39**,** 964-971.

YUNG, A. R., WOODS, S. W., RUHRMANN, S., ADDINGTON, J., SCHULTZE-LUTTER, F., CORNBLATT, B. A., AMMINGER, G. P., BECHDOLF, A., BIRCHWOOD, M. & BORGWARDT, S. 2012. Whither the attenuated psychosis syndrome? *Schizophrenia bulletin,* 38**,** 1130-1134.

YUNG, A. R., YUNG, A. R., PAN YUEN, H., MCGORRY, P. D., PHILLIPS, L. J., KELLY, D., DELL'OLIO, M., FRANCEY, S. M., COSGRAVE, E. M. & KILLACKEY, E. 2005b. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Australian & New Zealand Journal of Psychiatry,* 39**,** 964-971.

ZAMMIT, S., KOUNALI, D., CANNON, M., DAVID, A. S., GUNNELL, D., HERON, J., JONES, P. B., LEWIS, S., SULLIVAN, S. & WOLKE, D. 2013. Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *American Journal of Psychiatry,* 170**,** 742-750.

ZANINI, M. A., CASTRO, J., COELHO, F. M., BITTENCOURT, L., BRESSAN, R. A., TUFIK, S. & BRIETZKE, E. 2013. Do sleep abnormalities and misaligned sleep/circadian rhythm patterns represent early clinical characteristics for developing psychosis in high risk populations? *Neuroscience and Biobehavioral Reviews,* 37**,** 2631-2637.

ZANINI, M. A., CASTRO, J., CUNHA, G. R., ASEVEDO, E., PAN, P. M., BITTENCOURT, L., COELHO, F. M., TUFIK, S., GADELHA, A. & BRESSAN, R. A. 2015a. Abnormalities in sleep patterns in individuals at risk for psychosis and bipolar disorder. *Schizophrenia research,* 169**,** 262-267.

ZANINI, M. A., CASTRO, J., CUNHA, G. R., ASEVEDO, E., PAN, P. M., BITTENCOURT, L., COELHO, F. M., TUFIK, S., GADELHA, A., BRESSAN, R. A. & BRIETZKE, E. 2015b. Abnormalities in sleep patterns in individuals at risk for psychosis and bipolar disorder. *Schizophrenia Research,* 169**,** 262-267.

ZAVOS, H. M., FREEMAN, D., HAWORTH, C. M., MCGUIRE, P., PLOMIN, R., CARDNO, A. G. & RONALD, A. 2014. Consistent etiology of severe, frequent psychotic experiences and milder, less frequent manifestations: a twin study of specific psychotic experiences in adolescence. *JAMA psychiatry,* 71**,** 1049-1057.

ZHANG, W., ZHU, Y., SUN, M., GUO, R., WU, G., WANG, Z., XUE, Z., SHI, J., OUYANG, X. & PU, W. 2019a. Longitudinal trajectories of psychotic-like experiences and their relationship to emergent mental disorders among adolescents: a 3-year cohort study. *The Journal of clinical psychiatry,* 80**,** 0-0.

ZHANG, Y., QUIÑONES, G. M. & FERRARELLI, F. 2019b. Sleep spindle and slow wave abnormalities in schizophrenia and other psychotic disorders: Recent findings and future directions. *Schizophrenia research.*