SLEEP DISTURBANCES AND THE AT RISK MENTAL STATE: A SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Aims: To synthesise and investigate how sleep disturbances relate to psychotic symptoms, functioning and Quality of Life (QoL) in At Risk Mental State (ARMS) youth.

Method: A comprehensive search of six databases (MEDLINE, PsycINFO, Embase, CINAHL, Web of Science and CENTRAL) was conducted. Eligible studies provided data on sleep disturbances or disorders in ARMS patients.

Results: Sixteen studies met the inclusion criteria (n=1962 ARMS patients) including 7 cross-sectional studies, 2 RCT's and 7 cohort studies.Narrative synthesis revealed that self-reported sleep (e.g., general disturbances, fragmented night time sleep and nightmares) was poorer among ARMS patients compared to healthy controls. In the limited studies (n=4) including objective measurements of sleep disturbances, ARMS patients experienced higher levels of movement during sleep, more daytime naps and increased sleep latency compared to controls. Furthermore, sleep disturbances were associated with attenuated psychotic symptoms and functional outcomes cross-sectionally and longitudinally. Only one study investigated the relationship between sleep and QoL. The exploratory meta-analysis revealed a significant difference in self-reported sleep disturbances measured by the PSQI (mean difference in score: 3.30 (95% CI 1.87, 4.74), $p<0.00001$) and SIPS (mean difference in score: 1.58 (95% CI 0.80, 2.35), $p<0.00001$) of ARMS patients compared to control groups.

Conclusions: ARMS individuals report impaired sleep quality and reduced sleep quantity compared to healthy controls. However, further research is needed to explore the longitudinal relationship between sleep disruptions and QoL in early psychosis. Significant variations in how sleep is measured across studies highlights a need to assess disturbances to sleep using robust and consistent approaches in this patient group.

KEYWORDS: At Risk Mental State, Ultra High Risk, Psychosis, Youth Mental Health, Sleep

1 INTRODUCTION

Sleep is a fundamental biological need that is commonly disrupted in individuals that experience psychosis (Freeman et al., 2015; Kaskie et al., 2017; Rowland and Wickwire, 2018). 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 (Cohrs, 2008; Yung and McGorry, 1996a). 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 present 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 prodrome period suggests that they are not necessarily a consequence of disease chronicity or medication status (Keshavan et al., 2011b; 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 (Poulin et al., 2008; Zanini et al., 2013). 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 has suggested 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; Robustelli et al., 2017; Velthorst et al., 2013). Furthermore, functional deficits are 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 (Alderman et al., 2015; Fusar-Poli et al., 2017).

The relationship between disturbed sleep and Quality of Life (QoL) is also an important line of enquiry; as the prevalence and impact of reduced QoL is well

documented in ARMS groups (Fusar-Poli et al., 2015; Ohmuro et al., 2017; Ruhrmann et al., 2008). Furthermore, poor sleep has been implicated in the sustainment of decreased QoL in patients diagnosed with psychotic illness (Afonso et al., 2011; Hofstetter et al., 2005; Ritsner et al., 2004). This relationship can be explained by the distress/protection vulnerability model of QoL which suggests that sleep is a protective factor, but if impaired can be distressing resulting in reduced QoL (Felce and Perry, 1995; Ritsner et al., 2004). Consequently, it is important to clarify the nature of the relationship between sleep and QoL prior to a diagnosis of psychosis, as sleep difficulties may represent a target for interventions aimed at improving QoL in ARMS youth.

Several systematic reviews have thoroughly examined the relationship between sleep disruptions and psychotic symptoms and illness (Davies et al., 2017; Lunsford-Avery and Mittal, 2013; Reeve et al., 2015; Waite et al., 2019; Zanini et al., 2013). A recent high quality review reported on the nature of sleep disruptions in ARMS and First Episode Psychosis (FEP) 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, patient QoL and functional outcomes in ARMS youth. We will conduct an exploratory meta-analysis to quantitatively assess the magnitude of self-reported general sleep disturbance 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.

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).

2.1 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.

We performed all searches on 10th July and re-ran searches 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).

2.2 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., 2005); 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 (ARMS) were excluded.

All studies reported objective measurements (e.g. actigraphy which is a non-intrusive device worn to monitor and record movement/activity levels or polysomnography which is the gold standard assessment of sleep involving EEG and monitoring of heart rate, breathing, movement and oxygen levels) or self-reported data (e.g. validated self-reported measures, sleep diaries) on sleep or sleep related outcomes

(e.g. chronotype and daytime sleepiness). 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, case control studies involving <20 ARMS participants were excluded. Unpublished studies and meeting abstracts were screened but did not meet the inclusion criteria. Non English studies were excluded.

2.3 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).

2.4 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).

2.5 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.

2.6 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 RESULTS

3.1 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 eighteen 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 1).

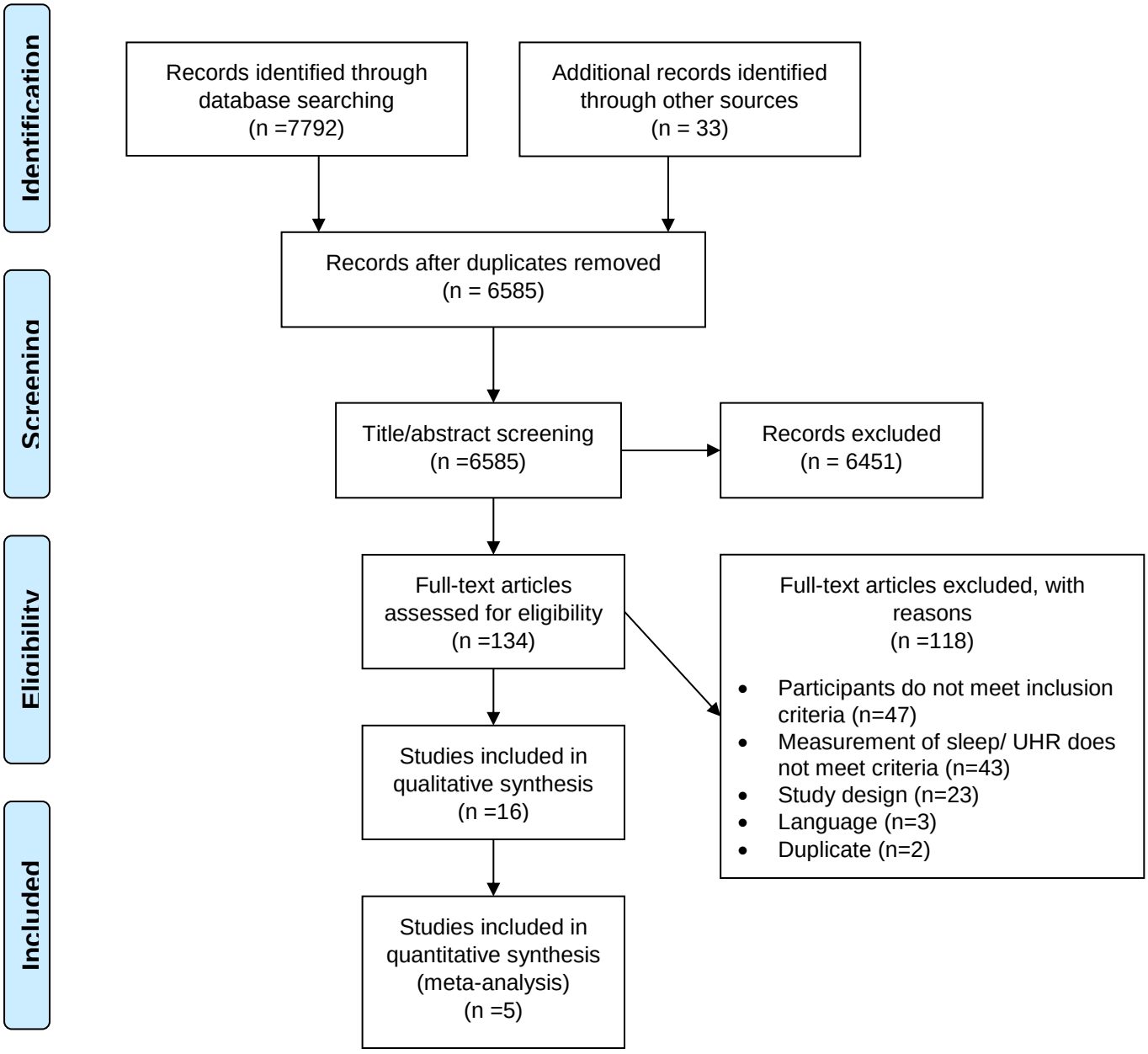


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

3.2 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; Goines et al., 2019; Lederman et al., 2017; Lindgren et al., 2017b; Lunsford-Avery et al., 2017b; Lunsford-Avery et al., 2015; Lunsford-Avery et al., 2013; Michels et al., 2014; Tso et al., 2017; Zanini et al., 2015) included a wide spectrum of participants including: Healthy Controls (HC), healthy relatives, First Episode Psychosis (FEP) 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., 2017a; Lunsford-Avery et al., 2017b; Lunsford-Avery et al., 2015; Lunsford-Avery et al., 2013) and two studies from The Program for Recognition and Intervention in Individuals at-risk Mental State (Castro et al., 2015; Zanini et al., 2015). 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 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., 2017b; Lunsford-Avery et

al., 2015) and fifteen consecutive days (Castro et al., 2015) and PSG was two consecutive nights (Zanini et al., 2015). 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) (Castro et al., 2015; Grivel et al., 2018; Lederman et al., 2017; Lindgren et al., 2017b; Lunsford-Avery et al., 2017b; Lunsford-Avery et al., 2015; Lunsford-Avery et al., 2013; Michels et al., 2014; Poe et al., 2017; Ruhrmann et al., 2010; Tso et al., 2017; Zanini et al., 2015).

4 MAIN RESULTS

4.1 Self-report and objective sleep disturbances in ARMS patients

4.1.1 Latency

Three studies reported sleep latency scores (defined as the amount of time taken to transition from wakefulness into a state of sleep, see table 2) (Lederman et al., 2017; Lunsford-Avery et al., 2013; Zanini et al., 2013). PSG and PSQI sleep latency scores were significantly higher in ARMS compared to HC's (Lunsford-Avery et al., 2015; Zanini et al., 2015). In contrast, Lederman et al. (2017) found no significant difference in the PSQI sleep latency scores of HC's, ARMS and FEP patients.

4.1.2 Efficiency

Four studies presented sleep efficiency findings (defined as the ratio of total sleep time to time spent in bed) (Lederman et al., 2017; Lunsford-Avery et al., 2015; Lunsford-Avery et al., 2013; Zanini et al., 2015). There were no significant differences in the PSG efficiency percentages or PSQI efficiency scores of ARMS compared to HC's. However, one study reported significantly reduced actigraphic measured sleep efficiency in an ARMS group (Lunsford-Avery et al., 2015). Furthermore, there was an association at trend level between PSQI efficiency and actigraphy efficiency scores among ARMS youth but not HC's (Lunsford-Avery et al., 2015).

4.1.3 WASO

Two studies reported Wake After Sleep Onset (WASO) (defined as the time spent awake after sleep onset) results (Lunsford-Avery et al., 2015; Zanini et al., 2015). In the first study, actigraphy WASO scores of ARMS were found to be significantly higher than HC youth (Lunsford-Avery et al., 2015). However, Zanini et al. (2015)

reported no significant difference in the PSG WASO scores of ARMS participants compared to HC counterparts.

4.1.4 Night time awakenings

Three studies reported on nightmare awakenings (Lederman et al., 2017; Lunsford-Avery et al., 2015; Lunsford-Avery et al., 2013). Findings from these studies revealed no significant differences in the mean actigraphy or self-reported PSQI scores for ARMS compared to HC participants (Lederman et al., 2017; Lunsford-Avery et al., 2015). Furthermore, no significant associations were revealed between self-reported (PSQI) and objectively measured (actigraphy) night time awakenings in ARMS or HC participants (Lunsford-Avery et al., 2015). Lunsford-Avery et al. (2013) reported that the ARMS group endorsed significantly more disturbances than HC's according to the PSQI disturbance subscale.

4.1.5 Total Sleep Time

Four studies provided data on Total Sleep Time (TST) (Lederman et al., 2017; Lunsford-Avery et al., 2015; Lunsford-Avery et al., 2013; Zanini et al., 2015). Polysomnographic and actigraphic TST scores were not found to be significantly different between ARMS and HC groups (Lunsford-Avery et al., 2015; Zanini et al., 2015). Similarly, there were no between group differences in PSQI sleep duration scores (Lederman et al., 2017; Lunsford-Avery et al., 2013). 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).

4.1.6 Movements

One study reported actigraphy measured night time movements to be significantly increased in ARMS patients compared to HC (Lunsford-Avery et al., 2015).

4.1.7 Day time naps

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

4.1.8 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., 2015). Tso et al. (2017) revealed that clinically higher risk patients (global score ≥ 7 on the SOPS) experienced greater levels of sleep disturbance compared to clinically lower risk patients (global score < 7 on the SOPS) according

to the SOPS. Grivel et al. (2018) also reported that ARMS patients with any lifetime trauma endorsed 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 reported a significant difference in scores between ARMS and HC's on the SIPS G1 subscale (Poe et al., 2017). There are seven items assessing sleep disturbances on the SIPS/SOPS; with higher scores suggesting higher levels of disturbed sleep (Miller et al., 2003a).

Zanini et al. (2015) revealed that 75% of ARMS patients and only 30% of HC's scored greater than 5 on the PSQI measure. In addition, another study reported the ARMS group (mean score 8.0, SD 3.3) PSQI mean score to be significantly higher than the HC group mean (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).

4.1.9 Daytime sleepiness

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

4.1.10 Dreaming and Parasomnia

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).

4.1.11 Circadian rhythm

Four studies reported on circadian rhythm (defined as the internal biological rhythms that that coordinate behavioural and physical activity with the environment during a 24h period) (Castro et al., 2015; Lunsford-Avery et al., 2015; Poe et al., 2017; Zanini

et al., 2015). Castro et al. (2015) revealed between group differences in the actigraphic autocorrelation function parameter, which is an indicator 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 healthy controls (mean score: -0.11. SD 0.02). However, Lunsford-Avery et al. (2015) did not find this parameter to be significantly different among ARMS (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. In a further study, ARMS participants reported increased 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).

4.2 Cross-sectional associations between sleep disturbances, psychotic symptoms, functioning and QoL

4.2.1 Sleep and positive symptoms

A total of five studies reported cross-sectional associations between sleep disturbances and positive symptoms (Goines et al., 2019; Lunsford-Avery et al., 2015; Lunsford-Avery et al., 2013; Poe et al., 2017). In one study, SIPS rated sleep disturbances were found to be significantly associated with severity of total positive symptoms ($p < 0.01$) 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 ($p = 0.006$) and perceptual abnormalities ($p = 0.001$). 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.

4.2.2 Sleep and negative symptoms

Three studies reported on the relationship between sleep disturbances and negative symptoms (Lunsford-Avery et al., 2017a; Lunsford-Avery et al., 2013; Poe et al., 2017). 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.

4.2.3 Sleep and functional outcomes

Two studies reported on the relationship between sleep disruptions and functional outcomes (Lunsford-Avery et al., 2017a; Poe et al., 2017). 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 as measured by the Global Assessment of Functioning (GAF), there were no significant difference between ARMS patients who scored ≤8 or >8 on the PSQI (Lunsford-Avery et al., 2017a).

4.2.4 Sleep and Quality of Life

In a sample of 160 ARMS patients, 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 measured by the Economic Patient Questionnaire interview. However, the authors acknowledged that the statistical tests may have been underpowered due to low completion rates of QoL measures (Reeve et al., 2018a).

4.3 Longitudinal relationship between sleep disturbances, psychotic symptoms, functioning and QoL

4.3.1 Positive symptoms

Six studies reported on sleep disturbances as a longitudinal predictor of positive psychotic symptoms and/or transition to psychosis (Lindgren et al., 2017b; Lunsford-Avery et al., 2017b; Lunsford-Avery et al., 2015; Poe et al., 2017; Reeve et al., 2018a; Ruhrmann et al., 2010). Reeve et al. (2018a) reported that shorter sleep duration (assessed using the Economic Patient Questionnaire Interview) predicted severity of delusional ideas (p=0.003) and hallucinations (p=0.01) across a 24 month follow up period. 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. In another 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). Another longitudinal study reported no significant differences in the SIPS measured sleep disturbance scores of ARMS individuals with or without intentional self-harm at follow up (Lindgren et al., 2017a).

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 (including SIPS positive subscale scores) (Ruhrmann et al., 2010). 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). Furthermore, Grivel et al. (2018) reported that trauma history (TH) correlated with SIPS sleep disturbance scores, however TH was not found to be significantly related to conversions to psychosis at two year follow up. There were no further studies included in this review that reported sleep problems at baseline predicting transition to psychosis at follow up.

4.3.2 Negative symptoms

Two studies reported on the longitudinal relationship between sleep disruptions 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).

4.3.3 Functional outcomes

One study revealed several actigraphic variables to predict functional outcome 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 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).

4.3.4 Quality of Life

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

462 **Table 1.** *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. (2015)†	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. (2018a)	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. (2017b)	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. (2010)	2010	Germany, Finland, the Netherlands and	Cohort study	245 UHR (137/108)	None	SIPS	SIPS	GAF	SIPS	SIPS	16

	England	

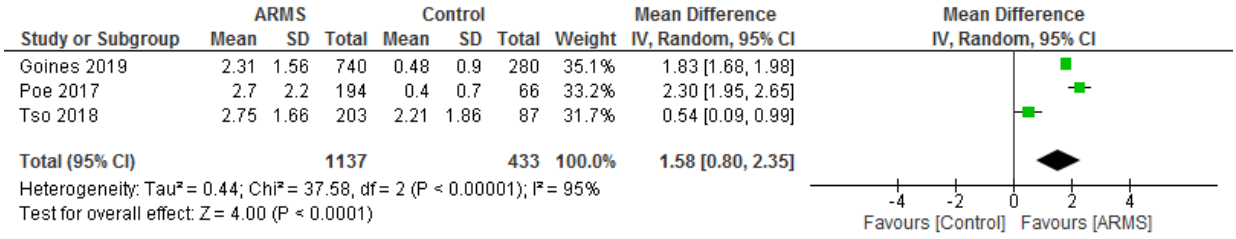
CAARMS: Comprehensive Assessment of the At Risk Mental State; SIPS/SOPS: Structured Interview for Prodromal Symptoms; PSG: Polysomnography; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; QME: Questionnaire of Morningness and Eveningness Scale;; PANSS: Positive and Negative Syndrome 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)

4.4 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 2). 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%).

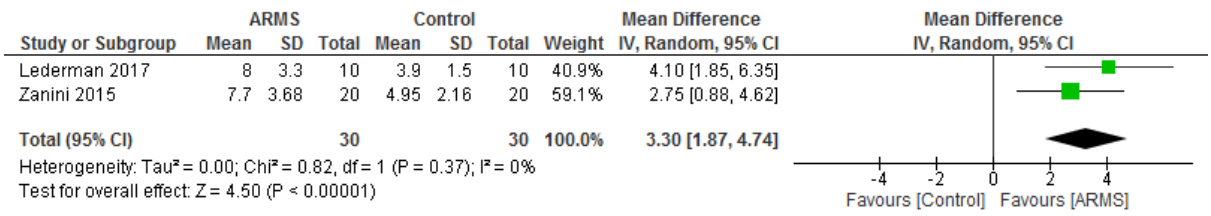
The mean difference in score remained significant when the study by Tso et al. (2017) was excluded from the analysis; mean difference in score was 2.04 (95% CI 1.58, 2.49) z=8.73, p<0.00001 (I^2=83%).

Figure 2. *Sleep disturbance (SIPS)*



Two studies were included in the meta-analysis for sleep disturbances measured using the PSQI (see figure 3) (Lederman et al., 2017; Zanini et al., 2015). 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 3. *Sleep disturbance (PSQI)*



4.5 Risk of bias assessment

Quality scores are summarised in table 1. 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, participants in these studies did not fulfil the UHR criteria and consequently were not included in this review. The majority of studies included were considered to be low quality according to the Downs and Black checklist.

Table 2. *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 regulate 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 (PSG)	PSG is the gold standard assessment of sleep which involves recording brain activity through EEG and monitoring 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 of 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.

5 DISCUSSION

5.1 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 amongst ARMS patients.

5.2 Self-report and objective sleep disturbances in ARMS patients

This review has highlighted that ARMS patients report higher levels of general sleep disturbances, increased night time disruption, and increased nightmares. However, sleep efficiency and duration were not reported to be reduced in ARMS groups. These findings are important as they demonstrate distinctions in self-reported sleep problems among 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 clinical assessment 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). Therefore, these measures can be considered appropriate for the assessment of global sleep disruptions in ARMS patients. However, as has been highlighted in research involving schizophrenia patients (Faulkner and Sidey-Gibbons, 2019) it is important to establish the utility

and cut-off scores of self-reported sleep tools such as the PSQI and SIPS in ARMS youth.

Several objectively assessed parameters of sleep were found to be disrupted in ARMS youth including quantity of sleep (e.g., PSG latency, daytime naps and night time movements) and circadian rhythm. 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=4) used PSG or actigraphy to assess sleep disturbances. It is important to acknowledge the significant challenges associated with conducting sleep studies, therefore exploration of the macro and micro architecture of sleep in such a limited number of studies provides significant gains in knowledge.

5.3 Cross-sectional associations between sleep disruptions and the ARMS

This review has reported several sleep parameters (e.g., reduced sleep efficiency, increased WASO, increased night time awakening and movements) to be associated with positive psychotic symptoms. Conversely, increased latency, duration and quality were reported to be related to negative symptoms. These findings complement previous research focused on patients with psychotic disorder (Blanchard et al., 2020; Reeve et al., 2015) as they show that a relationship between attenuated psychotic symptoms and sleep disturbances is present prior to diagnosis of psychotic disorder. The interaction 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.

5.4 Longitudinal relationship between sleep disruptions and the ARMS

The findings from longitudinal studies 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 systems thought to be implicated in the expression of schizophrenia and circadian pathways (Wulff et al., 2012). Alternatively, the complex-generic and environmental model of mental disorders provides a developmental explanation for the comorbidities between sleep disruptions and mental health disorders. It suggests that early sleep disturbances resulting from pre-natal/ early life stress impact on the regulation of the HPA axis and stress system, mediated by epigenetic factors, which increases the risk of developing stress related disorders in adulthood (Palagini et al., 2019). Other conceptual models and pathways have also been described in the literature, involving markers of oxidative stress in the brain (e.g. protein oxidation and lipid peroxidation), neuroprogression (e.g. hippocampal function), inflammatory molecules (e.g. cytokines) and disruptions to the HPA axis (Lopresti et al., 2013; Pandi-Perumal and Kramer, 2010). It is therefore clear that the pathways and mediating factors implicated in the development of dysfunctional sleep and mental illness are complex, 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 essential when considering appropriate treatments and the priorities of sleep interventions in clinical practice (Cosgrave et al., 2018; Freeman et al., 2017; Ohayon, 1997; Reeve et al., 2018b).

5.5 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. Those that did reported on correlations between sleep pattern disruption and general functioning; in addition to circadian rhythm variables predicting long term psychosocial functioning

levels. These findings support previous research suggesting that sleep difficulties are related to reduced functioning in schizophrenia spectrum disorders and that improving sleep could improve functional outcomes, 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 sample, with no significant findings 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 QoL and employability are both understudied and of high importance (Hofstetter et al., 2005; Yates, 2016). Adopting a holistic approach to care, which treats clinical symptoms whilst also prioritising improving QoL and functioning is invaluable to many individuals experiencing mental health problems (Katshnig 2006; Sagayadevan 2018). Therefore, there is a need for research which includes well defined and carefully measured QoL domains, in addition to exploration of distinct differences between direct and indirect impacts of sleep on QoL in ARMS youth.

5.6 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 2). 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 this area.

A second limitation is the unquestionable challenge of ascertaining the direction of causality between sleep disturbances and psychotic illness. 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). This would also provide an important opportunity for examining the putative role of sleep disruptions in the development and full manifestation of psychosis.

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 (12/16) 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.

5.7 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; Freeman et al., 2017; Myers et al., 2011) 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 defined as electrical brain activity typically observed in stage 2 sleep) in ARMS patients is key, particularly as research has suggested that they are implicated in reasoning, attention and memory consolidation in

schizophrenia patients (Ferrarelli et al., 2007; Göder et al., 2015; Keshavan et al., 2011a; Manoach et al., 2014; Manoach et al., 2016; Poulin et al., 2003; Wamsley et al., 2012) and that spindles and slow waves may be valid biomarkers for schizophrenia (Zhang et al., 2019). 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).

6 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 for establishing the relative importance of services prioritising sleep disturbance treatments in ARMS patients.

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Appendices

Appendix A: 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