The Role of Sleep and Circadian Rhythms in Bipolar Disorder

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And here, I wish to say to her now,
is a smaller gift – not the worn truth

that you can never repay your mother,
but the rueful admission that when she took
the two-tone lanyard from my hand,
I was as sure as a boy could be
that this useless, worthless thing I wove
out of boredom would be enough to make us even.
- Billy Collins (2005), The Lanyard

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Summary

The aim of this thesis was to investigate the multifaceted role of sleep, and, to a lesser extent, circadian rhythms in bipolar disorder (BD). In Chapter 3 we highlight the adverse sleep profile of BD when compared to two demographically homogeneous groups of people with major depression and health controls (n=1,072 each group). Although the sleep profile of BD and major depression were similar, people with BD showed increased insomnia symptoms, later chronotype, shorter sleep duration, increased need for sleep and greater dissatisfaction with sleep when compared to healthy controls. In Chapter 4, we sought to compare the sleep, rest-activity, mental health and cognitive functioning of BD high-risk offspring (n=11) to low-risk participants (n=21). Although all effects were in the direction we predicted, due to limitations in recruitment, none of these differences was statistically significant. In Chapter 5 we examine the effectiveness of behavioural and psychosocial interventions in BD that target sleep and circadian rhythms. The only modality with enough data to meta-analyse was the effect of bright therapy in depression, revealing a moderate-to-large improvement. Overall, the evidence base for the effectiveness of these interventions was limited, due to the lack of sleep and circadian outcomes, small samples and varied treatment protocols. Finally, in Chapter 6 we present findings from a mixed-methods, within-groups pilot trial of a digital cognitive behavioural therapy for insomnia, for people with BD-II (n=22). Our quantitative results show that the treatment is feasible, acceptable and potentially effective in improving insomnia, depression, anxiety, cognitive complaints, mental wellbeing and socio-occupational functioning both at post-treatment and at 3-month follow up. Our qualitative data emphasise the ubiquitousness and negative impact of sleep and circadian disruptions in BD, and the interest for relevant treatments. Overall, participants enjoyed the intervention, but highlighted the lack of therapeutic focus on excessive sleepiness alongside insomnia.

Covid-19 Statement

With my DPhil starting in October 2019 and the world going into lockdown in March 2020, most of the work contained in this thesis was conducted during the Covid-19 pandemic. Compounding on the universal effects of the pandemic to doctoral students, it was particularly difficult to conduct data collection for clinical research, especially on sleep and activity at a time when both were severely affected and/or restricted. As such, all studies proposed in my doctoral application were postponed, delayed, or fully cancelled. Together with my supervisor team we made the necessary adjustments to deliver on a work package that is scientifically sound and minimally affected by the circumstances around Covid-19.

Nevertheless, the effects of Covid-19 on our high-risk study in Chapter 4 were unavoidable. This study was designed in October-December 2019 in collaboration with the Flourish team in Canada. This was due to a deadline by UK Research and Innovation related to additional funding available. By February 2020, we had secured the funding, first drafts of the ethics applications were prepared, and the plan was for recruitment in Canada to be in-person during June-September 2020. In the end, recruitment started in May 2021 in the UK and July 2021 in Canada. Recruitment was paused in October 2021 owing to the spread of the Covid-19 omicron variant. At the same time, both Principal Investigators of the Flourish team stepped down from their positions. Following this, we struggled to recruit high-risk participants, and in September 2022 we decided to conclude the study.

Covid-19 influenced all other chapters, albeit to a lesser extent. The secondary data analysis of Chapter 3 was added retrospectively, and the survey was not designed specifically for people with bipolar disorder. Finally, our digital intervention study on Chapter 6 was conducted on a very tight schedule due to time lost during the pandemic.

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List of Abbreviations from the Main text

ASRMS	Altman Self-Rating Mania Scale
AUDIT	Alcohol Use Disorders Identification Test
BADS	Behavioural Activation for Depression Scale
BB-glasses	Blue-Light-Blocking glasses
BBC	British Broadcasting Corporation
BCCCI	British Columbia Cognitive Complaints Inventory
BD	Bipolar Disorder
BIS/BAS	Behavioural Inhibition/Behavioural Activation Scale
BLT	Bright Light Therapy
CBT(-I)	Cognitive Behavioural Therapy (for Insomnia)
CI	Confidence Intervals
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EEG	Electroencephalogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
GAD	Generalised Anxiety Disorder
GWAS	Genome Wide Association Study
HC	Healthy Controls
HDRS	Hamilton Depression Rating Scale
ICD-11	International Classification of Diseases, 11th Revision
IFIT	Integrated Family and Individual Therapy
IPSRT	Interpersonal and Social Rhythm Therapy
ISI	Insomnia Severity Index
MDD	Major Depression Disorder
MDQ	Mood Disorders Questionnaire
MEQ	Morningness Eveningness Questionnaire
NICE	National Institute for Health and Care Excellence
(N)REM	(Non) Rapid Eye Movement
PE	Psychoeducation
PHQ	Patient Health Questionnaire
PSQI	Pittsburgh Sleep Quality Index
QIDS	Quick Inventory of Depression Symptomatology

QoL	Quality of Life
RCT	Randomised Controlled Trail
(S)AEs	(Serious) Adverse Events
SCI	Sleep Condition Indicator
SD	Standard Deviations
SE	Sleep Efficiency
SOL	Sleep Onset Latency
TAU	Treatment as Usual
TC	Triple Chronotherapy
TranS-C	Transdiagnostic Intervention for Sleep and Circadian Disfunction
TSD	Total Sleep Deprivation
TST	Total Sleep Time
WASO	Wake After Sleep Onset
WEMWS	Warwick Edinburgh Mental Wellbeing Scale
WSAS	Work and Social Adjustment Scale

1

Sleep and Circadian Rhythms

Contents

*** Disclaimer: Part of the contents of this chapter have been published in the 4th edition of the Oxford Textbook of Psychopathology under Chapter 23: Sleep and Circadian Rhythm Disorders (Bisdounis et al., 2023)*

1.1 Circadian Rhythms and the Sleep-Wake Cycle

Chronobiology is a branch of science concerned with periodic phenomena that occur in humans and other living organisms. These periodic phenomena oscillate in temporal cycles which are referred to as *biological rhythms*. There are three biological rhythms: ultradian (less than 24 hours), circadian (around 24 hours) and infradian (more than 24 hours). The term *circadian* describes molecular, physiological and behavioral processes which operate periodically on a 24-hour cycle. These processes have a genetic origin and are endogenous in nature. As such, they are self-sustained and do not require rhythmic input from the environment to oscillate. Exogenous cues, called *zeitgebers*, synchronise these endogenous processes with the environment, in a process called *entrainment*. As such, biological rhythms

enable organisms to adapt, anticipate and respond to environmental changes while retaining a periodicity in bodily functions (Ayyar & Sukumaran, 2021).

The light-dark cycle induced by the earth's axial rotation is the most important zeitgeber. Light entering the eye through the retina is captured by circadian light receptors, called *photosensitive retinal ganglion cells*. These cells project via the retinohypothalamic tract to the central circadian pacemaker in the hypothalamus, the *suprachiasmatic nucleus*. The suprachiasmatic nucleus hierarchically controls the human circadian system, and allows peripheral clocks to entrain to environmental light. This process enables the internal circadian rhythm to align with the external light-dark cycle (Foster & Kreitzman, 2014). Examples of internal circadian rhythms being out-of-synch with the external environment are jet lag and working nightshifts. In addition to photic information, the suprachiasmatic nucleus receives non-retinal inputs from other brain regions and external cues, such as feeding and temperature (Ayyar & Sukumaran, 2021; Hastings et al., 2018).

The molecular basis of cellular circadian rhythms involves a panel of key clock genes and their *transcriptional/translational feedback loops*. The transcription regulators CLOCK and BMAL1 drive the expression of a host of genes regulating physiology and metabolism, including the clock genes PER1-2 and CRY1-2. In return, PER and CRY proteins form a complex which enters the nucleus and impedes the BMAL1-CLOCK transcriptional drive. This complex acts as a transcriptional repressor of its own genes, while additional feedback loops regulate the resetting of the properties of the core transcriptional/translational feedback loop. This mechanism is present in most cells of the body, rendering the human circadian system a distributed network of multiple, autonomous, peripheral clocks that are synchronised by the suprachiasmatic nucleus.

The most conspicuous process following circadian principles in humans is the sleep-wake cycle. The alteration between sleep and wakefulness is a highly regulated phenomenon,

dependent upon two processes: *sleep homeostasis* and circadian rhythms (Borbely, 1982; Borbély et al., 2016). Sleep homeostasis is defined as the pressure for sleep which accumulates during wakefulness and dissipates during the night of sleep. When the waking period is extended beyond typical levels (i.e. staying awake during the night) sleep pressure builds-up and leads to a sleep debt. In this instance, both duration and intensity of the subsequent sleep are increased, demonstrating the homeostatic drive for sleep. In return, the gradual increase of sleep pressure is counterbalanced by the endogenous circadian signal for alertness and sleep propensity. Overall, these two processes naturally maintain consolidated periods of sleep and wakefulness while regulating their timing and duration.

1.2 Characteristics of Sleep in Good Sleepers

On the behavioural level, sleep is defined as a reversible state of altered consciousness, perceptual disengagement, physical quiescence, recumbent posture, and eye closure. On a neurophysiological level, sleep can be divided into two distinct stages of vigilance: non rapid eye movement (NREM) and rapid eye movement (REM) sleep (Berry et al., 2020)

NREM typically precedes REM sleep and is marked by normal respiration, decreased muscular tonus, synchronous cortical activity, and gradual increase of sleep depth (i.e. the exogenous arousal threshold required to achieve awakening). Based on sleep depth, NREM is further subdivided into three stages: N1-3. These stages constitute an arousal continuum, with lighter sleep in N1 and N2, and deep sleep (or slow-wave sleep) in N3 (Berry et al., 2020). By contrast, REM sleep is characterised by cardiorespiratory variability, muscle atonia, episodic bursts of rapid eye movements, and desynchronous, low-amplitude, mixed-frequency electroencephalogram (EEG) activity. REM sleep can also be subdivided into two microstates: tonic and phasic. Tonic REM is parasympathetically driven and involves muscle

atonia and low amplitude EEG. Superimposed on tonic REM sleep, phasic REM is sympathetically driven and involves rapid eye movements, distal muscle twitches, and cardiorespiratory irregularity.

In healthy adults, sleep is initiated through NREM, marked by a brief period of N1. This process is a cornerstone of normal sleep. Sleep initiation through REM is a reliable marker of pathology in adults, most often of narcolepsy (American Academy of Sleep Medicine, 2014). During the first sleep cycle, N1 lasts 1-7 minutes, followed by N2 lasting 10-25 minutes. It takes good sleepers 10-15 minutes to reach N1 after lights are turned off. The subsequent N3 stage lasts 20-40 minutes. Prior to entering REM, a brief 5-10-minute ascent to N2 is typically observed. Finally, the first REM episode occurs on average 70-100 minutes after the first N1. This REM episode is short-lived, typically lasting less than 5 minutes. The alteration between NREM and REM sleep follows a neurophysiological ultradian pattern, and is referred to as the NREM-REM cycle. In good sleepers the NREM-REM cycle is repeated four to five times during nocturnal sleep. Although the duration of the NREM-REM cycle does not change throughout the night, the length of each sleep stage does. As the night progresses, REM sleep becomes longer and NREM becomes shorter. N3/slow wave sleep occupies less time in the second NREM-REM cycle and might disappear altogether in following cycles. N2 is subsequently expanded to occupy the remaining NREM portion of the cycle.

1.3 Measures of Sleep and Circadian Rhythms

The assessment of sleep and circadian rhythms includes several tools, conventionally classified into two broad types of measurement: *subjective* and *objective*. Subjective assessments include self- or clinician-administered measures such as clinical interviews, questionnaires and sleep diaries. Objective assessments include polysomnography, accelerometer devices

called actigraphs, and circadian phase assessments (i.e., the use of molecular, physiological or psychological processes to characterise a person's circadian phase). Given that terms such as objective and subjective overemphasise the accuracy of former and undermine the reliability of the latter (Fuoco, 2017), these measures are also referred to as laboratory and self or clinician-reported, respectively.

1.3.1 Clinical Interviews

Clinical interviews are essential for the diagnosis of all sleep and circadian disorders. To aid the conduct of the interview, several structured (Merikangas et al., 2014; Taylor et al., 2018) and semi-structured interview protocols (Edinger et al., 2004) have been developed (Espie, 2022). The clinical interview should include a thorough examination of the chief sleep complaint, covering elements like sleep hygiene, sleep environment, pre-bed behavior, work schedule, sleeping arrangements, circadian preference, and daytime functioning (Riemann et al., 2017). At a minimum, clinical interviews should also include a detailed medical history with current and past medication and substance use (including alcohol, caffeine, and nicotine). The presence of comorbid psychiatric disorders such as depression, anxiety, bipolar disorder and psychosis should be actively examined too.

1.3.2 Sleep Diaries

Sleep diaries constitute a form of experience sampling that capture daytime and night-time behaviours and the experience of the previous night. The assessment covers an extended period of time, usually two weeks. They are the mainstay assessment of sleep, due to being an ecologically valid, easy to administer and inexpensive tool. However, sleep diaries rely on participants' recollection of the sleep and wake times. A commonly used, standardised diary is the Consensus Sleep Diary (Carney et al., 2012). Typical parameters derived from sleep diaries include sleep onset latency (i.e., time needed to transition from wakefulness to sleep), wake-time after sleep onset (i.e., time spent awake after initial sleep

onset and prior to final awakening), total sleep time, time in bed, sleep efficiency (i.e., ratio of total sleep time to time in bed), and number of awakenings.

1.3.3 Polysomnography

Notwithstanding the importance of self- and clinician-reported measures, *polysomnography* is considered the reference standard sleep assessment. Polysomnography is a simultaneous overnight recording of several physiological measures, with internationally-recognised consensus guidelines for conduct and scoring (Berry et al., 2020). However, it is an expensive tool that requires trained personnel, appropriate facilities, and can be time-consuming and burdensome for the individual.

1.3.4 Actigraphy

An *actigraph* is a motion-sensor device typically worn on the wrist. It is low cost, with small participant burden, and can be used for longitudinal assessment over multiple weeks. Although it is a frequent tool in sleep and circadian research, its applications extend to any research question around activity. Actigraphs record gross motor activity and mathematical algorithms are applied to estimate rest and activity patterns from the motor data. Unlike polysomnography, there are no universal guidelines for the conduct and scoring of actigraphy. Analysis of actigraphy data can provide a graphical summary of sleep and wakefulness over time, as well as parametric and non-parametric variables about general rest and activity. Parametric variables include sleep onset latency, wake after sleep onset, total sleep time, time in bed, sleep efficiency, and awakenings. Nonparametric variables include: (1) L5, the average activity during the least active 5-hour period; (2) M10, the average activity during the most active 10-hour period; (3) the intradaily variability, a fragmentation index of daily rhythms; and (4) interdaily stability, an estimate of the synchronization to the 24-hour light–dark cycle (Gonçalves et al., 2014). Compared against polysomnography, actigraphy generally overestimates sleep and underestimates wakefulness. This discrepancy is small and actigraphy is generally good in detecting sleep periods in healthy individuals (Conley et al.,

2019). However, actigraphy is not as robust in people with sleep or other chronic disorders (Conley et al., 2019; M. T. Smith et al., 2018), and since it principally assesses rest-activity, it is only considered a proxy measure for sleep-wake. This discrepancy is probably due to the difficulty of actigraphy in detecting wake periods before and after sleep, exacerbated by the proneness of these populations to remain inactive in bed when trying to fall asleep (Conley et al., 2019; Williams et al., 2020). In terms of their availability, there are commercial 'wearables' (e.g., Fitbit by Fitbit Inc) and research grade actigraphs (e.g. MotionWare by CamNtech, Axivity by Axivity Ltd, and GENEActiv by Activinsights), with the validity and reliability of these devices - especially commercial ones - being a source of continuous scientific debate (Chinoy et al., 2021; Scott et al., 2019).

1.4 Sleep and Circadian Rhythm Disorders

Sleep and circadian rhythm disorders constitute a heterogeneous group of disruptions, with distinct clinical presentations, aetiologies, prognoses, and treatment needs. Although their debilitating nature has long been recognised, sleep disorder nosologies have only become available in the past four decades. Presently, there are three classification systems for sleep disorders. Two systems are incorporated within larger taxonomies: the *ICD-11 (World Health Organization, 2018)* and the *DSM-5 (American Psychiatric Association, 2013)*. The final system was developed by a scientific society in sleep medicine: the *International Classification of Sleep Disorders, 3rd Edition* (ICSD-3) (American Academy of Sleep Medicine, 2014). Despite some discrepancies, the three classification systems are more concordant than their previous iterations. The *ICD-11* and *ICSD-3* have maintained the same seven classifications (six for *ICD-11* which does not include the subgroup of 'other sleep disorders') as in their previous versions: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, sleep-related

movement disorders, parasomnias, and other sleep disorders. The *DSM-5* includes eight disorder categories: insomnia disorder, hypersomnia disorder, narcolepsy, breathing-related sleep disorders, circadian rhythm sleep-wake disorders, parasomnias, restless leg syndrome, and substance/medication-induced sleep disorder. An important point of convergence is that all three nosologies do not distinguish between 'primary' and 'secondary', or 'organic' and 'inorganic' disorders.

1.4.1 Insomnia Disorder

Insomnia is the most common sleep disorder (Ohayon, 2002), and the second most common psychiatric disorder, second only to anxiety (Wittchen et al., 2011). It is a condition characterised by a persistent difficulty in initiating or maintaining sleep despite adequate opportunity to do so, leading to day-time impairment. In terms of its prevalence, around one-third of the general population reports acute insomnia symptoms over a 12-month period (Perlis et al., 2020), while one in ten people experiences chronic sleep problems (Riemann et al., 2023). These prevalence estimates are found across different countries. The main factors related to the prevalence of insomnia are gender, age, and other illness. Insomnia is more prevalent in women than in men. Although insomnia symptoms and sleep fragmentation increase with age, insomnia diagnoses remain stable across different age groups (Morin et al., 2015). This phenomenon could be due to the fact that when compared to younger adults, older adults do not often attribute their daytime problems to poor sleep (Morin et al., 2015). In terms of comorbid disorders, insomnia is more common in people with psychiatric or other medical disorder compared to the general population. Research on the prevalence of insomnia in children and adolescents has found that 17-36% of children and 14-26% of adolescents report difficulties initiating or maintaining sleep (Falch-Madsen et al., 2021; Gradisar et al., 2011), although it is not yet clear what percentage of these cases would meet clinical criteria for the diagnosis of insomnia (Gradisar et al., 2011).

Insomnia is a heterogeneous disorder and often multiple tools are needed to capture all symptoms adequately (Buysse et al., 2006). Diagnostically, it relies on the subjective symptom experience. Across all nosologies, it is diagnosed on the basis of self-reported dissatisfaction with the quantity or quality of sleep, manifested as a difficulty getting to sleep and/or remaining asleep. This dissatisfaction also needs to be accompanied by some form of daytime dysfunction. Clinical interviews and sleep diaries constitute the essential items for the identification and characterisation of insomnia. Global scales of insomnia and sleep quality are also frequently used, especially in research settings. Polysomnography or actigraphy assessments of sleep are not necessary for the routine evaluation of insomnia in clinical practice, although they can complement the diagnostic accuracy (Buysse et al., 2006; Riemann et al., 2023).

There are two primary treatment modalities for the management of insomnia: cognitive behaviour therapy for insomnia (CBT-I), and medication. CBT-I is recognised as a safe and highly effective intervention with more long-lasting treatment effects compared to medication alone. On the other hand, medication for insomnia is only recommended for short-term use, given risks of side-effects, tolerance and withdrawal effects. Consequently, CBT-I is endorsed as the first line of treatment by numerous organisations worldwide, such as the National Institute for Health and Care Excellence (National Instiute for Health and Care Excellence, 2021), the British Association for Psychopharmacology (Wilson et al., 2019), the European Sleep Research Society (Riemann et al., 2017), and the American College of Physicians (Qaseem et al., 2016).

Nevertheless, due to limited resources, lack of training, high disengagement and drop-out -especially for digital modalities, pharmacotherapy is frequently administered for the treatment of insomnia (Crescenzo et al., 2022). In fact, the most common clinical response to insomnia is the prescription of hypnotic medication (Siriwardena et al., 2010).

Several medications are used for the management of insomnia, owing to their therapeutic effect. Their prescription, however, requires careful consideration given the risk-benefit profile of each drug and the contraindications of each individual (Riemann et al., 2023). Moreover, prescription recommendations might change depending on the country. For example, doxepin, ramelteon, suvorexant and lemborexant are authorised for the treatment of insomnia only in the US. Melatonin is not approved by the Food and Drug Administration (FDA) and it is sold over the counter in the US, while in the UK melatonin is a prescription-only medication. A comprehensive list of medications used in insomnia includes benzodiazepines, z-drugs (or non-benzodiazepines), melatonin and melatonin receptor agonists, selective histamine H1-antagonists, antidepressants, orexin (or hypocretin) receptor antagonists, antipsychotics, antihypertensives, non-selective antihistamines, and anticonvulsants (Crescenzo et al., 2022; Krystal et al., 2019; Morin et al., 2015; Riemann et al., 2023).

2

Bipolar Disorder

Contents

2.1 Diagnosis of Bipolar Disorder

Bipolar Disorder (BD) is a chronic psychiatric condition characterised by alternating episodes of depression and (hypo)mania, with interim periods of varied levels of less frequent or severe symptoms, called euthymia. The diagnosis of BD is based on a comprehensive clinical evaluation of a person's symptoms and medical history. The clinical presentation of BD is highly variable. The *ICD-11* and the *DSM-5* formally recognise two main subgroups within the bipolar spectrum: BD-I and BD-II, and a third classification of cyclothymic disorder (American Psychiatric Association, 2013; World Health Organization, 2018). In cases where symptom presentation includes atypical bipolar-like phenomena that do not fit the canonical subtypes, both nosologies include the option of "other specified and bipolar related disorders".

BD-I features a manic and usually a depressive episode, whereas BD-II is defined by the presence of both hypomanic and depressive episodes. Both manic and hypomanic episodes are states of elated mood, increased energy and goal-directed activity, yet they differ

in length and severity. Manic episodes last for at least one week and lead to severe impairments in social and occupational functioning, and often hospital admission. Around 75% of people in acute manic episodes also report psychotic symptoms (Kessing, Vradi, & Andersen, 2015). On the other hand, hypomania lasts for a minimum of four days and does not lead to severe impairments or hospitalisation. Across BD-I and BD-II, people spend 50-60% of every year in an acute episode, with depressive episodes being nine times more frequent than (hypo)manic ones (McKnight et al., 2017). Cyclothymic disorder is marked by recurring periods of depression and hypomania for at least two years, that do not meet the criteria for a major affective episode. Table 2.1 summarises the diagnostic criteria for BD-I and II, according to the DSM-5.

An initial diagnosis of BD is particularly challenging. This is primarily due to its shared clinical profile with major depression disorder (MDD) (Suen et al., 2021), and the fact that 85% of people with BD present with depression as their first episode (Marneros & Brieger, 2002; Suen et al., 2021). Only 20% of people with BD receive the correct diagnosis within the first year of seeking treatment (Hirschfeld et al., 2003), and approximately 69% of misdiagnoses in BD are for MDD (Hirschfeld et al., 2003). As a consequence, there is a 5-10 year delay between initial symptom presentation and appropriate treatment in BD (Baethge, Tondo, et al., 2003; Baldessarini et al., 2007; de Almeida & Phillips, 2013). This pattern of delays and misdiagnoses can lead to the delivery of inappropriate treatment (Bahji et al., 2020; Suen et al., 2021) and has been linked to an adverse prognostic profile, higher healthcare costs and increased risk of suicide (de Almeida & Phillips, 2013).

The age-at-onset of BD follows a trimodal distribution, with studies having identified early, mid and late onset periods (Bolton et al., 2021). The most frequent age-at-onset period is during adolescence and early adulthood, between the ages of 15 and 25 years, with the majority of individuals presenting with BD symptoms at the age of 17 (Bolton et al., 2021).

BD is associated with substantial mortality and morbidity early in the illness course (Kessing, Vradi, McIntyre, et al., 2015). Although it is often difficult to correctly identify age at onset due to the frequent misdiagnosis of BD, early onset of the disorder has been associated with a more adverse prognostic profile than mid or late onset periods (Bolton et al., 2021; Post et al., 2003). Compared to the general population, life expectancy in BD is reduced by 8-20 years depending on the age at the time of initial diagnosis, with earlier diagnoses associated with lower life expectancy (Kessing, Vradi, & Andersen, 2015). Early onset has also been linked to longer treatment delay, greater severity of depression symptoms, and higher comorbid rates of anxiety and substance use (Joslyn et al., 2016).

2.2 Prevalence and Burden of Disease of Bipolar Disorder

2.2.1 Prevalence

The World Mental Health Survey Initiative, a series of cross-sectional population-based studies of adults across the Americas, Europe, Africa, Middle East and Northern Africa, Asia and the Pacific, highlighted an aggregate lifetime and 12-month prevalence for BD of 2.4% and 1.5%, respectively (Merikangas et al., 2011). BD-I had a lifetime prevalence of 0.6% and a 12-month prevalence of 0.4%, whereas BD-II had a lifetime prevalence of 0.4% and a 12-month prevalence of 0.3%. Data regarding BD came from 11 countries in the in the Americas (Brazil, Colombia, Mexico and the US), Europe (Bulgaria and Romania), Asia (China, India and Japan), Lebanon and New Zealandn (Merikangas et al., 2011).

Prevalence rates for BD vary by country, potentially reflecting methodological discrepancies and cultural differences. For example, the China Mental Health Survey, reported a weighted lifetime and 12-month prevalence for BD of 0.6% and 0.5%, respectively (Huang et al., 2019). Weighted lifetime and 12-month prevalence for BD-I were

0.4% and 0.3%, respectively, while both estimates were less than 0.1% for BD-II (Huang et al., 2019).

BD-I is present in comparable rates across males and females, whereas there is suggestive evidence that BD-II is more frequent in females (Diflorio & Jones, 2010). Beyond prevalence rates, research has highlighted gender differences in the rate of comorbidities and the clinical course of BD. A study of over 1,600 people with BD found that male gender was associated with higher rates of substance abuse over the last 12 months (Buoli et al., 2019), corroborating previous meta-analytic findings showing that men with BD are twice as likely to exhibit symptoms of substance abuse compared to women with BD (Messer et al., 2017). Regarding clinical features, women with BD are typically more likely to report a predominant depressive polarity, a depressive onset, and depression symptoms during manic episodes (Buoli et al., 2019; Cremaschi et al., 2017; Nivoli et al., 2011). Women with BD also typically experience longer and more frequent hospitalisations, experience higher suicide ideation and have more suicide attempts (López-Zurbano & González-Pinto, 2019). In contrast, men with BD are more likely to report a manic predominance, take less antidepressant and hypnotic medication, and although they have fewer suicide attempts, these are typically more violent and lethal (López-Zurbano & González-Pinto, 2019).

2.2.2 Burden of Disease

BD is highly disabling disorder, ranking as the 17th leading source of disability worldwide (Vos et al., 2015). It is associated with reduced psychosocial functioning, emotional distress and increased financial costs for the individual, their caregivers and society at large. The population-level economic burden of BD in the UK was estimated at £6.43 billion for 2018-2019 (Simon et al., 2021). Of these costs, 68% was attributed to loss of productivity and informal care, 31% to healthcare costs and 1.5% to private out-of-pocket expenses and social care costs. Consequently, the majority of these costs fall on the individual

and their families rather than the healthcare system. Although there was no difference in the economic burden of BD-I and II, costs were related to symptom severity, as a unit increase on the average depressive and manic symptom score was associated with 7% and 11% higher social care costs, respectively (Simon et al., 2021).

Table 2.1. The DSM-5 diagnostic criteria for Bipolar Disorder I and II

The diagnosis of Bipolar I Disorder requires only a history of mania or the presence of mania. Episodes of major depression are not required. Bipolar II Disorder is characterised by at least one hypomanic episode and one major depressive episode

Mania
Mania is defined as a period of persistently elevated mood accompanied by increased goal-directed activity or energy. The manic episode lasts for at least a week and is present for most of the day, nearly every day. The disturbance must cause impairment in social or occupational functioning, necessitate hospitalisation, or be accompanied by psychotic features. Additionally, the episode is not attributable to the physiological effects of a substance or to another medical condition. During the manic period, at least three of the following symptoms are present:

- Inflated self-esteem or grandiosity
- Decreased need for sleep (e.g. feeling rested after only 3 hours of sleep)
- More talkative than usual or feeling pressure to keep talking
- Flight of ideas or subjective experience that thoughts are 'racing'
- Distractibility, as reported or observed
- Increase in goal-directed activity or psychomotor agitation
- Excessive involvement in activities that have high potential for painful consequences

Hypomania
Hypomania is defined as above for mania, although with a lower threshold for symptoms or lower severity. That is, symptoms do not cause occupational or social impairment. By definition, the symptoms are not severe enough to require hospitalization and are not psychotic in nature. The duration required to meet episode criteria is more than four days with an observable change by others from usual functioning. The presentation of psychotic symptoms during hypomania (although not for depression) classifies the episode as manic.

Major Depressive Episode
The symptoms of a major depressive episode cause clinically significant distress or impairment in social, occupational or other important areas of functioning, and the episode is not attributable to the physiological effects of a substance or another medical condition. During a major depressive episode, at least one of the symptoms is either depressed mood or loss of interest or pleasure, and at least five of the following symptoms are present during the same two-week period

- Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- Significant change in weight or decrease or increase in appetite nearly every day
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- Diminished ability to think or concentrate, or indecisiveness, nearly every day
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, a suicide attempt or a specific plan for committing suicide

People with BD are 20-30 times more likely to die by suicide compared to the general population (Plans et al., 2019), while BD is also associated with the highest risk of suicide compared to any other psychiatric disorder (Miller & Black, 2020). Indeed, 30-50% of people with BD have a lifetime history of suicide attempts, of whom up to 20% die by suicide (Dong et al., 2020). Some sources of evidence have found that BD-II is associated with higher rates of suicidality than BD-I, other sources have found higher rates among people with BD-I, and others have found no difference in suicidality between BD subtypes (Plans et al., 2019). Notwithstanding, a range of sociodemographic and clinical factors have been associated with higher rates of suicide in BD, including: male gender, living alone, divorced marital status, earlier age at onset, predominant depressive polarity, past suicide attempts, family history of attempted or completed suicide, and comorbid substance abuse or other psychiatric disorders (Dong et al., 2020; Miller & Black, 2020; Plans et al., 2019).

The lifetime prevalence of mental or physical comorbidities in BD is approximately 90%, while up to half of the people with BD experience *polymorbidity*, defined as having three or more comorbid conditions (McIntyre et al., 2020). Comorbidity in BD is associated with earlier age at onset, more complex symptom presentation and a less favourable prognosis profile and treatment response compared to BD without comorbidities (McIntyre et al., 2020). Anxiety disorders are the most common psychiatric comorbidities, with 70-90% of people with BD meeting diagnostic criteria for generalised anxiety disorder, social anxiety or panic disorder. Up to 56% of people with BD meet the criteria for a substance or alcohol use disorder, 25-45% for attention deficit hyperactivity disorder, and 20-40% for a personality disorder (Carvalho et al., 2020; McIntyre et al., 2020). Among physical comorbidities, 37% of people with BD meet the diagnostic criteria for a metabolic syndrome, 35% for chronic migraines, 21% for obesity and 14% for type 2 diabetes mellitus (Carvalho et al., 2020).

2.3 Treatment of Bipolar Disorder

Pharmacotherapy remains the cornerstone of any treatment plan for BD, given it has been studied to a greater detail than any other treatment modality. Lithium is recognised as the gold standard mood stabilising treatment for BD (Malhi et al., 2017), with anticonvulsant, antipsychotic or antidepressant medications also used adjunctively depending on the episodic phase of the disorder (Goodwin et al., 2016; Yatham et al., 2018). Adjunctive psychotherapy and psychoeducation are typically recommended for long-term maintenance and the management of subsyndromal symptoms (Goodwin et al., 2016; Yatham et al., 2018).

2.3.1 Pharmacotherapy Treatment Options

In acute mania, antipsychotic medication as monotherapy or in combination with a mood stabilising agent is the mainstay treatment option. The NICE guidelines recommend lithium as the primary mood stabiliser for BD (National Institute for Health and Care Excellence, 2020). A Cochrane Review of 36 randomised controlled trials (RCTs) found high certainty evidence that lithium is better than placebo as a treatment of acute mania, both in terms of response and remission (McKnight et al., 2019). The anticonvulsant, valproate, a GABA agonist, is recommended when lithium is not suitable, though valproate should not be prescribed to people of childbearing potential, owing to increased likelihood of fetal abnormalities and birth defects. The NICE guidelines subsequently focus on four main antipsychotics: haloperidol, olanzapine, quetiapine and risperidone. Haloperidol is a first-generation antipsychotic medication acting on dopamine D2 receptors, whereas olanzapine, quetiapine and risperidone are second-generation antipsychotics that block both dopamine D2 and serotonin 5-HT2A receptors. Aripiprazole and asenapine are also approved by NICE, the European Medicines Agency (EMA) and the FDA for use in bipolar mania. Cariprazine, paliperidone and ziprasidone are not available in the UK, but they are approved by the EMA and FDA. There is minimal evidence concerning the treatment options for

hypomania, with guidelines inferring or explicitly stating that the management of hypomania can be repurposed from recommendations made for mania (Parker et al., 2021).

Although people with BD typically spend more time in depression than in mania, fewer studies have focused on treatment options for bipolar depression. In acute episodes of bipolar depression, most guidelines recommend lithium as first-line treatment (Malhi et al., 2021; Yatham et al., 2018), even though its antidepressant effects are much less established compared to its antimanic effects. For acute depression in BD, the NICE guidelines recommend combination treatment with olanzapine and fluoxetine, or quetiapine monotherapy (National Institute for Health and Care Excellence, 2020). Fluoxetine is a selective serotonin reuptake inhibitor, while quetiapine is a second-generation antipsychotic with antagonistic activity on dopamine D2 and serotonin 5-HT2A receptors, with additional affinity for other neurotransmitter receptors including histamine H1, serotonin 5-HT1A, and alpha-adrenergic receptors. If the person prefers, NICE recommends that the option of olanzapine monotherapy should be provided, and if none of these treatments work, then lamotrigine monotherapy, a triazine inhibiting voltage-gated sodium channels and presynaptic glutamate, should be considered. Lurasidone, a benzisothiazole, is approved by the EMA and FDA for bipolar depression, but in the UK, it is only licensed for the treatment of schizophrenia in adults.

The use of antidepressants in BD is controversial. This is due to the limited evidence regarding their effectiveness, and the risk of a switch to mania following their administration (Pacchiarotti et al., 2013). A meta-analysis found small yet statistically significant improvements in depression symptoms in people with BD treated with second-generation antidepressants compared to placebo control (McGirr et al., 2016). However, there was no significant difference in clinical response or remission rates between the treatment and control arms. An expert panel from the International Society for Bipolar Disorders

concluded that the evidence base for the use of antidepressants in BD is small, but individuals might benefit from them (Pacchiarotti et al., 2013). Given that affective switches following antidepressant medication are more common in BD-I than BD-II, these agents are typically not prescribed in BD-I and when they are they are accompanied by a mood stabilising agent (Pacchiarotti et al., 2013).

The chronic and recurring nature of BD makes maintenance treatment particularly salient. Nevertheless, RCTs on maintenance treatment options for BD are limited, primarily due to costs, the complexity of the disorder, and the ethical concerns related to maintaining people with BD on placebo treatment for multiple years (McIntyre et al., 2020). Lithium monotherapy has the strongest evidence base as a maintenance treatment for BD, although a recent meta-analysis of RCTs found that combining lithium with aripiprazole, divalproex, quetiapine, olanzapine or risperidone is more effective at delaying relapse compared to lithium monotherapy (Nestsiarovich et al., 2022). Nevertheless, an early network meta-analysis showed that compared to placebo, lithium had a 0.62 risk ratio of relapse to an acute bipolar phase (Miura et al., 2014). Subsequent treatment guidelines endorsed the use of lithium in maintenance therapy (Goodwin et al., 2016; Yatham et al., 2018), with more recent evidence even showing its effectiveness in real-world settings compared to other pharmacological treatments (Hayes et al., 2016; Lähteenvuo et al., 2018). Some RCTs have also investigated the effectiveness of antipsychotics in long-lasting injectable forms as maintenance treatment options for BD with preliminary evidence that they might delay or prevent relapse (Calabrese et al., 2017; Vieta et al., 2012). However, the comparative effectiveness between these agents and oral antipsychotics remains largely unknown (Lähteenvuo et al., 2018).

All pharmacological agents approved for use in BD are associated with potentially important side effects to various degrees (Carvalho et al., 2020). Although there are

differences between agents in the type and severity of side effects reported, a greater number of such effects manifests in depressive rather than (hypo)manic episodes (Carvalho et al., 2020). More specifically, lithium has been associated with renal toxicity, hypothyroidism, polyuria, tremors and an increase in peripheral calcium and parathyroid hormone levels (McKnight et al., 2012). Lithium has also been associated with a greater risk of chronic kidney disease compared to the general population. However, epidemiological studies have described the risk as negligible, especially given recent advances in renal monitoring and targeted lithium concentrations (Kessing, Gerds, et al., 2015). Short-term use of lithium does not appear to be associated with weight gain, although one year in maintenance treatment, evidence suggests that it might lead to an average weight increase of 1-4 kilos (Kemp, 2014). According to the same line of evidence, the highest average weight increase is observed in people who were already obese, prior to taking lithium (Kemp, 2014). The antipsychotic agents approved for use in BD have also been linked to safety and tolerability concerns that are particularly relevant during long-term exposure. Such concerns include weight gain, metabolic disruptions, prolactin elevation, sedation and somnolence, akathisia, QT interval prolongation corrected for heart rate, and tardive dyskinesia (McIntyre et al., 2020). Quetiapine and olanzapine (as monotherapy or in combination with fluoxetine) in particular, have been found to have a high propensity for sedation, somnolence, weight gain and metabolic disruptions (Kemp, 2014).

2.3.2 Psychotherapy Treatment Options

Compounding on the aforementioned safety and tolerability concerns, even when following best-practice guidelines, pharmacological treatments in BD are only partially effective with varied acceptability rates (DePaulo, 2006; Novick & Swartz, 2019). Additionally, given the complex symptom presentation and the high affinity for comorbid conditions, combination drug treatments have become the mainstay method of care in BD

(Fung et al., 2019). Up to 85% of people with BD report using two or more concomitant medications, and more than one third use four or more (Fornaro et al., 2016). This phenomenon is called *polypharmacy*, and there are growing concerns that efforts to improve persistent symptoms in BD with added pharmacotherapy can lead to this (Ghaemi et al., 2006). Therefore, considering the accumulated evidence showing that pharmacotherapy alone cannot fully alleviate bipolar symptoms, restore functioning and prevent remission, there is increasing recognition that a comprehensive treatment plan in BD should include both medication and psychotherapy (Miklowitz et al., 2021; Novick & Swartz, 2019).

In a network meta-analysis of 39 psychotherapy RCTs in BD, the authors found that pharmacology in combination with psychotherapy was associated with a greater reduction in the recurrence of acute episodes compared to pharmacology and treatment as usual (Miklowitz et al., 2021). In this review, cognitive behavioural therapy (CBT), interpersonal and social rhythm therapy (IPSRT) and family or conjoint therapy yielded comparable effects in improving depression outcomes. There was greater precision in the effects sizes associated with CBT according to a surface under the curve analysis, potentially due to the larger volume of trials that investigated CBT. CBT, psychoeducation and family or conjoint therapy also yielded comparable outcomes in improving (hypo)manic symptoms, although all effect sizes were associated with low precision estimates. An important caveat in this line of research is that participants are rarely recruited during an acute affective episode, meaning that improvement pertains mostly to symptom stabilisation during periods of euthymia. Finally, family or group-delivered treatments were more closely related to symptom improvement compared to individual formats (Miklowitz et al., 2021), corroborating evidence from previous reviews in this area showing that caregiver-focused psychotherapies are highly effective in preventing or delaying the recurrence of BD episodes (Chatterton et al., 2017).

2.4 Sleep and Circadian Rhythms in Bipolar Disorder

From the earliest conceptualisation of BD as a diagnosable condition, sleep disruptions have been a hallmark of the disorder's presentation. In 1921, Emil Kraepelin wrote:

> *"The attacks of manic-depressive insanity are invariably accompanied by all kinds of bodily changes. By far the most striking are the disorders of sleep and general nourishment. In mania sleep is in the more severe states of excitement always considerably encroached upon; sometimes there is even almost complete sleeplessness, at most interrupted for a few hours, which may last for weeks, even months… In the states of depression in spite of great need for sleep, it is for the most part sensibly encroached upon; the patients lie for hours, sleepless in bed, … although even in bed they find no refreshment."*
>
> *- Kraepelin E, Manic-Depressive Insanity and Paranoia, Edinburgh, Livingstone,* 1921

Over one hundred years later, and despite undeniable advances in the understanding of BD, this notion remains relevant. Sleep and circadian disturbances are highly prevalent symptoms of the disorder, and salient to people with BD, their caregivers and clinicians.

2.4.1 Sleep and Circadian Symptoms in Bipolar Disorder

The ICD-11 and DSM-5 recognise a decreased need for sleep as a diagnostic symptom of mania, and insomnia or hypersomnia as diagnostic symptoms of depression (American Psychiatric Association, 2013; World Health Organization, 2018). Their prevalence in acute episodes is remarkably high. During (hypo)mania, a decreased need for sleep is reported in 69-99% of cases. During bipolar depression, 78% of people report symptoms of hypersomnia and 100% report symptoms of insomnia during bipolar depression (Harvey, 2008). Around 70% of people with BD report the persistence of sleep and circadian disruption in euthymia. More specifically, increased sleep onset latency, subjective daytime dysfunction, and increased use of hypnotics have all been reported during euthymia (Cretu et al., 2016; Harvey et al., 2005). Due to the frequency and impact of these disruptions, a diagnosis of a comorbid sleep disorder is often necessary , yet it is rarely

provided. It is estimated that 55% of people with BD meet the criteria for a comorbid diagnosis of insomnia, and 30% meet the criteria a comorbid diagnosis of hypersomnia (Grigolon et al., 2019; Harvey et al., 2005). Although insomnia is the most common sleep disorder in BD, it is more common for insomnia and hypersomnia to co-occur in BD, than for hypersomnia to present independently (Soehner et al., 2014). Adittionally, individuals presenting with a depressive episode and both insomnia and hypersomnia symptoms have an up to three-fold increased risk of life-time BD (Geoffroy et al., 2018). The co-occurrence of insomnia and hypersomnia symptoms can manifest as an inability to initiate or maintain sleep accompanied by excessive fatigue, sleepiness, anergia and increased time in bed. A caveat in our understanding of hypersomnia in BD is that research in this area is sparse, despite evidence that hypersomnia is a recurrent complaint in bipolar depression and that it might be a useful criterion to differentiate unipolar depression from BD, especially in the case of BD-II (Kaplan & Harvey, 2009).

Even less attention has been given to circadian disruptions. Across the disorder, people consistently exhibit delayed sleep-wake phase and an evening chronotype, favouring a late bed- and rise-time, and report more unstable daily routines, including irregular sleep-wake cycles (Melo et al., 2017). Around one third of people with BD meet the criteria for a diagnosis of a circadian rhythm disorder, with 77% of those meeting the criteria for a delayed sleep phase disorder (Takaesu et al., 2016). The presence of a delayed phase has also been proposed as a characteristic feature of BD, with delayed sleep phase disorder being significantly more prevalent in people with BD compared to people with unipolar depression and healthy controls (Takaesu, 2018).

The assessment of other sleep disorders in BD is rare. A meta-analysis of obstructive sleep apnoea in serious mental illness identified 4 studies with relevant polysomnography data in BD, and found a 24.5% prevalence rate for obstructive sleep apnoea in BD (Stubbs

et al., 2016). A recent systematic review on nightmares in mental health disorders identified three studies reporting on nightmares in BD, with only one study containing a prevalence estimate of 25%, derived from 8 participants (Akkaoui et al., 2020). There is almost complete paucity on studies about sleep-related movement disorders in BD, other than case-reports. Such reports detail the onset of self-reported restless-leg symptoms following the administration of different types of psychotropic medication, and the cessation of these symptoms once medication was discontinued or the dosage was reduced (Cuellar, 2012).

2.4.2. Importance of Sleep and Circadian Rhythms

Sleep disruptions can be associated with several markers of poorer outcomes in BD. In a sample of 6,000 people with BD, the presence of a sleep disorder was significantly associated with an increased likelihood of suicide attempts (OR: 8.98; 95%CI=8.24-9.80) (Bishop et al., 2020). This relationship was larger than the one observed in depression, substance-use disorder, schizophrenia, post-traumatic stress disorder, and anxiety disorders (Bishop et al., 2020). The presence of such disturbances has also been linked to lower quality of life in symptomatic episodes and euthymic phases, with sleep being recognised as an important contributory factor to quality of life in BD overall (De la Fuente-Tomás et al., 2018; Gruber et al., 2009). Sleep disturbance has been linked to self-reported decreases in productivity (Gruber et al., 2009) and objective measures of reduced work performance, such as higher unemployment and more frequent occurrences of job termination (Bessonova et al., 2020). Recent work has further highlighted that sleep disruptions might be primary causes of cognitive problems in BD. People with BD and sleep disruptions perform worse in tasks of sustained attention and processing speed tasks compared to healthy controls and people with BD without such disruptions, with the latter two groups performing at an equal level (Bradley et al., 2020). In addition to their adverse effects in their own rights, sleep disruptions can also exacerbate mood symptomatology in BD. Sleep related variables

account for over a third of the variance in bipolar mood symptom changes over longitudinal assessments (Soehner et al., 2019), and they are predictive of a shorter episode relapse even when accounting for residual mood symptoms (Cretu et al., 2016). Circadian rhythm disruptions have also been described among multiple behavioural and physiologic parameters in individuals with BD. Some studies also suggest that such disruptions may be an important predictor of relapse with acute circadian rhythm phase-advances occurring prior to the onset of mania (Moon et al., 2016), and phase-delays prior to the onset of depression (Steinan, Morken, et al., 2016). Studies examining seasonal trends in BD symptom presentation suggest that the condition displays some seasonality. Indeed, a review of health service utilisation studies for people with BD highlighted a seasonal pattern with the frequency of hospital admissions for manic and mixed episodes peaking in the spring and summer and depressive episodes peaking during the winter (Geoffroy et al., 2014). Circadian rhythm disturbance arising from seasonal changes in the photoperiod are hypothesised to contribute to seasonal differences in hospitalisation. Knowledge of how and why individuals with BD are more sensitive to environmental circadian rhythm disturbance may have important implications for public health, especially in regions with profound fluctuation in daylength.

Most importantly, sleep and circadian rhythm function is a domain particularly salient to people with BD, caregivers and clinicians. In a survey of people with unipolar and bipolar depression, fatigue, low energy, insomnia and hypersomnia were reported among the most important outcomes of interest (Chevance et al., 2020). In another study, activity, energy and sleep were the most frequently used domains for longitudinal symptom self-monitoring by individuals with BD (Gordon-Smith et al., 2021). As such, the importance of sleep and circadian disruptions and their association with functional outcomes, render them an important target for independent assessment and treatment. Nevertheless, clinical trials

in BD exceedingly focus on mood and ignore these disruptions (Bisdounis et al., 2022), even despite their tendency to persist standard care (Cretu et al., 2016).

2.4.3 Methods of Assessment

As in other psychiatric disorders, the examination of sleep disruptions in BD relies on phenomenology and self-report measures. Clinical interviews and sleep diaries are the cornerstone of their assessment, while self-reported questionnaires such as the Insomnia Severity Index, the Pittsburgh Sleep Quality Inventory, the Morningness-Eveningness Questionnaire, the Sleep Hygiene Inventory and the Epworth Sleepiness Scale are also common (Morton & Murray, 2020). As a minimum it is recommended that in people with BD clinicians assess sleep quality, insomnia symptoms, chronotype, sleep hygiene, and excessive sleepiness (Morton & Murray, 2020). Recently, rest-activity assessments have also been used to complement such assessments. According to a review of rest-activity research in this area, people with BD are less active, have lower sleep efficiency and spend more time awake than healthy controls (De Crescenzo et al., 2017). Notable limitations here are that 69% of the included studies only recruited people in euthymic and the median duration of recording was one week (De Crescenzo et al., 2017), as opposed to the general recommendation of two weeks of recording (Smith et al., 2018). In one study looking at BD inpatients, it was found that those admitted with depression were less active than healthy controls and those admitted with mania, especially in the first hours of the morning (Krane-Gartiser et al., 2014). Conversely, inpatients with mania showed increased variance in the high frequency part of the activity spectrum, and despite the medication, their rest-activity profile generally resembled more that of people with schizophrenia than people with bipolar depression (Krane-Gartiser et al., 2014).

Neurophysiological measures of sleep are rare in BD. In a review of studies using polysomnography, the authors observed increased sleep latency and REM sleep density

across all stages of BD, and reduced spindle activity during depression and euthymia (Zangani et al., 2020). However, two thirds of the included studies were conducted before the year 2,000, and there was notable variation both in the diagnosis of the BD groups as well as the conduct and scoring of the polysomnography data.

In terms of circadian assessments, physiologic parameters that usually express robust circadian rhythms are found to be attenuated or expressing an atypical circadian period in BD. For example, melatonin rhythms are reduced in amplitude and delayed in phase during bipolar depression, whereas there is a phase advance can be observed during (hypo)mania. (Bradley et al., 2017; McCarthy et al., 2022). Research on cortisol release is in line with the differential patterns of release during depression and (hypo)mania in BD, with a 4-5-hour phase delay in bipolar depression and a 7-hour phase advance in (hypo)mania (Moon et al., 2016). Evidence also points to a hypersensitivity to short-wavelength light in people with BD in which they are subject to greater phase delay in melatonin synthesis; a phenotype which may contribute to non-optimally entrained circadian rhythms in the disorder (Ritter et al., 2022).

2.4.4 Sleep and Circadian Phenotyping

BD is an inherently heterogeneous condition with symptom profiles varying greatly within this single diagnostic group. This issue is compounded by the poor operational definition and lack of appropriate measures for several of these symptoms. As we covered, sleep and circadian rhythms offer robust measurable outcomes for concepts related to BD. Disruptions in these areas are also ubiquitous across disorder subtype and episodic phase, while dysregulation in underlying sleep and circadian mechanisms might be shared in up to 80% of bipolar cases (Carpenter et al., 2021). Therefore, given their prevalence and importance, as well as the wide availability of measurement tools, sleep and circadian rhythms offer a potent domain for the clinical stratification of BD into 'treatment meaningful

subgroups' (Carpenter et al., 2021). For example, in a recent study, polygenic risk scores for excessive daytime sleepiness and morningness were positively and negatively associated with increased odds of BD, respectively (Lewis et al., 2020) . However, polygenic risk scores for insomnia were associated with increased risk of BD-II but not BD-I, while polygenic risk scores for sleep duration were associated with increased odds of BD-I but not BD-II (Lewis et al., 2020). Similarly, another study suggested that sleep loss might lead to worse outcomes for people with a BD-I as opposed to a BD-II diagnosis (Lewis et al., 2017). Sleep and circadian rhythms appear to be intrinsic trait markers of the disorder. Cerebrospinal fluid melatonin levels are decreased across episodes in BD when compared to unipolar depression (Bumb et al., 2016), in line with previous literature showing that a delayed sleep-wake phase might be a distinguishable marker between bipolar disorder and unipolar depression (Takaesu, 2018).

Nevertheless, the assessment of sleep and circadian rhythms in BD is rare even among studies specifically involving these pathways (Bisdounis et al., 2022). When present, the establishment of relevant phenotypes relies on global measures of insomnia, overlooking more granular outcomes and variables related to other prevalent disorders in BD such as hypersomnia and circadian rhythm disorders (Kaplan & Williams, 2017). Such assessments, although useful, are not conducive to the establishment of meaningful BD subgroups characterised by sleep and circadian disruption. Preliminary evidence indicates that such subgroups might be marked by a more severe clinical presentation and illness course, be more sensitive to changes in sleep and light, and respond preferentially to sleep and circadian interventions (McCarthy et al., 2022; Takaesu et al., 2018).

2.4.5. Sleep and Circadian disruptions as risk factors

Transcending initial beliefs of sleep and circadian disruptions as only symptoms of BD, converging sources of evidence have demonstrated that such disturbances precede the onset of BD and the recurrence of acute episodes.

Genetic vulnerability

Sleep and circadian gene polymorphisms have been implicated in the genetic diathesis and drug response of BD. In animals, the disruption of circadian genes has been used to model both mania (Roybal et al., 2007) and depression (Landgraf et al., 2016). In one such model, deletion of exon 19 of the circadian gene CLOCK resulted in a dominant-negative CLOCK protein capable of binding but unable to activate transcription (Roybal et al., 2007). Mice carrying this mutation exhibited increased dopaminergic activity and a behavioural profile consistent with mania, including greater risk-taking and impulsivity, hyperactivity and reduced sleep (Roybal et al., 2007). Subsequent treatment with lithium or restoration of a functional CLOCK gene resulted in the dissipation of these manic-like symptoms in mutated mice (Roybal et al., 2007). Over the years, several circadian candidate genes have been implicated in BD, including CLOCK, NPAS2, ARNTL1, NR1D1, PER3, RORA, RORB, CSNKε, and GSK3β (Geoffroy, 2018), yet none have been identified in genome wide-association studies (GWAS) as significant risk factors of BD (Gordovez & McMahon, 2020; McCarthy, 2019). In the most recent GWAS study in over 40,000 people with BD and 371,000 control participants, the genetic risk of BD was associated with decreased morningness and increased sleep duration (Mullins et al., 2021). Mendelian randomisation analyses showed that the association between BD and chronotype is unidirectional, indicating a potential causal role for generic liability in BD, whereas the relationship between BD and sleep duration was bidirectional (Mullins et al., 2021). Beyond

genetic correlation, the polygenic overlap between BD and chronotype, sleep duration, and insomnia has been estimated at 68%, 73%, and 86%, respectively (O'Connell et al., 2021).

Predictors of acute episode relapse

In people with a diagnosis of BD, SCR disturbances have been implicated in various ways in episode relapse. Notwithstanding the lack of consensus over whether such disturbances are causal factors or prodromal signs, they are of paramount importance in predictive models of the disorder. In a systematic review of bipolar prodromes, sleep disruptions were reported as the most robust early symptom of mania, and the sixth most frequent symptom in depression (Jackson et al., 2003). Retrospective studies have also shown that life events associated with major sleep changes, such as transmeridian travelling, bereavement and childbirth, often precede the onset of mania (Plante & Winkelman, 2008). Prospective studies in this area are sparse, but there is suggestive evidence that lower and more variable total sleep time is predictive of a shorter relapse to mania and depression, respectively (Gruber et al., 2011). In another prospective study, reduced sleep quality in euthymia was predictive of a shorter episode relapse even when controlling for residual mood symptoms (Cretu et al., 2016). More robust evidence about the involvement of sleep in the multifaceted causality of BD is provided by work on total sleep deprivation. Initial reports by Thomas Wehr described sleep loss as *a final common pathway in the genesis of mania*, owing to findings that total sleep deprivation acutely reduces depression symptoms but also leads to the emergence of symptoms of mania (Wehr et al., 1987). Since then, new protocols for total sleep deprivation in bipolar depression have emerged and evolved, suggesting that when the intervention is combined with lithium, the episode conversion rate is between 1.4-9% (Gottlieb et al., 2019). A recent review of RCTs on sleep deprivation in BD and MDD emphasised that conversion rates in BD are poorly defined, as many studies do not report

on any adverse events (Mitter et al., 2022). In this review, conversion rates were rare and only present in severely unwell inpatients (Mitter et al., 2022).

High-Risk and Prodromal Stages

Unlike psychosis where guidelines for prodromal states have been widely established, this research is still at its infancy in BD. Central to efforts in early identification is the concept of clinical staging (Vallarino et al., 2015). The notion that individuals progress through incremental and identifiable stages within a disorder continuum. In this continuum, stage 0 includes individuals who are at high-risk of developing the disorder but have not yet manifested any symptoms. Stage 1 represents individuals that present with non-specific subsyndromal symptoms that do not yet meet the criteria for a diagnosis. Stage 2 signifies the first episode of the disorder (here this is usually (hypo)mania given its presence is necessary to discern BD from unipolar depression), with stages 3 and 4 reflecting an established, severe and recurring disorder.

In BD, stage 0 includes those with a family history of BD, given that familial risk is the strongest predictor of later development of the disorder, with heritability estimates around 85% (Bienvenu et al., 2011). There is a paucity of evidence to characterise individuals in stage 1 with no familial history of BD. In a prospective study including over 3,000 adolescents and young adults assessed over a period of 10 years, poor sleep quality at baseline increased the subsequent risk of receiving a diagnosis of BD by 1.75-fold (Ritter et al., 2015). This effect remained even after controlling for age, gender, familial history of mood disorders, alcohol and cannabis use. Together with sleep, anxiety and cyclothymia (i.e. rapid oscillation in mood) have been proposed as phenomenological signals of the emergence of BD (Kapczinski et al., 2014), but greater specificity is needed. As such, much of the focus of early identification of BD has been directed towards individuals at stage 0.

Given this clinical staging model, children of bipolar parents comprise stage 0 and are a salient, high-risk population that can inform the scientific endeavour of identifying the emergence of BD. Cumulative research over the past two decades using BD high-risk offspring has indeed identified such markers of vulnerability. In large cohort studies of high-risk offspring, the presence of a sleep disorder or disruption is predictive of the development of a subsequent mood disorder. In one such study, the presence of a sleep disorder predicted a 1.63-fold increase in the risk of being diagnosed with a mood disorder in the future (Duffy et al., 2019), while in another study, participants classified as poor sleepers at baseline were twice as likely to be diagnosed with BD in the future compared to participants classified as good sleepers (Levenson et al., 2017). Increased energy levels and social jet lag (Sebela et al., 2019), decreased need for sleep (Sebela et al., 2019), increased sleep onset latency (Levenson et al., 2017), irregularity of sleep patterns (Singh et al., 2008), and delayed circadian rhythms (Levenson et al., 2017; Melo et al., 2017) are among the sleep and circadian risk factors that emerged in prospective studies in high-risk offspring. In a systematic review that included 16 studies on high-risk and prodromal phases in BD (i.e. prospective studies on bipolar offspring, prospective studies on people with sleep disruptions that later developed BD, or retrospective studies on people with BD) sleep and circadian disruptions manifested at least a year prior to the diagnosis of BD (Pancheri et al., 2019).

2.4.6. Sleep and Circadian disruptions as treatment targets

Owing to the high prevalence of sleep and circadian rhythm disruptions and their potential involvement in the multifaceted causality of BD, there is growing interest in the chronotherapeutic effects of existing pharmacological treatments, and the use of sleep and circadian rhythms as potent targets of adjunctive psychotherapy.

Current guidelines recommend lithium as the first line of treatment, and either quetiapine monotherapy or combination treatment with fluoxetine and olanzapine for

bipolar depression (Goodwin et al., 2016; Yatham et al., 2018). With the exception of fluoxetine, studies have shown that the rest of these medications might have a chronotherapeutic effect. A meta-analysis of RCTs showed that quetiapine has a sleep-promoting effect in both healthy and psychiatric populations (Lin et al., 2023), as it was associated with an improvement in self-reported sleep quality. Quetiapine was also associated with an increase in sleep duration when compared to placebo, but not when compared to other psychiatric medication. Dosage analysis highlighted that 50, 150 and 300 mg/day were effective, but 25 mg/day were not (Lin et al., 2023). Actigraphic evidence has also linked the administration of quetiapine with increases in sleep duration and efficiency, and a delay in final wake time (Rock et al., 2016). Regarding olanzapine, in a double-blind cross-over RCT in healthy participants, a single dose of olanzapine was associated with a consistent hypnotic effect, indexed by an increase in total sleep time and sleep efficiency, and a decrease in wake time (Giménez et al., 2007). Polysomnography on the night after olanzapine administration showed an increase in the duration of SWS and REM sleep, and a decrease in wakefulness, while participants also reported an increase in subjective sleep quality (Giménez et al., 2007). In the same study, risperidone and haloperidol, the two remaining main antipsychotic medications highlighted by NICE, were not associated with strong hypnotic effects.

Lithium response in particular is shown to be genetically determined (McCarthy et al., 2022), with chronotype and cellular circadian rhythms being potent markers of response. On a behavioural level, lithium responders show increased morningness, and morningness at baseline predicts favourable response to lithium (McCarthy, 2019; Rohr & McCarthy, 2022). Studies have also suggested that lithium can increase rest-activity amplitude, while actigraphic differences in intra-daily variability, median activity level, amplitude and relative amplitude can distinguish lithium responders from non-responders (Scott, Hennion, et al., 2022). On a molecular level, cells from lithium responsive individuals with BD exhibit a

shorter circadian period or can be potentially shortened with lithium in vitro (McCarthy, 2019). On the other hand, cells from lithium non-responders exhibit longer circadian periods that are less influenced by lithium administration in vitro (McCarthy, 2019). Subsequent research has also found that fibroblasts of people with BD that exhibit longer circadian periods also display muted circadian responses to lithium and other chronomodulators that phenocopy lithium, suggesting that lithium acts in a person-specific manner, with effects dependent on the person's circadian phenotype (Sanghani et al., 2021). Notwithstanding, sleep and circadian rhythms are not explicitly acknowledged as direct treatment targets in BD treatment manuals, apart from the short-term use of GABA modulators for sedative purposes (Goodwin et al., 2016; Yatham et al., 2018).

Owing to the involvement of circadian disruptions in BD, melatonin and melatonin receptor agonists (e.g. agomelatine and ramelteon) have also been explored as possible treatment options. Evidence regarding their efficacy relies on a limited number of trials, with reviews suggesting that the effects of these medications on depression, mania and sleep quality are small and non-significant (Kishi et al., 2019; McGowan et al., 2022). Recent work has further highlighted that no such trial has directly examined the chronotherapeutic mechanism of action of melatonin or melatonin receptor agonists in BD (McGowan et al., 2022). Despite presumptions of a chronobiotic mechanism of action in the justification of these trials, there is a stark absence of physiologic assessment of circadian parameters, with all trials focusing almost exclusively on assessing mood.

Adjunctive psychotherapy in BD, such as cognitive behavioural therapy and interpersonal therapy, is typically administered for long-term maintenance or to treat subsyndromal symptoms (Goodwin et al., 2016; Yatham et al., 2018). In professional treatment manuals, regularisation of sleep-wake and other daily rhythms is a recommended component of all such treatments, but never the sole treatment target (Goodwin et al., 2016;

Yatham et al., 2018). More contemporary treatment manuals diverge in this respect and recognise sleep and circadian rhythms both as assessment outcomes and as independent treatment targets (Malhi et al., 2021). The 2020 treatment guidelines by the Royal Australian and New Zealand College of Psychiatrists acknowledge circadian rhythms as a prominent factor in the aetiology of BD, highlight the need for circadian assessments in routine clinical practice (i.e. chronotype, daily rhythms and sleep-wake patterns), and recommend bright light therapy (BLT) for bipolar depression and interpersonal and social rhythm therapy (IPSRT) as a maintenance treatment (Malhi et al., 2021).

Both BLT and IPSRT are presumed to work via modulating circadian disturbances. Exposure to bright light in the morning or afternoon has the potential to advance the circadian phase and shift people's endogenous rhythms earlier. IPSRT combines interpersonal therapy with a protocol aimed at stablising people's daily activities, such as sleep-wake schedule, meal times and social activities, as a proxy for regulating circadian rhythms (Frank et al., 2007). The manual by the Royal Australian and New Zealand College of Psychiatrists also mentions the therapeutic potential of total sleep deprivation (TSD) but concludes that there is not enough evidence to recommend its general use. Other psychological and behavioural interventions that target sleep and circadian rhythms include blue-light blocking glasses, cognitive behaviour therapy for insomnia, and a combination of TSD, BLT and phase advance, called triple chronotherapy. Reviews have reported predominantly positive findings about the efficacy of these interventions in BD (Gottlieb et al., 2019), yet these conclusions are often based on small and heterogeneous studies.

3

The Sleep Profile in Bipolar Disorder: Results from the UK Sleep Census

Contents

3.1 Background and Rationale

Sleep disruptions are a hallmark characteristic of BD, and core symptoms of acute mood episodes. Both the DMS-5 and ICD-11 recognise disruptions in sleep as diagnostic features of both mania and depression (American Psychiatric Association, 2013; World Health Organization, 2018), and research has indicated that these disruptions are ubiquitous across episodes (Harvey, 2008). Over 55% of people with BD meet the diagnostic criteria for a comorbid diagnosis of insomnia and over 30% meeting the criteria for a comorbid diagnosis of hypersomnia (Grigolon et al., 2019; Harvey et al., 2005). Approximately 83% of people with BD report persistent difficulties with their sleep during euthymia (Rocha et al., 2013), typically indexed as lower sleep efficiency, longer sleep onset latency and greater daytime impairments (Cretu et al., 2016; Rocha et al., 2013). Meta-analytic evidence on actigraphy studies in euthymia have corroborated these findings (Geoffroy et al., 2015). As

such, sleep disruptions are conceptualised as a cross-cutting features across all episodes of BD (Kaplan, 2020).

Notwithstanding, the assessment of sleep problems in BD remains relatively poor and is often neglected (Bisdounis et al., 2022; Faulkner & Bee, 2016). Phenotyping protocols either employ a very small number of participants (Harvey, 2008) or characterise sleep disturbances on the basis of singular items from mood questionnaires. For example, one of the largest epidemiological studies to date that examines sleep problems in BD (n=563) used four items from the Inventory of Depressive Symptomatology as proxy measures for sleep disorders (Steinan, Scott, et al., 2016). Even in large cohorts, research on sleep in BD is limited. In the case of the UK BioBank, actigraphy derived sleep items have been published for n=123 people with BD (Dennison et al., 2021). Other UK BioBank investigations so far have focused on circadian outcomes derived from actigraphy devices, such as relative amplitude (n=581; Lyall et al., 2018) and light exposure (n=1,192 Burns et al., 2023).

A caveat in our understaning of the sleep profile of BD is that research insofar has overwhelmingly focused on strict characterisations of sleep, centred around disorders and diagnostic symptomatology. Although this is a general tendency in sleep medicine research (Buysse, 2014), there are convergent calls to adopt a person-centred approach to sleep that is not solely defined by the presence or absence of a disorder. (Buysse, 2014). Here, *sleep health* is operationally defined as a multidimensional pattern of sleep-wake that is not specific to any single disorder but is relevant on the individual and systemic level. Good sleep health is marked by subjective satisfaction, appropriate timing, adequate duration, high efficiency and sustained alertness during wake (Buysse, 2014; Ravyts et al., 2021). The adoption of a sleep health approach to BD research would see the inclusion of items on sleep thoughts and behaviours that might not be relevant to a specific disorder, but are relevant to a comprehensive sleep health profile.

Research has also suggested that improved resolution in the characterisation of the BD sleep profile could contribute to its demarcation from major depression disorder (MDD) and thus reduce misdiagnoses (Leseur et al., 2024). Comparisons between BD and MDD have shown that although sleep is significantly disrupted in both conditions, their profiles are distinct (Jermann et al., 2022; Leseur et al., 2024; Slyepchenko et al., 2019). In these studies, MDD was typically characterised by more severe insomnia symptoms, longer sleep onset, and lower sleep duration. On the other hand, BD was characterised by a higher prevalence of hypersomnia, increased total sleep time and reduced motor activity.

The aim of the present study was to identify the sleep profile of people with BD, and compare it against health controls without any mental health diagnoses (HC), and people with a diagnosis of MDD. Our pre-registered hypothesis was that compared to HC, people with BD will show greater scores in insomnia, depression and cognitive complaints, and lower scores on quality of life.

3.2 Methodology

3.2.1 Study Design and Setting

Data were retrieved from a national online survey about sleep that took place between 31st March 2021 and 10th April 2022. This survey, called the UK Sleep Census, was commissioned by the British Broadcasting Corporation (BBC) and carried out by the Sir Jules Thorn Sleep and Circadian Neuroscience institute at the University of Oxford via the platform Qualtrics. The survey was advertised through the BBC2 Horizon programme, an ongoing and long-lasting documentary series that covers topics around science and philosophy. There was also a special BB2 Horizon episode on the results of the UK Sleep Census, hosted by Dr Michael Mosley. Ethical approval was sought and obtained by the

University of Oxford Medical Sciences Interdivisional Research Ethics Committee (Ref: R75232/RE003).

3.2.2 Participant Information

Participants were people that responded to the UK Sleep Census. Our sample included three groups of equal size. The first group consisted of participants who reported a diagnosis of BD by a mental health professional. The two other groups were matched with the BD group using a 1:1 nearest neighbour propensity score matching, controlled for age, gender, educational attainment and current occupation. One group included HC that reported no mental health diagnosis, and the final group included people who reported a diagnosis of MDD.

3.2.3 Outcomes

Outcomes included validated questionnaires and bespoke items about sleep-related thoughts and behaviours. A detailed list of all questionnaires and response options can be found on our study dedicated Open Science Framework page: https://osf.io/hxdn3/. Appendix 1 in the Supplementary Materials contains a detailed list of all questions and possible answers from the UK Sleep Census.

Our primary pre-registered outcome was insomnia scores as reported using the Sleep Condition Indicator. Secondary outcomes included depression scores using the Patient Health Questionnaire-4, cognitive complaints using the British Columbia Cognitive Complaints Inventory, chronotype using the reduced Morningness-Eveningness Questionnaire, and quality of life using a percentage visual analogue scale. All other variables were bespoke items and were analysed in an exploratory manner. These included: self-reported past diagnoses of sleep and circadian disorders (categorical), sleep satisfaction (categorical), typical sleep duration of main sleep episode excluding naps (continuous, measured in hours), typical sleep need for main sleep episode excluding naps (continuous,

measured in hours), sleep quality compared to others (categorical), timing of going to bed, turning the lights off, wake time and getting out of bed for work and free days (HH:MM), prescription medication for sleep (categorical), effectiveness of prescription medication for sleep (categorical), non-prescription medication for sleep (categorical), effectiveness of non-prescription medication for sleep (categorical), psychological treatments for sleep (categorical), effectiveness of psychological treatments for sleep (categorical), napping frequency (categorical), napping duration (categorical), time of last caffeinated drink (categorical), alcohol to aid sleep (categorical), exercising frequency (categorical), timing of exercise (categorical), and device use before bedtime (categorical).

Sleep Condition Indicator (Espie et al., 2014). The SCI is a brief 8-item measure of insomnia, modelled after the DSM-5 diagnostic criteria for the disorder. The scale assesses both day- and night-time disruptions. Items are scored on a 5-point scale ranging from 0 to 4. Total scores range from 0 to 32, with higher values indicative of better sleep. A cut-off score of 16 is used to reflect minimum criteria for the diagnosis of insomnia disorder. There is also the option to rescale the SCI to a 10-point scale by dividing the total score by 3.2, which was the method that was adopted in this paper. The SCI has good internal consistency (Cronbach's α: 0.87) (Espie et al., 2014).

Reduced Morningness-Eveningness Questionnaire (Adan & Almirall, 1991). The reduced MEQ is an abbreviated form of the original Morningness Eveningness Questionnaire (Horne & Ostberg, 1976), aimed at determining an individual's chronotype, i.e., their preference for morning or evening activities. The measure contains 5-items, and yields a total score of 4-25. Lower scores indicate a preference for eveningness, while higher scores indicate a preference for morningness. Eveningness is typically defined as a score lower than 21 and morningness as as score higher than 17. Inbetween scores are classified

as intermediated types. The MEQ has shown adequate internal consistency (Cronbach's α: 0.71) (Chelminski et al., 2000).

Patient Health Questionnaire-4 (Kroenke et al., 2009). The PHQ-4 integrates two core items from the PHQ-2 (depressive symptoms) and two from the GAD-2 (anxiety symptoms), rendering a brief tool for the assessment of depression and anxiety. Each item is scored on a 4-point scale from 0 (not at all) to 3 (nearly every day), with the total score thus ranging from 0 to 12. A score of 3 or higher is indicative of moderate to severe depression or anxiety. The PHQ-4 has good internal consistency (Cronbach's α: 0.82-0.85) (Kroenke et al., 2009; Löwe et al., 2010).

British Columbia Cognitive Complaints Inventory (Iverson & Lam, 2013). This is a scale aimed at measuring subjective cognitive functioning, covering concentration, memory, trouble expressing thoughts, word finding, and problem-solving. The 6 included items are rated on a 4-point scale ranging from 0 (not at all) to 3 (very much). Total scores range from 0 to 18, with higher scores indicating greater severity of cognitive complaints. Scores of 9 and above indicate moderate to severe cognitive complaints. The measure has good internal consistency for people with depression (Cronbach's α: 0.86) (Iverson & Lam, 2013).

Quality of life was assessed using a horizontal visual analogue scale asking people to rate their current quality of life from 0 (worst possible quality of life) to 100 (best possible quality of life). Although internal consistency cannot be estimated on single-item measures, this single-item visual analogue scale measure constitutes a validated outcome for quality of life, with good validity and excellent reliability that produces comparable outcomes to multi-component measures of quality of life (de Boer et al., 2004).

3.2.4 Analysis Plan

All analyses were performed in R, version 4.2.0. All analyses were pre-registered on our study dedicated Open Science Framework Page (https://osf.io/hxdn3/) and the analysis source code is freely available online.

Single missing items from otherwise complete questionnaires were replaced using mean imputation. Means and standard deviations were estimated for continuous variables, while frequencies and percentages were estimated for binary and categorical variables. Confirmatory analyses of the primary and secondary outcomes relied on independent samples t-tests between the BD and HC groups, with Bonferroni corrections for multiple comparisons. T-values, p-values, Cohen's d effect sizes and accompanying 95% CIs were estimated. We followed conventional benchmarks of referring to effect sizes as small for ES=0.20, moderate for ES=0.50 and large for ES=0.80 (Cohen, 2013).

The sole deviation from our pre-registered analysis plan was the addition of chronotype as a secondary outcome, which was missed in error on our pre-registration document. Here, a preference for an evening chronotype was predicted. Inferential analyses were performed for sleep duration and need, but these remained exploratory in nature and no specific direction was predicted. Comparisons between BD and MDD were exploratory in nature and no specific hypothesis was pre-registered. Appendix 2 in the Supplementary Materials contains the study pre-registration.

3.3 Results

Out of 275,050 survey responders, 1,072 reported a diagnosis of BD (0.39% of the total sample). This group had a mean age of 45.56 years (d=13.80) with a relatively equal split between male and female participants (45.99% male and 52.05% female). The group

was also mostly white (93.29%), highly educated (58.39% having at least an undergraduate degree), and either in part or full-time employment (54.66%). The HC and UD groups were matched with the BD group on age, gender, education and employment and were equal in size. More information about the demographic characteristics of the three groups are presented on Table 3.1.

Table 3.1 Demographic characteristics of the Bipolar Disorder, Major Depression and Healthy Control Groups

	Bipolar Disorder n=1,072	**Major Depression** n=1,072	**Healthy Controls** n=1,072
Gender, no (%)*			
Male	493 (45.99)	498 (46.46)	482 (44.96)
Female	558 (52.05)	556 (51.87)	568 (52.99)
Non-binary	16 (1.49)	13 (1.21)	16 (1.49)
Age, mean (sd)*	45.56 (13.80)	45.70 (13.53)	45.46 (13.87)
Employment, no (%)*			
Full-time employed	461 (43.00)	463 (43.12)	461 (43.00)
Part-time employed	116 (10.82)	131 (12.22)	117 (10.91)
Employed (furloughed)	9 (0.84)	6 (0.56)	10 (0.93)
Unemployed, looking for work	33 (3.08)	29 (2.71)	30 (2.80)
Unemployed, not looking for work	53 (4.94)	54 (5.04)	53 (4.94)
Full-time student	47 (4.38)	46 (4.29)	48 (4.48)
Part-time student	12 (1.12)	4 (0.37)	11 (1.03)
Unable to work	152 (14.18)	164 (15.30)	154 (14.37)
Retired	137 (12.78)	134 (12.50)	136 (12.69)
Other	46 (4.29)	38 (3.54)	47 (4.38)
Marital status, no (%)			
Single	311 (29.01)	294 (27.43)	216 (20.15)
In a relationship (living together)	544 (50.75)	575 (53.64)	728 (67.91)
In a relationship (not living together)	66 (6.16)	65 (6.06)	61 (5.69)
Divorced/Separated	116 (10.82)	109 (10.17)	46 (4.29)
Widowed	20 (1.87)	22 (2.05)	15 (1.40)
Bedpartner, no (%)			
Never or No bed partner	459 (42.82)	455 (42.44)	315 (29.38)
Rarely, less than twice a week	55 (5.13)	57 (5.32)	37 (3.45)
Sometimes, 1-3 times a week	67 (6.25)	65 (6.06)	54 (5.04)
Often, 4-6 times a week	50 (4.66)	46 (4.29)	39 (3.64)
Always, every night	438 (40.86)	443 (41.32)	621 (57.93)
Sharing house with children, no (%)			
Yes	246 (22.95)	276 (25.75)	348 (32.46)
No	818 (76.31)	792 (73.88)	722 (67.35)
Ethnicity, no (%)			
White	1,000 (93.29)	1,024 (95.52)	999 (93.19)
Black/African/Caribbean	7 (0.65)	1 (0.09)	5 (0.47)
Asian/Asian British	25 (2.33)	21 (1.95)	42 (3.92)
Arab	2 0.19	1 (0.09)	0 (0.00)

Mixed/Multiple ethnic groups	21 (1.95)	21 (1.95)	16 (1.50)
Other ethnic group	6 (0.56)	2 (0.19)	3 (0.28)
Education, no (%)*			
None	30 (2.80)	22 (2.05)	19 (1.77)
Secondary education or equivalent	171 (15.95)	169 (15.76)	172 (16.04)
A-levels or equivalent	235 (21.92)	247 (23.04)	227 (21.18)
University undergraduate	317 (29.57)	310 (28.92)	325 (30.32)
University postgraduate	309 (28.82)	310 (28.92)	318 (29.66)
Area of residence, no (%)			
Urban, densely populated city or town	403 (37.59)	365 (34.05)	350 (32.65)
Suburban, on the edge of town or at a city or village with more than 10,000 inhabitants	490 (45.71)	528 (49.25)	559 (52.15)
Rural, sparsely populated area	172 (16.04)	178 (16.60)	160 (14.93)
Shift-work, no (%)			
No, no work	457 (43.07)	471 (44.06)	466 (43.59)
No, worked standard hours (e.g. 9am-5pm)	447 (42.13)	474 (44.34)	506 (47.33)
Yes, evening shifts (work finishes between 9pm-5am)	29 (2.73)	28 (2.62)	20 (1.87)
Yes, morning shifts (work starts between 4-7am)	16 (1.51)	23 (2.15)	21 (1.96)
Yes, night shifts (work takes place between 9pm-8am)	16 (1.51)	9 (0.84)	4 (0.37)
Yes, rotating shifts (shift periodically change or irregular work schedules)	87 (8.20)	61 (5.71)	50 (4.68)
Comorbid diagnoses, no (%)			
No illness/disorder/disease	33 (3.08)	19 (1.77)	558 (52.05)
Diabetes	97 (9.05)	81 (7.56)	38 (3.54)
Arterial hypertension	65 (6.06)	82 (5.65)	47 (4.38)
Cardiovascular disorder	35 (3.27)	24 (2.24)	39 (3.64)
Cerebrovascular disorder	3 (0.28)	4 (0.37)	2 (0.19)
Other neurological disorder	58 (5.41)	64 (5.97)	35 (3.27)
Asthma	174 (16.23)	180 (16.79)	127 (11.85)
Chronic obstructive pulmonary disease	28 (2.61)	15 (1.40)	20 (1.87)
Rheumatic disorder	44 (4.10)	52 (4.85)	46 (4.29)
Cancer/use of cytostatic medications	22 (2.05)	31 (2.89)	22 (2.05)
Allergy (atopy, seasonal, other allergy)	182 (16.98)	190 (17.72)	136 (12.69)
Autoimmune disorder	83 (7.74)	73 (6.81)	64 (5.97)
Depression	422 (39.37)	1,072 (100.00)	0 (0.00)
Anxiety/panic disorder	468 (43.66)	555 (51.77)	0 (0.00)
Bipolar disorder	1,072 (100.00)	0 (0.00)	0 (0.00)
Problems with attention or concentration/Attention Deficit Hyperactivity Disorder	94 (8.77)	52 (4.85)	0 (0.00)
Other mental health problem	212 (19.78)	121 (11.29)	0 (0.00)
Myalgic encephalomyelitis or chronic fatigue	62 (5.78)	61 (5.69)	38 (3.54)
Digestive disorder	141 (13.15)	136 (12.69)	66 (6.16)
Hormonal Disorder	76 (7.09)	56 (5.22)	23 (2.15)
Other	123 (11.47)	159 (14.83)	142 (13.25)

** Groups were matched based on gender, age, employment status and education*
Abbreviations: no, number; sd, standard deviation

3.3.1 Bipolar Disorder and Healthy Controls

Table 3.2 provides data on sleep outcomes for all three groups, while Table 3.3 provides unadjusted data on mood, cognition and quality of life. Table 3.4 presents the inferential analysis of the independent samples t-test, p-values with Bonferroni corrections, and Cohen's d effect sizes with associated 95% confidence intervals for all three groups. Figure 3.1 offers illustrations for these relationships.

Compared to the HC group, the BD group reported higher insomnia scores ($t=16.10$; $p<0.001$; $d= -0.72$ [95%CI: -0.81 to -0.63]) and were more likely to meet the clinical threshold for insomnia (61.10% for BD; 40.39% for HC). The BD group also reported shorter sleep duration ($t=4.56$; $p<0.001$; $d= -0.20$ [95%CI: -0.29 to -0.12]), higher sleep need ($t=3.65$; $p<0.001$; $d= 0.16$ [95%CI: 0.08 to 0.25]), albeit both effects sizes were small. There was a small-to-moderate effect with people with BD showing a preference for an evening chronotype ($t=8.66$; $p<0.001$; $d= -0.40$ [95%CI: -0.49 to -0.31]). In our sample, 26.68% of the participants in the BD group met the criteria for an evening chronotype (and 28.82% for a morning chronotype), compared to 15.11% of the participants of the HC group doing so (and 48.32% for a morning chronotype). The BD group reported more frequent use of prescription medication for sleep (26.09% and 4.59% of the BD and HC groups, respectively, reported weekly use), longer and more frequent napping (weekly or biweekly napping [≥40min]; 75.13% [54.82%] for BD; 60.83 [34.33%] for HC), and even though they were more likely to have received a psychological treatment for their sleep (18.99% of BD; 3.26% of HC), they were more dissatisfied with their sleep (63.54% of BD were dissatisfied or very dissatisfied with their sleep in comparison to 42.03% of the HC group).

There was a large effect size regarding depression severity, with the BD group reporting higher depression scores ($t=23.91$; $p<0.001$; $d= 1.09$ [95%CI: 1.00 to 1.19]) compared to HC, and almost half of participants in this group (46.18%) meeting the clinical

threshold for moderate to severe depression. There was a large difference in perceived cognitive impairments, with the BD group reporting more frequent cognitive complaints (t=18.20; p<0.001; d= 0.83 [95%CI: 0.74 to 0.93]) compared to controls. There was a moderate difference in quality of life, with people with BD reporting a lower quality of life (t=13.36; p<0.001; d= -0.58 [95%CI: -0.67 to -0.49]) than controls.

The two groups also reported similar behaviour patterns regarding exercise and alcohol consumption and electronic device use before bed as it can be seen from Table 3.2.

3.3.2 Bipolar Disorder and Major Depression Disorder

The BD and MDD groups had comparable sleep and mental health profiles. The only significant difference, albeit with a small effect size, was in the BD group reporting more frequent cognitive complaints (t=2.96; p=0.003; d= 0.14 [95%CI: 0.05 to 0.23]). In our sample, 35.82% of the participants in the BD group met the criteria for moderate to severe cognitive complaints compared to 33.21% of the participants in the MDD group.

Table 3.2 Sleep outcomes of the Bipolar Disorder, Major Depression and Healthy Control Groups

	Bipolar Disorder n=1,072	**Major Depression** n=1,072	**Healthy Controls** n=1,072
Sleep Condition Indicator (0-10)			
Total scores, mean (sd)	3.98 (2.69)	4.17 (2.56)	5.89 (2.57)
Insomnia cases ≥5, no (%)	655 (61.10)	694 (64.74)	433 (40.39)
Sleep and Circadian disorder diagnoses, no (%)			
Ever been diagnosed with a sleep disorder	162 (15.15)	118 (11.01)	39 (3.64)
Insomnia	99 (9.24)	52 (4.85)	14 (1.31)
Sleep disordered breathing	57 (5.32)	55 (5.13)	17 (1.59)
Sleep related movement disorder	25 (2.33)	22 (2.05)	3 (0.28)
Parasomnia	21 (1.96)	5 (0.47)	3 (0.28)
Circadian rhythm disorders	5 (0.47)	6 (0.56)	0 (0.00)
Hypersomnia	4 (0.37)	4 (0.37)	3 (0.28)
Other sleep disorder	16 (1.49)	11 (1.03)	5 (0.47)
Morningness-Eveningness Questionnaire (4-25)			
Total scores, mean (sd)	14.73 (4.12)	14.71 (3.90)	16.26 (3.61)
Morning types > 17, no (%)	309 (28.82)	344 (32.09)	518 (48.32)
Intermediate types 12-17, no (%)	305 (28.45)	345 (32.18)	360 (33.58)
Evening types < 12, no (%)	286 (26.68)	311 (29.01)	162 (15.11)

Sleep satisfaction, no (%)			
Very satisfied	42 (4.80)	32 (3.20)	77 (7.44)
Satisfied	130 (14.86)	130 (13.00)	302 (29.18)
Neutral	146 (16.69)	189 (18.90)	220 (21.26)
Dissatisfied	260 (29.71)	357 (35.70)	307 (29.66)
Very dissatisfied	296 (33.83)	292 (29.20)	128 (12.37)
Sleep duration and need			
Sleep duration, mean (sd) in hours	6.60 (1.83)	6.65 (1.73)	6.93 (1.31)
Short sleepers < 6 hours, no (%)	281 (26.21)	276 (25.75)	164 (15.30)
Long sleepers > 9 hours, no (%)	58 (5.41)	40 (3.73)	15 (1.40)
Sleep duration need, mean (sd) in hours	8.06 (1.71)	7.99 (1.36)	7.83 (1.04)
Sleep quality compared to other people of the same age, no (%)			
Much better	42 (4.2)	29 (2.76)	61 (5.82)
Somewhat better	118 (12.14)	123 (11.73)	225 (21.45)
About the same	185 (19.03)	251 (23.93)	348 (33.17)
Somewhat worse	309 (31.79)	360 (34.32)	291 (27.74)
Much worse	301 (30.97)	278 (26.50)	120 (11.44)
Timings during work days, median HH:MM			
Going to bed	22:00	22:00	22:15
Turning the lights off	22:00	22:30	22:30
Wake time	06:45	07:00	06:45
Getting out bed	07:15	07:15	07:00
Time in bed during work days, mean (sd)	8.00 (1.57)	8.00 (1.39)	7.75 (1.04)
Timings during free days, median HH:MM			
Going to bed	22:00	22:00	22:15
Turning the lights off	22:00	22:00	22:30
Wake time	07:45	08:00	07:30
Getting out bed	08:30	09:00	08:15
Time in bed during free days, mean (sd)	8.27 (2.05)	8.29 (1.88)	8.15 (1.43)
Prescription medication for sleep, no (%)			
Not during the past month	613 (65.28)	828 (80.70)	971 (93.01)
Less than once a week	63 (6.71)	43 (4.19)	17 (1.63)
Once or twice a week	43 (4.58)	30 (2.92)	11 (1.05)
Three or more times a week	202 (21.51)	116 (11.31)	37 (3.54)
Effectiveness of prescribed medication for sleep, no (%)			
Not at all effective	25 (8.17)	17 (8.99)	6 (9.23)
Somewhat effective	132 (43.14)	90 (47.62)	36 (55.38)
Quite a bit effective	77 (25.16)	42 (22.22)	14 (21.54)
Very much effective	71 (23.20)	39 (20.63)	9 (13.85)
Non-prescription medication for sleep, no (%)			
Not during the past month	722 (77.30)	779 (76.07)	881 (84.39)
Less than once a week	62 (6.64)	81 (7.91)	61 (5.84)
Once or twice a week	65 (6.96)	67 (6.54)	45 (4.31)
Three or more times a week	80 (8.57)	91 (8.89)	51 (4.89)
Effectiveness of non-prescribed medication for sleep, no (%)			
Not at all effective	41 (19.90)	45 (18.83)	26 (16.56)
Somewhat effective	112 (54.37)	135 (56.49)	98 (62.42)
Quite a bit effective	35 (16.99)	39 (16.32)	24 (15.29)
Very much effective	15 (7.28)	19 (7.95)	9 (5.73)
Psychological treatments for sleep, no (%)			
No/Never	751 (80.58)	867 (84.75)	1004 (96.17)
Yes, but not in the past month	159 (17.06)	136 (13.29)	32 (3.07)

Yes, currently receiving treatment	18 (1.93)	16 (1.56)	2 (0.19)
Effectiveness of psychological treatment for sleep, no (%)			
Not at all effective	81 (46.02)	65 (42.76)	14 (36.84)
Somewhat effective	66 (37.50)	54 (35.53)	13 (34.12)
Quite a bit effective	16 (9.09)	22 (14.47)	7 (18.42)
Very much effective	10 (5.68)	9 (5.92)	4 (10.53)
Napping frequency, no (%)			
Daily	118 (12.70)	133 (13.00)	68 (6.51)
More than once a week	238 (25.62)	275 (26.88)	169 (16.19)
Three to four times per month	155 (16.68)	156 (15.25)	134 (12.84)
Once or twice per month	187 (20.13)	220 (21.51)	264 (25.29)
Not at all	231 (24.87)	239 (23.36)	409 (39.18)
Napping duration, no (%)			
0-20 minutes	120 (17.27)	157 (20.05)	199 (31.34)
21-40 minutes	184 (26.47)	176 (22.48)	207 (32.60)
41-60 minutes	156 (22.45)	185 (23.63)	127 (20.00)
1-2 hours	189 (27.19)	191 (24.39)	78 (12.28)
More than 2 hours	36 (5.18)	54 (6.90)	13 (2.05)
Don't know	10 (1.44)	19 (2.43)	11 (1.73)
Time of the last caffeinated drink, no (%)			
Early morning	81 (8.94)	63 (6.20)	91 (8.75)
Late morning	91 (10.04)	113 (11.12)	129 (12.40)
Early afternoon	176 (19.43)	195 (19.19)	198 (19.04)
Late afternoon	198 (21.85)	212 (20.87)	208 (20.00)
Between evening meal and bedtime	189 (20.86)	248 (24.41)	244 (23.46)
Varies significantly	89 (9.82)	87 (8.56)	53 (5.10)
No caffeinated drinks at all	1 (0.11)	1 (0.10)	1 (0.10)
Consumed alcohol to aid sleep, no (%)			
Daily	42 (4.47)	31 (3.02)	15 (1.44)
More than once a week	83 (8.84)	81 (7.89)	55 (5.27)
Three to four times a month	50 (5.32)	40 (3.90)	22 (2.11)
Once to twice a week	82 (8.73)	97 (9.45)	77 (7.38)
Not at all	679 (72.31)	776 (75.63)	871 (83.43)
Exercising frequency, no (%)			
Daily	219 (23.75)	224 (21.98)	317 (30.39)
More than once a week	305 (33.08)	334 (32.78)	393 (37.68)
Three to four times a month	118 (12.80)	137 (13.44)	111 (10.64)
Once to twice a week	86 (9.33)	99 (9.72)	82 (7.86)
Not at all	130 (14.10)	147 (14.43)	70 (6.71)
Unable to exercise	61 (6.62)	75 (7.36)	69 (6.62)
Timing of exercise, no (%)			
Early morning	104 (14.27)	124 (15.58)	188 (20.84)
Late morning	113 (15.50)	128 (16.08)	137 (15.19)
Early afternoon	131 (17.79)	113 (14.20)	128 (14.19)
Late afternoon	105 (14.40)	103 (12.94)	101 (11.20)
Evening, before meal	44 (6.04)	66 (8.29)	82 (9.09)
Between evening meal and bedtime	25 (3.43)	27 (3.39)	29 (3.22)
Varies significantly	203 (27.85)	232 (29.15)	234 (25.94)
Device use before bedtime, no (%)			
Use them in bed	473 (52.21)	548 (53.94)	466 (44.81)
Less than an hour before bed	312 (34.44)	356 (35.04)	454 (43.65)
One to two hours before bed	84 (9.27)	85 (8.37)	95 (9.13)

Two to three hours before bed	18 (1.99)	13 (1.28)	11 (1.06)
Three hours or longer before bed	18 (1.99)	11 (1.08)	12 (1.15)
Not applicable	1 (0.11)	2 (0.20)	1 (0.10)

Abbreviations: HH:MM, hours;minutes; no, number; sd, standard deviation

Table 3.3 Mood, Cognition and Life Quality of the Bipolar Disorder, Major Depression and Healthy Control Groups

	Bipolar Disorder n=1,072	**Major Depression** n=1,072	**Healthy Controls** n=1,072
Patient Health Questionnaire-4 (0-12)			
Total scores, mean (sd)	6.36 (3.83)	6.13 (3.68)	2.75 (2.74)
Moderate to severe depression ≥3, no (%)	495 (46.18)	512 (47.76)	146 (13.62)
British Columbia Cognitive Complaints Inventory (0-18)			
Total scores, mean (sd)	8.01 (4.88)	7.35 (4.64)	4.37 (3.72)
Moderate to severe complaints ≥9, no (%)	384 (35.82)	356 (33.21)	131 (12.22)
Overall health rate, no (%)			
Excellent	43 (4.01)	60 (5.60)	204 (19.03)
Good	385 (35.91)	396 (36.94)	558 (52.05)
Fair	385 (35.91)	408 (38.06)	193 (18.00)
Poor	250 (23.32)	203 (18.94)	113 (10.54)
Do not know	5 (0.47)	5 (0.47)	3 (0.28)
Quality of life, mean (sd)	60.08 (22.37)	61.37 (20.23)	72.05 (18.31)

Abbreviations: no, number; sd, standard deviation

Table 3.4 Group comparisons between Bipolar Disorder, Major Depression and Healthy Controls

	Bipolar Disorder group vs Heathy Control group	**Bipolar Disorder group vs Major Depression group**
Sleep Condition Indicator	*t=16.10; p<0.001; Cohen's d= -0.72 [95%CI: -0.81 to -0.63]*	*t=1.48; p=0.138; Cohen's d= -0.07 [95%CI: -0.15 to 0.02]*
Sleep duration	*t=4.56; p<0.001; Cohen's d= -0.20 [95%CI: -0.29 to -0.12]*	*t=0.52; p=0.601; Cohen's d= -0.02 [95%CI: -0.11 to 0.06]*
Sleep need	*t=3.65; p<0.001; Cohen's d= 0.16 [95%CI: 0.08 to 0.25]*	*t=0.56; p=0.576; Cohen's d= 0.02 [95%CI: -0.06 to 0.11]*
Morningness-Eveningness Questionnaire	*t=8.66; p<0.001; Cohen's d= -0.40 [95%CI: -0.49 to -0.31]*	*t=0.28; p=0.776; Cohen's d= 0.01 [95%CI: -0.08 to 0.10]*
Patient Health Questionnaire	*t=23.91; p<0.001; Cohen's d= 1.09 [95%CI: 1.00 to 1.19]*	*t=1.47; p=0.141; Cohen's d= 0.07 [95%CI: -0.02 to 0.16]*
British Columbia Cognitive Complaints Inventory	*t=18.20; p<0.001; Cohen's d= 0.83 [95%CI: 0.74 to 0.93]*	*t=2.96; p=0.003; Cohen's d= 0.14 [95%CI: 0.05 to 0.23]*
Quality of Life	*t=13.36; p<0.001; Cohen's d= -0.58 [95%CI: -0.67 to -0.49]*	*t=1.43; p=0.152; Cohen's d= -0.06 [95%CI: -0.15 to 0.02]*

Abbreviations: CI, confidence intervals

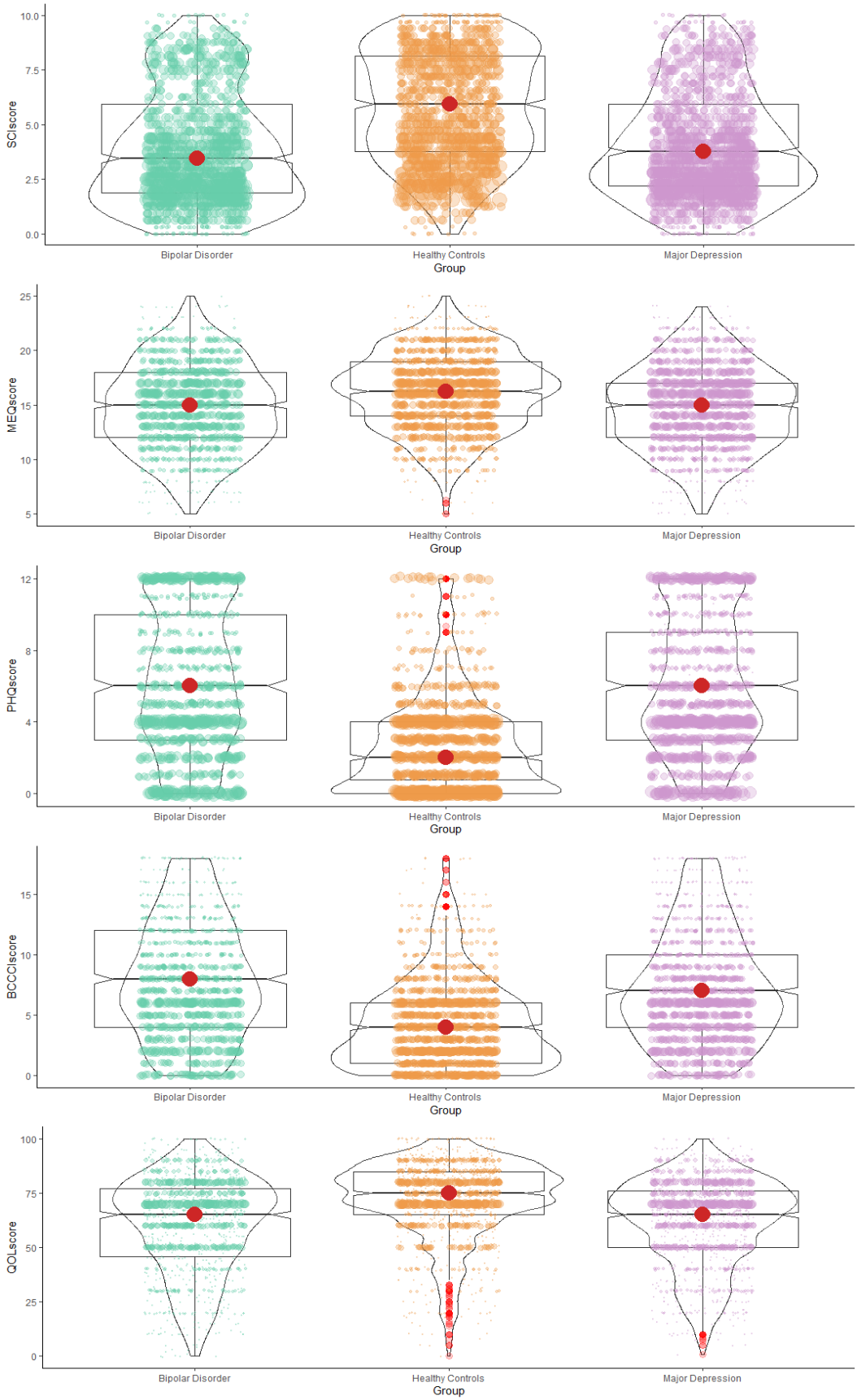


Figure 3.1 Group comparisons between the Bipolar Disorder, Major Depression and Healthy Control Groups. The red point indicates the mean score per group.

Abbreviations: BCCCI, British Columbia Cognitive Complaints Inventory; MEQ; Morningness-Eveningness Questionnaire; PHQ, Patient Health Questionnaire; QOL, Quality of Life; SCI, Sleep Condition Indicator

3.4 Discussion

Our findings suggest that individuals with BD have an impaired sleep profile compared to healthy controls. The BD sleep profile was characterised by increased insomnia symptoms, shorter sleep duration, increased perceived sleep need and medication use, longer and more frequent napping, higher use of hypnotics and greater dissatisfaction with their sleep. These results are in line with the existing literature on sleep disruptions across episodes in BD (Morton & Murray, 2020), and the major importance of sleep for people with BD and their caregivers (Chevance et al., 2020; Gordon-Smith et al., 2021). Similar to Harvey et al (2005) who reported that 55% of people with BD meet the criteria for a comorbid diagnosis of insomnia, 61% of the people in our BD group met the diagnostic criteria for insomnia according to the SCI. As predicted, the BD group also showed a preference for an evening chronotype. Meta analytic evidence supports the notion that people with BD are more likely to report an evening chronotype compared to controls (Melo et al., 2017; Romo-Nava et al., 2020), and longitudinal studies have shown that this preference is irrespective of the episode polarity and appears to be a trait marker of BD (Seleem et al., 2015).

People with BD also reported higher depression scores, more cognitive complaints and lower quality of life. High depression scores are naturally present in acute depression episodes, but they are also among the most common residual symptoms in euthymia, with reports that persistent depression symptoms in euthymia significantly affect functioning (Bonnín et al., 2010; Samalin et al., 2016; Serafini et al., 2018). In turn, there is evidence that both cognition (Samamé et al., 2017; Van Rheenen et al., 2020) and quality of life (Gutiérrez-Rojas et al., 2008; Michalak et al., 2005) are also impaired in BD across episodes.

No differences between the BD and MDD groups were detected in any outcome apart from cognition, with people with BD reporting more cognitive complaints than people with MDD. Converging evidence shows that people with BD report exhibit persisting

cognitive deficits in memory, attention and executive functioning, and similar but potentially milder deficits are also present in MDD (Samamé et al., 2017). There is conflicting evidence about whether the cognitive profiles of BD and MDD are distinct, with some studies supporting that they are (Cotrena et al., 2016; Gildengers et al., 2012; D. J. Smith et al., 2006), and others that they are not (Samamé et al., 2017; Szmulewicz et al., 2017). Although our study offers some preliminary evidence that there might be differences in these domains, our outcome concerns self-reported complaints regarding cognitive function, and does not directly measure the magnitude of any potential impairments.

The sleep profiles between people with BD and MDD were comparable, and this is in line with previous research that has shown no difference in insomnia (Jermann et al., 2022), sleep quality (Slyepchenko et al., 2019) or chronotype (Chung et al., 2012; Jermann et al., 2022; Slyepchenko et al., 2019) between BD and MDD. The lack of a significant difference in depression and quality of life is also in line with previous published studies (Jermann et al., 2022). Both in BD and MDD, sleep disruptions have been linked to poorer prognosis (Cretu et al., 2016; O'Brien et al., 2011), worse treatment outcomes (Pigeon et al., 2008), and increased suicidality (Geoffroy et al., 2021). In our sample, 46% of people with BD reported moderate to severe depression, a comparable rate to the 48% of people with MDD that did so as well. This is not surprising. People with BD spend more time in depression than in (hypo)mania (Vieta et al., 2018), and depressive predominance polarity is the most common symptom presentation across BD (Carvalho et al., 2014; Colom et al., 2006). As such, it is possible that the similar sleep profile is also a consequence of both groups experiencing considerable levels of depression at the time of recruitment.

Notwithstanding, results on the sleep profiles between BD and MDD are not yet conclusive. Other sources of evidence have highlighted that although there are notable sleep disruptions in both conditions, MDD is characterised by lower sleep quality and worse

insomnia symptoms, whereas BD is characterised by worse hypersomnia symptoms, decreased motor activity, and lower L5 and M10 average values (Leseur et al., 2024).

Strengths and limitations

Our study benefits from a comprehensive and multidimensional account of self-report outcomes on sleep and mental health. Owing to the population-level perspective of the UK Sleep Census, our study characterised sleep beyond the disorder level, offering new potential loci of interest for future research. Additionally, our sample size far exceeds that of most other observational studies in sleep in BD. This, coupe led with the large volume of data in the original UK Sleep Census allowed us to construct well-controlled comparison groups that were almost identical to the BD group on age, sex, current employment and educational attainment.

However, there are also important limitations. First, our sample size is older, predominantly white and highly educated. This might be due to the typical viewership of the advertisements TV episodes and of the BBC2 Horizon programme in general. As such, despite adding age and education as moderators in our matching algorithm, future investigations should try to capture a more diverse audience that is representative of the population at large. Second, it is likely that the findings reported here are quite conservative, given the influence of selection bias in online surveys. In our sample, over 40% of the healthy controls met the criteria for a diagnosis of insomnia based on the SCI, effectively rendering the healthy controls a group with notable sleep disruptions to begin with. The same selection bias could also affect the BD and MDD groups, with poorer sleepers deciding to complete the online survey. Although, this is possible phenomenon, its interference might be limited by the fact that sleep disruptions are ubiquitous in BD (Harvey, 2008) and present in 92% of depression cases (Geoffroy et al., 2018). Third, this study relied on self-reported diagnoses. There were no available outcomes to reliably confirm the reported diagnoses and

measure core symptoms of either BD or MDD, owing to the fact that the UK Sleep Census was no designed specifically for people with BD or MDD. Finally, although self-reported outcomes constitute the mainstay assessment for the majority of sleep problems in BD, future studies should expand on their assessment protocols in order to construct a more comprehensive sleep profile in BD. This includes assessments of hypersomnia and circadian rhythm sleep-wake disorders, as well as integrated measures of daytime functioning and alertness, rest-activity, circadian phase and sleep architecture.

4

Sleep and Activity Phenotyping in Individuals at High-Risk of Bipolar Disorder

Contents

4.1 Background and Rationale

Despite the typical age at onset for BD being between 15-25 years of ages, the clinical reality is that an accurate and timely diagnosis of BD is challenging. Only 20% of people receive an initial diagnosis of BD (Hirschfeld et al., 2003), while the average delay between initial symptom presentation and diagnosis of BD is 10 years (Baethge, Smolka, et al., 2003; Post et al., 2003). This delay in diagnosis has been linked to the delivery of inappropriate treatment, increased hospitalisation, and elevated risk of suicide (Keck et al., 2008). As such, there have been several research endeavours to improve the early identification of BD.

Presently, familial risk is the strongest predictor of later development of BD, with a heritability estimate of 85% (Bienvenu et al., 2011), rendering children of bipolar parents a salient, high-risk population that can inform the scientific endeavour of identifying

prodromal symptoms of BD. Cumulative research over the past two decades using bipolar high-risk offspring has indeed identified such markers of vulnerability. Among the proposed loci of interest, sleep and circadian rhythm disruptions are the most well-replicated and widely generalised markers (Melo et al., 2016). In these studies, increased energy levels and a decreased need for sleep were among the earliest identified symptoms (Sebela et al., 2019), followed by irregularity in sleep patterns (Singh et al., 2008) and delayed sleep-wake rhythms (Melo et al., 2016). In a sample of high-risk offspring, individuals classified as poor sleepers were twice as likely to develop BD compared to peers classified as good sleepers (Levenson et al., 2017). Combined with self-reported outcomes, actigraphy measures of rest-activity indicated a decreased need for sleep as a risk marker, together with lower social jet lag and a larger discrepancy on sleep duration and sleep onset latency between weekends and weeknights (Sebela et al., 2019).

Building upon the evidence that sleep and circadian rhythms are among the most well-replicated modifiable risk factors, two meta-analyses sought to quantify the magnitude and specificity of such disruptions in BD high-risk individuals (Aguiar et al., 2021; Scott, Etain, et al., 2022). Aguilar et al (2021) focused specifically on bipolar high-risk offspring, whereas Scott et al (2022) focused on high-risk offspring as well as people meeting recognised at-risk criteria. Aguiar et all (2021) found that there are 10 studies on high-risk offspring that have provided at least some data on sleep. Out of those, 5 extracted a sleep outcome from an otherwise non-sleep specific measurement (Duffy et al., 2019; Egeland et al., 2012; Sebela et al., 2019; Shaw et al., 2005; Singh et al., 2008). Of the remaining 5 studies, 3 assessed sleep quality using the PSQI (Jones et al., 2006; Sebela et al., 2017; Soehner et al., 2016), 2 used actigraphy (Jones et al., 2006; Sebela et al., 2017), 2 used an adolescent specific sleep-profile questionnaire (Levenson et al., 2015, 2017), and 1 used the MEQ (Sebela et al., 2017). The authors of the review argued that very few studies provided enough data on comparable domains to meta-analyse, with meta-analytic models having between 2 and 3

studies included for each outcome (Aguiar et al., 2021). Following different inclusion criteria, the review by Scott et al (2022) identified 21 studies of high-risk offspring that include at least one sleep outcome, 13 of which provided enough details on some domain to be meta-analysed. The authors found that, compared to low-risk controls, high-risk offspring had worse self-reported sleep quality, longer actigraphy measured TST and later actigraphy measured time to bed (Scott et al., 2022). However, the observed finding around actigraphy measured TST was reversed in people meeting recognised BD at-risk criteria, where sleep duration was significantly shorter than that of people who did not meet recognised BD at-risk criteria.

However, the non-specificity of these sleep and circadian antecedent symptoms limits their utility in research and clinical practice. Despite their trans-diagnostic value, sleep characteristics change with age, while self-reported appraisals of sleep are often incongruous with lab-based ones. Thus, current research is limited due to its focus on age groups younger than the typical age of onset of BD and the sparse use of methods beyond global questionnaires to assess sleep (Sebela et al., 2019). Most importantly, the markers explored so far capture a narrow fraction of sleep and circadian disruptions, focusing primarily on night-time insomnia symptoms. As such, we currently only have a snapshot of the potential sleep problems in high-risk offspring. These gaps in the literature do not allow for the adequate characterisation of sleep and activity profiles in high-risk offspring, limiting the applicability of such metrics in longitudinal models of vulnerability.

An additional outcome domain of interest is cognitive functioning. Cognitive impairments are evident following the first episode of BD (Lee et al., 2014), and meta-analyses have shown that those deficits are also present in young adults with familial high risk of BD (Bora & Özerdem, 2017). Problems in sustained attention (Cohen's d=0.36), inhibitory control (d=0.30), and processing speed (d=0.26) have been among the strongest

and the most prevalent manifestations of such cognitive impairments (Bora & Özerdem, 2017). Recent experimental work has also shown that in BD these three cognitive traits are highly prevalent (Laskemoen et al., 2019; Sparding et al., 2017) and associated with sleep problems (Bradley et al., 2020). Replication work is necessary to confirm the presence of cognitive deficits in high-risk offspring, and to explore whether the association between sleep and cognitive problems observed in people with BD is also present in high-risk offspring.

Our study aimed to profile the sleep and activity rhythm profile in BD high-risk offspring, using a variety of methods. We built upon previous studies and capitalised on a large existing well-characterised Canadian bipolar high-risk offspring cohort, the Flourish cohort. The research group behind the Flourish cohort pioneered the developmental trajectory of BD and identified that insomnia and sleep disruptions on a sub-syndromal level, are robust predictors of emerging BD (Duffy et al., 2019). According to publications from the Flourish cohort, sub-threshold sleep symptoms are the only marker of transition from wellness, while diagnosable insomnia increases the risk of a potential mood disorder by 1.6-fold (Duffy et al., 2019). Our pre-registered hypothesis was that high-risk individuals would report lower sleep quality and higher insomnia severity scores compared to the control group. All other goals were exploratory in nature.

4.2 Methodology

4.2.1 Study Design and Setting

This was a 2-week case-control, cross-sectional study. Group was the only independent variable, with two arms: high-risk and low-risk. The high-risk arm was recruited through the Flourish cohort in two Canadian provinces: Ontario and Quebec. The low-risk cohort comprised of volunteers living in Oxfordshire, England. Both groups were recruited

concurrently between 2021-2022, and different ethics boards were responsible for each site. In Canada, the study was integrated within the Flourish project ethics was approved by the Advarra Institutional Review Board (Ref: 152976). In Oxford, ethical approval was sought and obtained by the University of Oxford Medical Sciences Interdivisional Research Ethics Committee (Ref: R74009/RE001).

4.2.2 Participant Information

Our pre-registered intended sample size was 66: 33 high-risk and 33 low-risk participants. This was estimated based on previous work in bipolar high-risk individuals showing a large difference in sleep quality with healthy controls, as indexed by the PSQI (Zanini et al., 2015). So, to observe an effect size of 0.7 with 0.80 power and an alpha level of 0.05, we estimated that we need 66 participants in total.

The high-risk participants were recruited from the Flourish cohort, a dynamic prospective cohort that started recruiting parents with BD and their children in 1996 (Duffy et al., 1998). The parents in the cohort were diagnosed with BD-I or II based on clinical interviews using the Schedule for Affective Disorders and Schizophrenia–Lifetime version. The interviews were conducted by a psychiatrist and confirmed in a blind evaluation by two independent research psychiatrists (Duffy et al., 1998). The available information regarding the parents includes current and lifetime mental health diagnoses and response to lithium treatment. The high-risk offspring were assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version in childhood and adolescence, and then using the Schedule for Affective Disorders and Schizophrenia–Lifetime version during adulthood (Duffy et al., 2019). The assessments of the Flourish high-risk offspring in were carried out annually (Duffy et al., 2019), and included information on current and lifetime mental health diagnoses. In its latest iteration, the Flourish cohort included 279 high-risk offspring.

In our study, the inclusion criteria for the high-risk group were: (1) being participant in the Flourish cohort with a parent that has received a diagnosis of BD; (2) willing and able to give informed consent for participation in the study; (3) between 15-29 years of age; (4) able to read and understand English; (5) with a reliable internet access; (6) not allergic to rubber bands; (7) no occupation that requires shift work; (8) no current pregnancy; (9) no plan to move between time zones during the two weeks of data collection or having travelled between more than 2 time-zones in the previous 3 months.

The inclusion criteria for the low-risk group were: (1) living in Oxfordshire, England; (2) not having any first degree relative (blood parent or blood sibling) that to their knowledge has a mental health diagnosis, including sleep disorders; (3) no diagnosis of any mental health disorder; (4) between 15-25 years of age; (5) able to read and understand English (6) with a reliable internet access; (7) not allergic to rubber bands (8) no occupation that requires shift work; (9) no current pregnancy; (10) no plan to move between time zones during the two weeks of data collection or having travelled between more than 2 time-zones in the previous 3 months.

4.2.3 Outcomes

There were four types of outcomes employed in our study: questionnaires, cognitive tasks, sleep diaries and actigraphy.

Questionnaires. The following questionnaires were administered on day 1 of the study, before the sleep diaries or the actigraphy were provided. All questionnaires were delivered through the Gorilla Experiment Builder.

Insomnia Severity Index (Bastien et al., 2001). The ISI is based on the *DSM-4* and *ICD-2* diagnostic criteria for insomnia, and is designed to assess the frequency and severity of both night-time and day-time symptoms of insomnia. Each one of its 7 item is rated on a

4-point scale, yielding a total score range from 0 to 28. Although different cut-off scores have been proposed, a cut-off score of 10 has been suggested as the optimal point for detecting insomnia in community samples (Morin et al., 2011). The ISI has been validated in numerous studies across various populations, demonstrating good internal consistency in community (Cronbach's α: 0.90) and clinical samples (Cronbach's α: 0.91) (Morin et al., 2011). The ISI has also been used in BD research for assessing insomnia symptoms (Harvey et al., 2015; Jernelöv et al., 2022).

Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI is a 19-item measure principally designed to quantify general sleep quality. Although this scale was not initially designed to screen for insomnia, it shows good validity and reliability, and expert panels have recommended it for the routine evaluation of insomnia (Buysse et al., 2006; Morin et al., 2015). The PSQI generates 7 composite scores reflecting various dimensions of sleep quality and its effects on daytime functioning. Each component is scored from 0 to 3, leading to a cumulative score ranging from 0 to 21, where higher scores denote poorer sleep quality. A global PSQI score greater than 5 is suggestive of significant sleep disturbances. Meta-analytic evidence has shown that the PSQI exhibits good internal consistency (Cronbach's α: 0.70-0.83) (Mollayeva et al., 2016).

Reduced Morningness-Eveningness Questionnaire (Adan & Almirall, 1991). The reduced MEQ is an abbreviated form of the original Morningness Eveningness Questionnaire (Horne & Ostberg, 1976), aimed at determining an individual's chronotype, i.e., their preference for morning or evening activities. The measure contains 5-items, and yields a total score of 4-25. Lower scores indicate a preference for eveningness, while higher scores indicate a preference for morningness. The MEQ has shown adequate internal consistency (Cronbach's α: 0.71) (Chelminski et al., 2000).

Epworth Sleepiness Scale for Children and Adolescents (Wang et al., 2017). The ESS-CHAD is an adaptation of the original Epworth Sleepiness Scale (Johns, 1991), specifically designed to assess daytime sleepiness in children and adolescents. The measure comprises of 8 items, with each item scored from 0 to 3, leading to a total score range from 0 to 24. Scores greater than 10 are typically indicative of excessive daytime sleepiness. The ESS-CHAD has shown good internal consistency (Cronbach's α: 0.75) (Wang et al., 2017).

Sleep Disturbances Questionnaire (Espie et al., 1989). The SDQ was developed to identify physiological, behavioural and cognitive contributory factors to sleep disturbances. It contains 12 items measured on a 5-point Likert scale from 1 to 5, yielding a total score of 12-60, with higher scores indicating greater disturbances. The SDQ has been used in insomnia research (Espie et al., 1989) and has shown adequate internal consistency (Cronbach's α: 0.67) (Espie et al., 2000).

British Association for Psychopharmacology – Circadian Rhythm Sleep Disorder (S. Wilson et al., 2019; Wilson et al., 2010). The BAP guidelines include a consensus statement on the assessment and diagnosis of sleep and circadian disorders. The Circadian Rhythm Sleep Disorder subscale comprises of 5 yes or no questions that lead to a binary outcome regarding the possibility of a circadian disorder diagnosis.

Sleep Hygiene Index (Mastin et al., 2006). The SHI is a 13-item scale that aims to assess sleep hygiene behaviours and practices. The included items are scored on a 5-point Likert scale from 1 to 5, with total scores ranging from 13 to 60, and higher scores indicating poorer sleep hygiene. The SHI shows adequate internal consistency (Cronbach's α: 0.66) (Mastin et al., 2006).

Patient Health Questionnaire-9 (Kroenke et al., 2001). The PHQ-9 is a self-report measure assessing depression symptomatology based on the DSM-IV diagnostic criteria for major depressive disorder, and it has been primarily used in primary care to screen for

depression. It consists of 9 items scores from 0-3, yielding a total score of 0-27. Although various cut-off scores have been proposed to indicate mild, moderate and severe depression, meta-analytic evidence has found a cut-off point of 10 or above to be the most optimal score for screening for depression. The PHQ-9 has shown good internal consistency in community samples (Cronbach's α: 0.86-0.89) (Kroenke et al., 2010) as well as clinical populations (Cronbach's α: 0.83-0.92) (Cameron et al., 2008).

Generalised Anxiety Disorder-7 (Spitzer et al., 2006). The GAD-7 is a 7-item scale designed to screen for and measure the severity of generalised anxiety disorder symptoms. Each item is rated on a 4-point Likert scale from 0 to 3, with total scores between 0 and 21. Total scores of 5, 10, and 15 represent thresholds for mild, moderate, and severe anxiety levels, respectively. The GAD-7 has been widely used in primary care and community samples and has shown to have good internal consistency (Cronbach's α: 0.92) (Kroenke et al., 2010; Spitzer et al., 2006).

Mood Disorders Questionnaire (Hirschfeld et al., 2000). The MDQ is a 3-part questionnaire specifically designed to screen for BD in primary care. The first part includes 13 yes or no questions probing lifetime symptoms of (hypo)mania. If the participant endorses 7 or more items, then they move on to the second part which includes a single yes or no question on symptom clustering. The final question is an item assessing the level of impairment associated with the reported symptoms, and it is scored on a 4-point Likert scale. The outcome of the MDQ is a binary point on whether there is a possible BD condition or not. The MDQ has been widely used to screen for BD, with adequate sensitivity (61.3%) and positive predictive value (58.0%), as well as good specificity (87.5%) and negative predictive value (88.9%) (Zimmerman & Galione, 2011).

Behavioural Inhibition System/Behavioural Activation System Scale (Carver & White, 1994). The BIS/BAS is a scale measuring two related yet arguably distinct

motivational systems of human behaviour: (1) sensitivity to punishment under the behavioural inhibition system, and (2) sensitivity to reward under the behavioural activation system. The BIS scale contains 7-items, and the 13-item BAS scale is subdivided into three subscales: drive, fun seeking and reward responsiveness. Higher scores indicate greater sensitivity. Although there is recent evidence suggesting a possible unidimensional factor of reward sensitivity underlying both scales (Maack & Ebesutani, 2018), the total scores for the BIS/BAS are typically calculated separately for each scale. Both scales have demonstrated good internal consistencies for all subscales (Cronbach's α of 0.74, 0.73, 0.76 and 0.66 for the BIS, reward responsiveness, drive, and fun seeking scales, respectively). The BIS/BAS has been used in BD to draw on research towards an evidence-based framework on reward sensitivity in BD (Urošević et al., 2008).

Cognitive tasks. We administered two cognitive tasks during the study: the Stroop Colour Word Task and the Continuous Performance Test, identical pairs version (CPT-IP). Both tasks were delivered through the Gorilla Experiment Builder, and were presented to participants once they had returned all questionnaires. Figure 4.1 illustrates and explains both tasks.

Stroop Colour Word Task (Stroop, 1935). The Stroop task is a widely used cognitive task that measures selective attention, response inhibition and processing speed. It involves presenting the participant with colour words in congruent or incongruent ink colours and asking them to indicate the ink colour while ignoring the word itself. The main outcomes of the task are accuracy and response time. Accuracy was indexed as the rate of correct over incorrect responses, and reaction time was indexed as the time in milliseconds for participants to respond to a stimulus. Both outcomes were stratified by type, for congruent and incongruent trials. Reaction time was indexed by a measure of interference called the 'Stroop effect', calculated as the mean difference in reaction time between congruent and

incongruent trials. The Stroop task has been widely used in BD research to explore cognitive impairments in sustained attention and processing speed (Kronhaus et al., 2006). Details of the composition of the Stroop task are displayed in Figure 4.1.

Continuous Performance Test - Identical Pairs Version. The CPT-IP is designed to evaluate sustained attention, inhibitory control and working memory. In this task, participants are required to respond whenever a stimulus appears that is identical to the one immediately preceding it. Stimuli are typically numbers presented in rapid succession on a computer screen. The main outcome measure is the d' index, a quantifiable estimate of the participant's ability to discriminate between targets (i.e. hit rate) and noise (i.e. false alarm rate). A higher d' value indicates better discriminability, meaning the participant is more capable of distinguishing between target and non-target stimuli. In our study, we estimated the d' index using the following formula:

$$d' = Z(HR) - Z(FAR)$$

where Z is the z-score of either the hit rate (HR) or false alarm rate (FAR). We adjusted our scores by adding 0.5 to the numerator and 1 to the denominator of both the hit and false alarm rates, to account for issues arising with 0 and 1 values whose z-score are undefined. Details of the composition of the CPT-IP task are displayed in Figure 4.1.

Sleep diary. Participants were asked to complete a modified version of the consensus sleep diary for two weeks (Carney et al., 2012). This diary was completed twice daily, in the morning and evening. In the morning, participants reported their SOL, WASO, TST and SE for the preceding night, rated their sleepiness level on a visual analogue scale, and answered a 5-point Likert scale about their sleep quality, restfulness, dreaming and cognitive arousal while in bed. In the evening, they rated their sleepiness level on another visual analogue scale, and answered questions on napping, caffeine and alcohol consumption. They also rated on a 5-point Likert scale the extent to which 6 mood items

described their mood throughout the day. These items were included based on published literature on prospective mood monitoring in BD (Tsanas et al., 2016), and included feeling: sad, anxious, irritable, happy, energetic and relaxed. Based on previous published literature (Kyle et al., 2023), if fewer than 4 days of a sleep diary, then the diary scores for that participant were treated as missing.

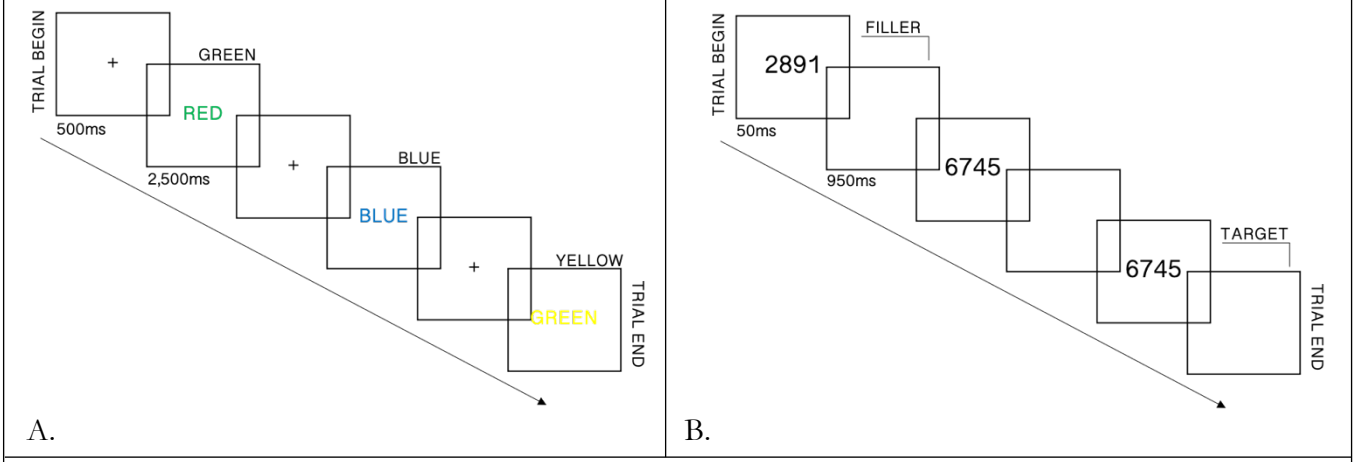


Figure 4.1 (A) The Stroop Colour Word Task, and (B) The Continuous Performance Test-Identical Pairs
(A) In the Stroop Task, the colours red, green, yellow, and blue were presented in congruent or incongruent colour names. The task was presented in one run with 64 stimuli in counterbalanced order. 75% of the trials were incongruent and 25% congruent. Consecutively, each text colour/colour name combination stimulus was presented 4 times. The task included a practise number with 3 stimuli. Each trial started with a fixation cross presented for 500ms and a stimulus presented for 2500ms. The task typically lasted 3.5-4 minutes in total.
(B) The Continuous Performance Task-Identical Paris version followed a rapid presentation paradigm. Participants were asked to ignore distractors and detect sequentially presented stimuli. The stimuli were 4-digit numbers. Each stimulus was presented for 50ms followed by a blank screen for 950ms. There were 3 types of stimuli: targets, identical number pairs; distractors, number pairs where only one digit is different; and fillers, numbers that are unrelated to the preceding or proceeding stimulus. Following 50 practise trials, 150 trials were presented, constituting one full test trial. Out of the 150 trials, 30 were targets (20%), 28 were distractors (19%), and 92 were fillers (63%).

Actigraphy. Concurrently with the sleep diary, participants wore an actigraph watch (MotionWatch 8, CamNTech Ltd.) on their dominant wrist. In line with recording settings from previous studies in clinical populations (Maurer et al., 2020), the watches were set to record activity in tri-axial mode and light over 60-second epochs. Participants were instructed to press an event marker on the watch when initiating sleep and upon their final awakening. Prior to actigraphy scoring, a guideline manual was written up and reviewed by

members of the research team. Herein, events markers were used to demarcate the start and end of a sleep episode. In the absence of these markers, a sleep period was defined based on bed and rise time specified in the sleep diary or by indicators of light and activity measures. All corresponding rest-activity variables calculated by the validated build-in algorithm of the MotionWare software 1.4.20. Similar to sleep diaries, a minimum of 4 days was required for the participant record to be included in the actigraphy analysis.

4.2.4 Procedure

Following a positive screen based on the inclusion/exclusion criteria, participants in the high-risk group were seen by an attending member of the Flourish team that discussed the study with them, ensured its appropriateness for the participant, and conducted a clinical assessment to record information on current as well as lifetime mental health disorders. Participants in the low-risk group were able to start the study immediately. Both groups followed the same procedure. On day 0 participants were invited to an online meeting where they completed a set of questionnaires and cognitive tasks. Following this meeting, participants were asked to complete a paper-version of a sleep diary twice daily for 2 weeks and concurrently wear an actigraphy watch. During this 2-week period they were offered the opportunity to have up to 3 online meetings with a member of the study team. At the end of the 2-week period participants returned the sleep diaries and watches and this marked the end of the data collection. All meetings took place over Microsoft Teams.

4.2.5 Analysis Plan

All analyses were conducted in the statistical software R 4.3.1 (16/06/2023).

Missing values and descriptive analyses. Although a full dataset was sought, missing data were expected. Single missing items from otherwise complete questionnaires were replaced using mean imputation. Means and standard deviations were estimated for

continuous variables; while frequencies and percentages were estimated for binary and categorical variables. For all values 95% confidence intervals were also estimated.

Questionnaires and Cognitive tasks. Independent samples t-tests were used for questionnaires that yield continuous scores, for the Stroop effect of the Stroop task, and for the d' index outcome of the CPT-IP. T-values, degrees of freedom, p-values, Cohen's d effect sizes and accompanying 95% CIs were estimated. We followed conventional benchmarks of referring to effect sizes as small for ES=0.20, moderate for ES=0.50 and large for ES=0.80 (Cohen, 2013). Chi-square tests were used for questionnaires with binary outcomes. Chi-square and p-values as well as odd ratios were estimated. For the accuracy and reaction time outcomes of the Stroop Task, as pre-registered, we employed a two-way ANOVA, with group (high- and low-risk) and type (congruent and incongruent trial) as the independent variables, and either accuracy or reaction time as the dependent variables.

Sleep diaries and Actigraphy. For sleep diary outcomes, namely SOL, WASO, TST and SE, we followed the same principles as with questionnaires that yield continuous total scores. For actigraphy, sleep periods were scored based on a standard operating procedure established and maintained by the research team. Parametric rest-activity outcomes, namely SOL, WASO, TST and SE were derived via the validated build-in algorithm of the MotionWare software 1.4.20. They were then treated in the same way as sleep diary outcomes.

4.2.6 Pre-registration, Data and Code Availability

The methods and analysis plan were both pre-registered and are publicly available on a study dedicated Open Science Framework page: https://osf.io/2dvsm/. There were few minor deviations from our pre-registered analysis plan. First, we did not use the GGIR package in R to analyse our actigraphy data, given the sufficiency of the outcomes provided directly from the Motioware software. Second, we extended the age range in the high-risk

group to 15-30 instead of 15-25 with the intention to increase recruitment. Although this change was meant to be implemented to the low-risk group, we paused recruitment before we needed to do so. Third, we pre-registered an exploratory plan to investigate the relationship between sleep and cognitive outcomes, however, given the low number of participants, we decided that we did not have enough power to conduct such analyses. Finally, we did not conduct any analyses on questionnaires with binary outcomes where all participants scored one way, as it would be mathematically impossible to do so. Appendix 3 in the Supplementary Materials contains the study pre-registration.

4.2.7 Out of Scope Data

Although the greatest proportion of collected data in this study were included in this thesis, outcomes that were not primary or secondary targets were judged to be outside the scope of my doctoral thesis given time and word limitations. These data are not discussed further in this chapter. These data include the mood, nightmare, sleepiness and sleep quality items of the sleep diary questionnaires, as well as non-parametric circadian outcomes of actigraphy, such as L5, M10, intradaily stability, interdaily variability, and relative amplitude, as well as light data captured by actigraphy.

4.3 Results

Participants in this study were 32 individuals recruited across the two sites: 11 low-risk participants (33% of intended sample) from the Flourish cohort recruited in Canada, and 21 low-risk participants (64% of intended sample) recruited in Oxfordshire. Thus, we did not reach our intended sample size.

The demographic characteristics of the sample are presented in Table 4.1. The low-risk group contained more female participants and participants that were younger in age

compared to the high-risk group. The high-risk group was exclusively white, with little variability in the low-risk group too, given over 80% of the participants were white. More than half of the participants in both groups were university students (55% for high-risk and 57% for low-risk), some of whom were also in full- or part-time employment. The majority of people in both groups had an undergraduate university degree (55% for high-risk and 48% for low-risk), with more people in the low-risk group currently being at high-school (24%) compared to the high-risk group (9%). Most people did not report any physical health comorbidities in either group (73% for high-risk and 90% for low-risk), with the ones doing so reporting either irritable bowel syndrome or asthma.

Table 4.1 Demographic characteristics of participants

	High-risk (n=11)	**Low-risk (n=21)**
Age in years, mean (sd)	22.55 (3.83)	20.95 (2.97)
Gender, no (%)		
Male	4 (36.36%)	2 (9.52%)
Female	7 (63.64%)	19 (90.48%)
Ethnicity, no (%)		
White	11 (100%)	17 (80.95%)
South/East Asian	0 (0.0%)	3 (14.29%)
Black/African/Caribbean	0 (0.0%)	1 (4.76%)
Employment type, no (%)		
High-school student	1 (9.09%)	5 (23.81%)
University student	6 (54.55%)	12 (57.14%)
Full-time occupation	4 (36.36%)	4 (19.05%)
Part-time occupation	3 (27.27%)	3 (14.29%)
Unemployed	1 (9.09%)	1 (4.76%)
Education level, no (%)		
Currently at high school	1 (9.09%)	5 (23.81%)
High school diploma	3 (27.27%)	4 (19.05%)
College diploma	1 (9.09%)	0 (0.0%)
Undergraduate degree	6 (54.6%)	10 (47.62%)
Postgraduate degree	0 (0.0%)	2 (9.52%)
Physical health comorbidities, no (%)		
No	8 (72.73%)	19 (90.48%)
Yes, Irritable Bowel Syndrome	2 (18.18%)	1 (4.76%)
Yes, asthma	1 (9.09%)	1 (4.76%)

Abbreviations: SD, Standard Deviations

The clinical characteristics of the high-risk participants is illustrated on Table 4.2. There was an event split in the BD subtype of the parental diagnosis, with 55% having received a diagnosis of BD-I and 45% a diagnosis of BD-II, and an average age of having received their diagnosis at 36.18 (sd=8.86) years. Additionally, two thirds (64%) of the parents with a BD diagnosis in the high-risk sample were lithium responders. In terms of their own mental health, no new diagnoses were assigned at the time of recruitment. Most high-risk participants did not have any mental health diagnosis (73%), with lifetime anxiety (18%) and lifetime depression (9%) being the only diagnosis present in the group.

Table 4.2 Clinical characteristics of high-risk individuals

	High-risk (n=11)
Parental BD diagnosis, no (%)	
BD-I	6 (54.55%)
BD-II	5 (45.45%)
Age at parental BD diagnosis in years, mean (sd)	36.18 (8.86)
Lithium response of parent, no (%)	
Lithium responder	7 (63.64%)
Lithium non-responder	4 (36.36%)
Own mental health diagnosis, no (%)	
None	8 (72.73%)
Yes, lifetime anxiety disorder	2 (18.18%)
Yes, lifetime major depression disorder	1 (9.09%)

Table 4.3 presents the unadjusted mean scores and SDs, as well as the accompanying t-test comparisons for all questionnaire and cognitive tasks. Figures 4.2-4 present the unadjusted mean scores for all questionnaires and cognitive tasks. Although on average the high-risk group reported more insomnia symptoms, lower sleep quality, more sleep disturbances, poorer sleep hygiene, worse depression and anxiety, none of these differences was statistically significant. The high-risk group also showed a preference for eveningness, greater behavioural inhibition sensitivity and greater drive sensitivity, but these effects were also not statistically significant. On the other hand, the low-risk group score higher on sleepiness, fun seeking and reward sensitivity. None of these differences was statistically

significant. None of the participants in either group scored positive for a potential circadian disorder or for possible BD.

In the Stroop task, there was a main effect of type and accuracy, with participants being better at identifying the ink colour in congruent than incongruent trials. There was no main effect of group and no group*type interaction. Although the high-risk group had longer reaction times for both congruent and incongruent trials, there was no type or group main effect and no type*group interaction in terms of reaction time. Similarly, the Stroop effect was larger in the high-risk compared to the low-risk group, but the difference was not statistically significant. In the CPT-IP, there was a small difference indicating that the high-risk group has better discriminability than the low-risk group, but this difference was not statistically significant.

Table 4.3 Questionnaire and Cognitive task outcomes for high and low risk participants

	High-risk (n=11)	**Low-risk (n=21)**	
Insomnia Severity Index	8.55 (4.78)	5.29 (3.04)	*t (31) = 2.05; p-value = 0.06* *Cohen's d=0.88; 95%CI: 0.09 to 1.67*
Pittsburgh Sleep Quality Index	6.0 (2.93)	4.95 (1.99)	*t (31) = 1.06; p-value = 0.31* *Cohen's d=0.45; 95%CI: -0.33 to 1.22*
Morningness Evenignness Questionnaire	13.9 (2.84)	14.5 (3.41)	*t (31) = -0.50; p-value = 0.62* *Cohen's d=-0.18; 95%CI :-0.94 to 0.59*
Epworth Sleepiness Scale for Children and Adolescents	4.73 (2.69)	4.76 (2.43)	*t (31) = -0.04; p-value = 0.97* *Cohen's d=-0.01; 95%CI :-0.77 to 0.75*
Sleep Disturbances Questionnaire	33.6 (10.2)	29.3 (6.46)	*t (31) = 1.24; p-value = 0.23* *Cohen's d=0.53; 95%CI: -0.24 to 1.30*
BAP Circadian Rhythm Disorder			
No possible circadian disorder Possible circadian disorder	11 (100%) 0 (0.00%)	21 (100%) 0 (0.00%)	*NA*
Sleep Hygiene Index	31.2 (7.35)	31.1 (5.16)	*t (31) = 0.02; p-value = 0.99* *Cohen's d=0.01; 95%CI: -0.75 to 0.77*
Patient Health Questionnaire – 9	7.0 (6.94)	3.76 (2.81)	*t (31) = 1.48; p-value = 0.16* *Cohen's d=0.70; 95%CI: -0.08 to 1.48*
Generalised Anxiety Disorder-7	6.27 (6.47)	3.0 (2.26)	*t (31) = 1.63; p-value = 0.13* *Cohen's d=0.79; 95%CI: -0.01 to 1.57*
Mood Disorders Questionnaire			
No possible bipolar disorder Possible bipolar disorder	11 (100%) 0 (0.00%)	21 (100%) 0 (0.00%)	*NA*
Behavioural Activation Scale/ Behavioural Inhibition Scale			
Behavioural Inhibition scale	13.6 (4.84)	13.2 (2.79)	*t (31) = 0.22; p-value = 0.83*

Drive scale	11.0 (1.55)	9.76 (2.28)	*Cohen's d=0.10; 95%CI: -0.66 to 0.86* *t (31) = 1.82; p-value = 0.08*
Fun seeking scale	8.91 (2.98)	9.24 (1.97)	*Cohen's d=0.60; 95%CI: -0.18 to 1.38* *t (31) = -0.33; p-value = 0.75*
Reward responsiveness scale	8.73 (2.33)	9.14 (2.06)	*Cohen's d=-0.14; 95%CI: -0.90 to 0.62* *t (31) = -0.50; p-value = 0.62* *Cohen's d=-0.19; 95%CI: -0.95 to 0.57*
Stroop task			
Accuracy: congruent trials	1.0 (0.0)	0.99 (0.08)	*Type: F(1,59)=12.93; p<0.001*
Accuracy: incongruent trials	0.97 (0.16)	0.96 (0.19)	*Group: F(1,59)=0.96; p=0.33* *Group*Type: F(1,59)=0.09; p=0.76*
Reaction time: congruent trials	948.19 (190.92)	909.88 (198.73)	*Type: F(1,59)= 2.94; p=0.092*
Reaction time: incongruent trials	1048.13 (195.19)	990.82 (206.41)	*Group: F(1,59)= 0.79; p=0.38* *Group*Type: F(1,59)= 0.03; p= 0.86*
Stroop effect	123.62 (132.72)	80.94 (75.98)	*t (31)=0.95; p-value = 0.36* *Cohen's d=0.44; 95%CI: -0.35 to 1.23*
Continuous Performance Task – Identical Pairs version	1.88 (0.71)	1.76 (0.70)	*t (31) = 0.46; p-value = 0.65* *Cohen's d=0.17; 95%CI: -0.59 to 0.93*

Abbreviations: CI, Confidence Intervals

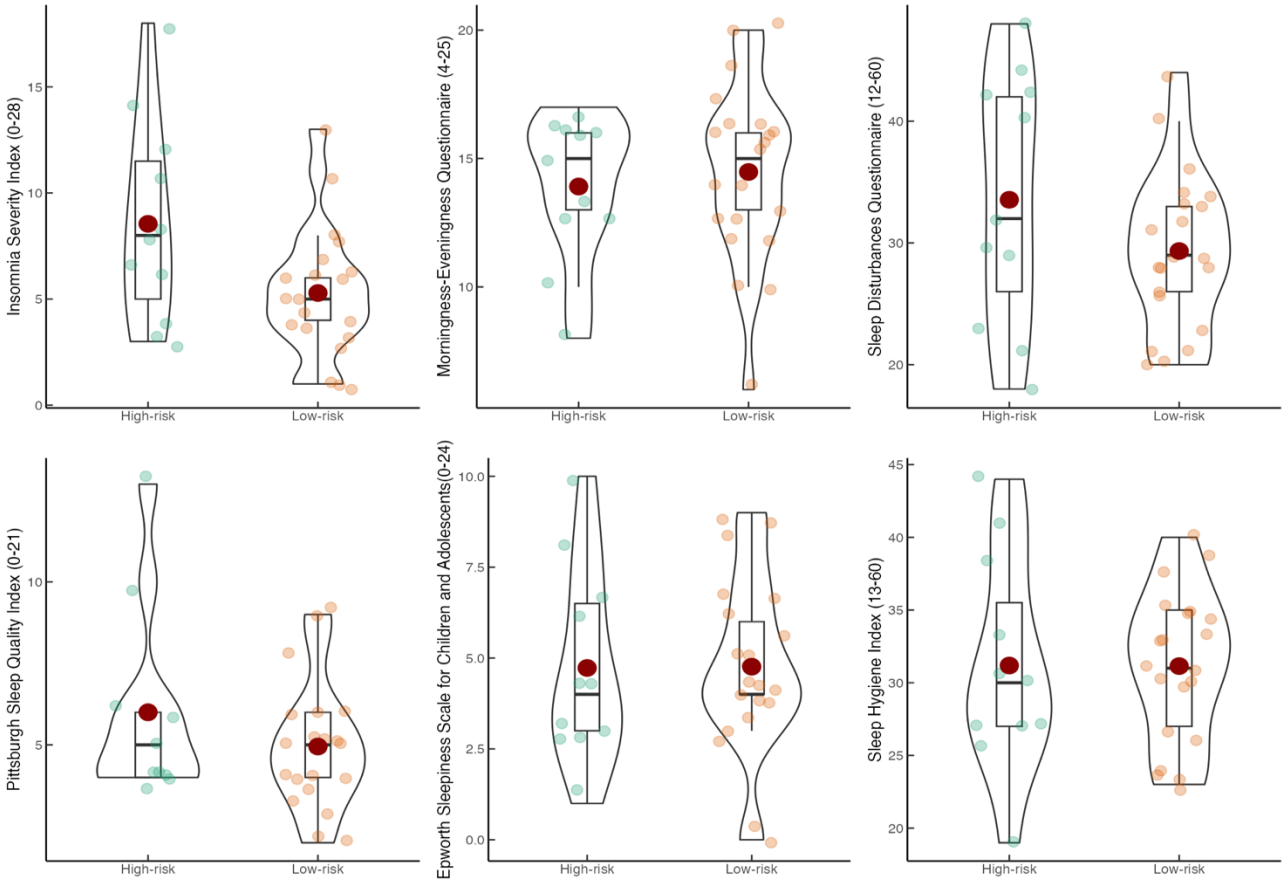


Figure 4.2 Questionnaire outcomes for sleep variables for high and low risk participants. The red points represent mean values

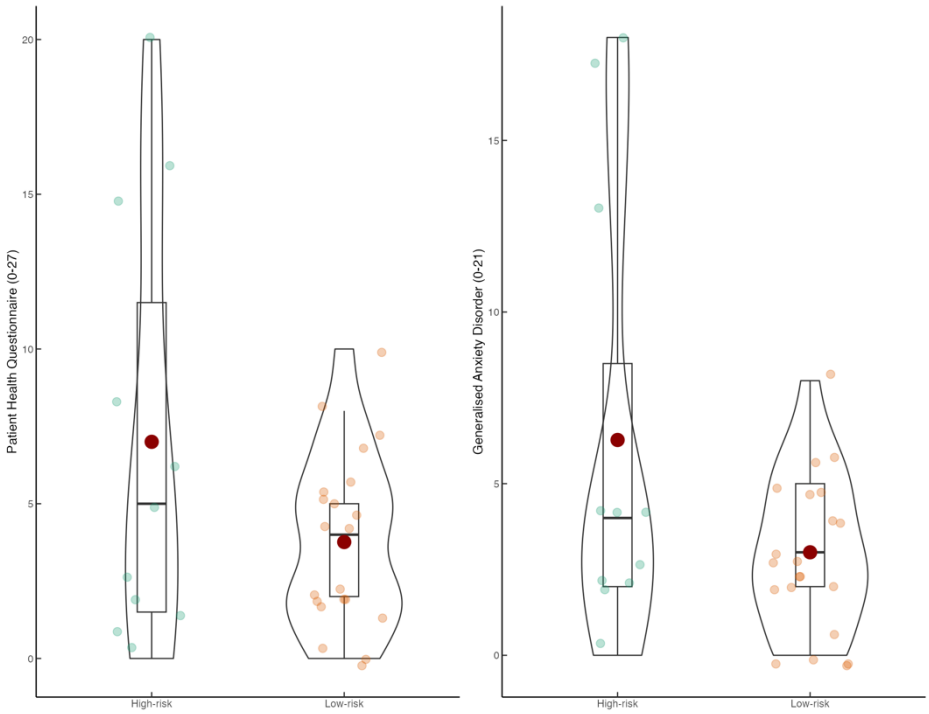


Figure 4.3 Questionnaire outcomes for depression and anxiety for high and low risk participants. The red points represent mean values

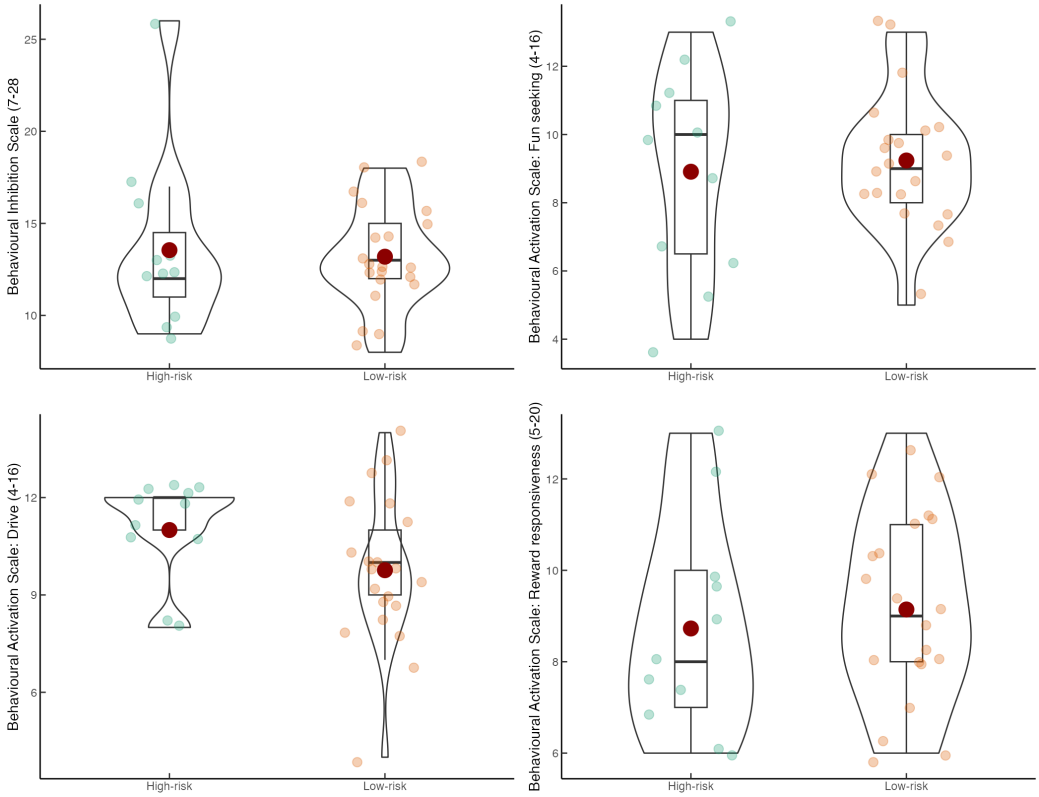


Figure 4.4 Behavioural activation and inhibition outcomes for high and low risk participants. The red points represent mean values

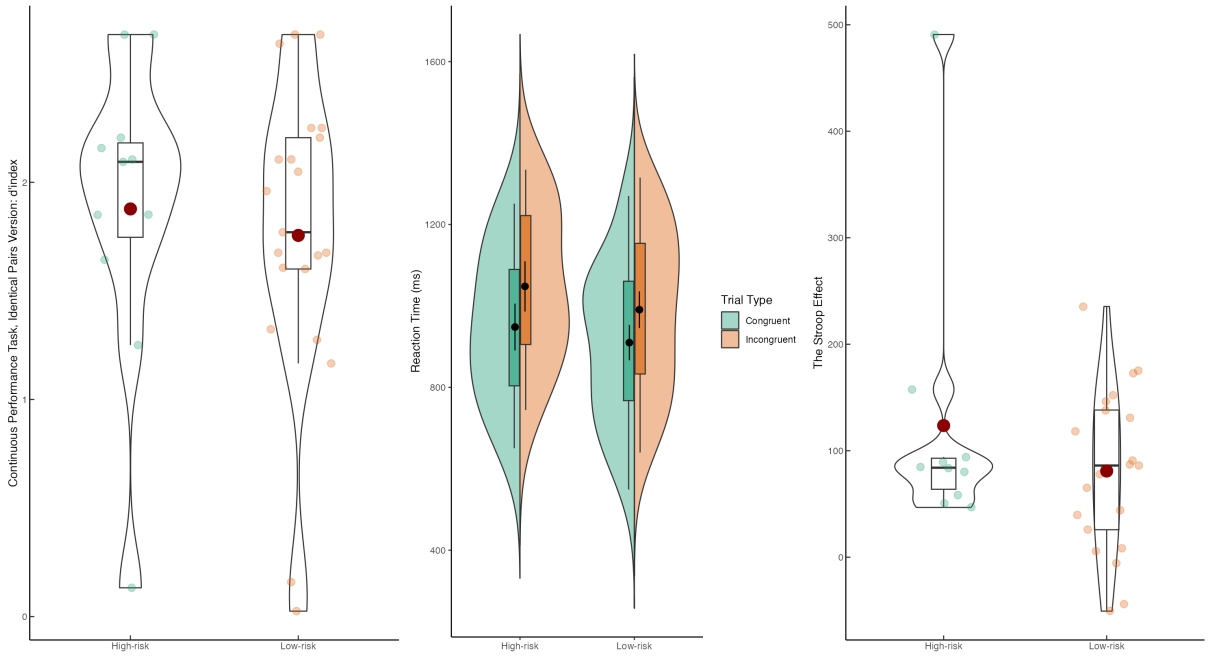


Figure 4.5 Cognitive task outcomes for high and low risk participants. The red and black points represent mean values

Table 4.4 presents the unadjusted mean scores and SDs, as well as the accompanying t-test comparisons for all diary and actigraphy outcomes. Figure 4.6 illustrates the unadjusted scores for sleep diary and actigraphy outcomes. High-risk participants generally had a worse sleep profile compared to low-risk participants. They had longer SOL and WASO and lower SE, as measured using both sleep diaries and actigraphy. They also had longer diary and actigraphy measured TST. However, none of these differences was statistically significant.

Table 4.4 Sleep diary and Actigraphy outcomes for high-risk and low-risk participants

	High-risk (n=11)	**Low-risk (n=21)**	
Sleep diary outcomes			
Sleep Onset Latency	19.56 (9.71)	18.39 (9.79)	*t (31) = 0.32; p-value = 0.75* *Cohen's d=0.12; 95%CI: -0.64 to 0.88*
Wake After Sleep Onset	18.04 (16.79)	9.43 (10.98)	*t (31) = 1.54; p-value = 0.15* *Cohen's d=0.65; 95%CI: -0.13 to 1.43*
Total Sleep Time	455.22 (27.99)	423.44 (61.43)	*t (31) = 1.98; p-value = 0.06* *Cohen's d=0.60; 95%CI: -0.21 to 1.40*
Sleep Efficiency	81.02 (8.56)	79.10 (9.16)	*t (31) = 0.57; p-value = 0.58* *Cohen's d=0.21; 95%CI: -0.58 to 1.01*

Actigraphy outcomes			
Sleep Onset Latency	6.64 (5.29)	5.13 (4.30)	*t (31) = 0.81; p-value = 0.43* *Cohen's d=0.32; 95%CI: -0.45 to 1.10*
Wake After Sleep Onset	72.59 (25.57)	61.67 (26.34)	*t (31) = 1.13; p-value = 0.27* *Cohen's d=0.42; 95%CI: -0.36 to 1.19*
Total Sleep Time	444.58 (34.96)	420.81 (48.00)	*t (31) = 1.58; p-value = 0.13* *Cohen's d=0.54; 95%CI: -0.24 to 1.32*
Sleep Efficiency	84.42 (4.68)	86.17 (4.88)	*t (31) = -0.99; p-value = 0.34* *Cohen's d=-0.37; 95%CI: -1.14 to 0.41*

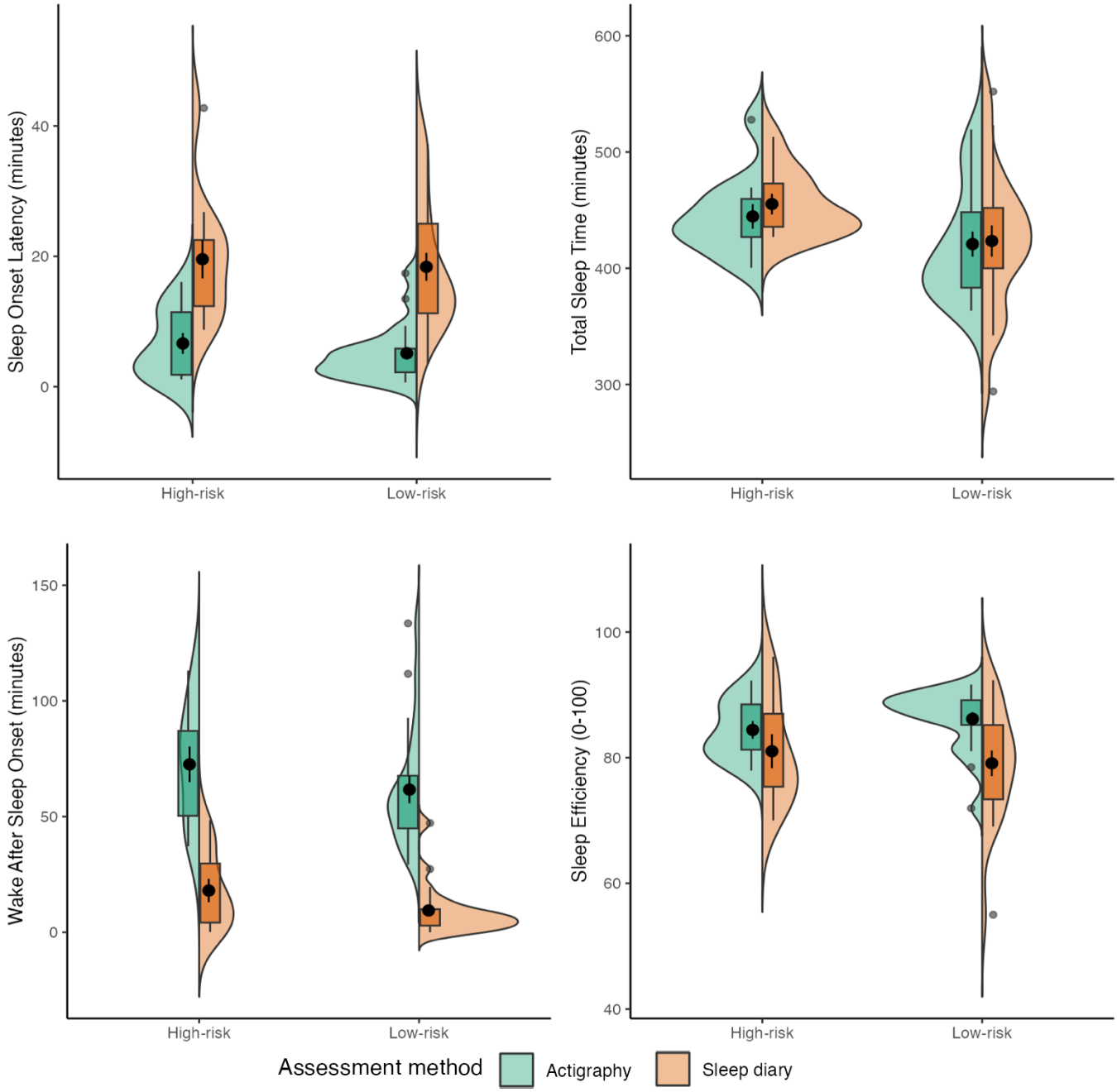


Figure 4.6 Sleep diary and Actigraphy outcomes for high and low risk participants

4.4. Discussion

Our study attempted to profile high-risk offspring in a comprehensive manner, using a range of global scales of sleep, corroborated by both sleep diaries and actigraphy. Notwithstanding, although the direction of effects followed predicted patterns, no difference reached statistical significance, so our results should be interpreted with caution.

The shortcomings in recruitment were due to two main reasons. First, recruitment was affected by Covid-19. Due to restrictions, there was a 1.5-year delay between designing the study in 2019, and recruitment of the first participant in May 2021. During this time there were also changes in the procedure, such as switching from in-person assessments conducted during a 3-month fellowship in Canada, to a remote recruitment led from UK. Efforts to identify a time when both UK and Canada had minimal Covid-19 restrictions were also impeded by the fact that lockdown restrictions in Canada were regulated on the province rather than federal level. Second, during the lockdown, the two principal investigators of the Flourish cohort stepped down from their positions, leaving the cohort with no director. Our study was the last one to be conducted using the Flourish cohort. Recruitment at both sites stopped when all participants from the Flourish cohort had been invited multiple times and it became evident that it would not be possible to recruit any additional participants.

Despite the lack of a significant effect, the study of sleep and circadian rhythms in high-risk offspring remains highly relevant. In two meta-analyses around the role of sleep and circadian rhythms in high-risk offspring, the authors called for: (1) more hypothesis-driven studies rather than 'opportunistic' (Scott, Etain, et al., 2022) inclusion of sleep and circadian outcomes, (2) expansion of phenotyping protocols to assess sleep and circadian rhythms beyond just sleep quality and insomnia, and (3) the integration of global scales and sleep diaries with actigraphy measures of rest-activity (Aguiar et al., 2021; Scott, Etain, et al., 2022). Our study addressed these gaps, following a pre-registered, hypothesis driven

protocol, administering a comprehensive phenotyping protocol, and employing global measures of sleep as well as sleep diaries and actigraphy.

In addition to the predictive value of sleep and circadian disruptions in the emergence of BD in high-risk offspring, research has also shown that high-risk offspring in general experience a disproportionate amount of mental health problems compared to peers with healthy parents. Longitudinal studies have shown that although the lifetime prevalence of BD in bipolar offspring varies between 4-28% (Birmaher et al., 2021; Duffy et al., 2019; Vandeleur et al., 2012), 62-68% of high-risk offspring present with at least one lifetime mental health disorder (Duffy et al., 2019; Vandeleur et al., 2012), with the most frequent diagnoses being anxiety, depression and attention deficit hyperactivity disorder (Birmaher et al., 2010; Vandeleur et al., 2012). Insomnia is also among the most frequent diagnoses of high-risk offspring (Duffy et al., 2019). A recent study found that in high-risk offspring, sleep disruptions are potent predictors of later development of any mental health disorder, not specifically BD (Levenson et al., 2024). Consequently, given the prevalence of sleep and circadian disruptions in this high-risk individuals, future research should explore relevant early interventions in this population regardless of the future emergence of BD.

However, there are several limitations to our work. First, we only recruited one third of our intended sample size of high-risk individuals and two thirds of our intended sample size of low-risk individuals. As such, our results should be interpreted with caution, since our study is currently not powered enough to identify any meaningful effects. Second, this is a cross-sectional comparison, so we are unable to make any predictions on whether the presence of disrupted sleep increases the likelihood of bipolar high-risk offspring of developing BD themselves in the future. The initial plan of this study was to form the basis of future longitudinal work, but as it stands this might not be a feasible possibility. Third, there are limitations with some of the items used. For example, our measure on excessive

sleepiness is overly clinical, focusing on instances of the onset of involuntary sleep. As such, it is possible that we missed cases of hypersomnia or subsyndromal excessive daytime sleepiness. Future studies should not focus solely on measurements of disorders, but incorporate assessments aimed at characterising sleep behaviours multidimensionally. Finally, the group we recruited is only referred to as high-risk due to their association with a parent with BD, and at the point of recruitment none of the high-risk participants were diagnosed with BD, despite a clinical assessment taking place prior to entering the study.

5

Behavioural and Psychosocial Sleep and Circadian Rhythm Interventions for Bipolar Disorder: Systematic Review and Meta-Analysis

Contents

** Disclaimer: This chapter was published in the journal Neuroscience and Behavioral Reviews in January 2022 and is presented as is (Bisdounis et al., 2022)*

5.1 Background and Rationale

At present, treatment guidelines for BD do not directly address sleep and circadian disruptions, besides the short-term use of GABA modulators for sedative purposes (Goodwin et al., 2016; Yatham et al., 2018). Psychotherapy is mainly recommended as maintenance treatment (Goodwin et al., 2016; Yatham et al., 2018) or for the management of subthreshold symptoms (Goodwin et al., 2016). However, psychological and behavioural interventions that target sleep and circadian rhythms, have been explored in other transient and chronic psychiatric conditions, with improvements observed in sleep, circadian rhythms,

and mood (Okajima & Inoue, 2018; Wu et al., 2015), setting the precedent for these effects being observed in individuals with BD too.

Recent reviews have produced mostly positive findings regarding the effectiveness of psychological and behavioural interventions in BD that target sleep and circadian rhythms. Such interventions typically rely on the therapeutic effects of light (e.g. bright light therapy or blue-light blocking glasses), the stabilisation of daily rhythms (e.g. interpersonal and social rhythm therapy), the modification of dysfunctional beliefs and behaviours around sleep (e.g., cognitive behavioural therapy for insomnia), or changes in mood following acute sleep loss (e.g., total sleep deprivation). Bright light therapy (BLT) and total sleep deprivation (TSD) were found to be effective both as monotherapies and in combination (D'Agostino et al., 2020; Dallaspezia & Benedetti, 2020; Gottlieb et al., 2019, 2021; Humpston et al., 2020; Ramirez-Mahaluf et al., 2020; Takeshima et al., 2020). Antidepressant treatment standard effect sizes for BLT or BLT in combination with TSD ranged from -1.48 to -0.25 (Dallaspezia & Benedetti, 2020; Humpston et al., 2020; Takeshima et al., 2020), and response rates to TSD ranged from 27.4% to 59.4% (Gottlieb et al., 2019, 2021). However, conclusions from these reviews should be interpreted cautiously, as they relied predominantly on uncontrolled non-randomised trials or studies that largely recruited participants with unipolar depression. Review findings may be different if only RCTs are included. For example, a commentary recently highlighted that the antidepressant effect of BLT in unipolar depression decreases substantially when only controlled trials are meta-analysed (Freeman et al., 2020; Stewart, 2018). Additionally, due to the unique symptom profile of BD, and concerns over the effect of sleep loss on mania, it is necessary to evaluate data about the effects of these interventions in BD independently from other psychiatric disorders.

Therefore, the aim of this review was to critically appraise the efficacy of psychological and behavioural interventions in BD that target sleep and circadian rhythms, as observed in the context of the gold standard design for intervention evaluation, RCTs. A narrative synthesis approach was generally adopted. Consistent with pre-registered plans, quantitative meta-analytic models were applied when at least five studies evaluated the same intervention and measured the same outcome.

5.2 Methodology

This systematic review was conducted in accordance with the PRISMA guidelines (Moher et al., 2015) and was preregistered in PROSPERO (ID: CRD42019156782).

5.2.1 Literature Review

EMBASE, PsycINFO, MEDLINE and AMED were searched through Ovid, and CINAHL was searched through SOLO (i.e. the Bodleian Libraries of the University of Oxford online search platform). Databases were searched from inception to the 3rd of January 2021. Two previous iterations were conducted, one on the 13th of November 2019 and one on the 28th of March 2020. The terms used in the search were: *"sleep"* or *"sleep disorder"* or *"sleep disturb*"* or *"i*nsomnia" or *"circadian"* or *"parasomnia"* or *"hypersomnia"* AND *"bipolar"* or *"bipolar disorder"* or *"mania"* or *"bipolar depression"* or *"euthymia"* AND *"cognitive behav* therapy"* or *"therapy"* or *"intervention"* or *"treatment*"* or *"chronotherapy"* or *"s*leep deprivation" or "bright light therapy" or *"darkness therapy"*. Bibliographies from other relevant reviews were also hand-searched (D'Agostino et al., 2020; Dallaspezia & Benedetti, 2020; Gottlieb et al., 2019, 2021; Humpston et al., 2020; Ramirez-Mahaluf et al., 2020; Takeshima et al., 2020). Grey literature was not included. All records were screened by two

members of the research team. In the case of uncertainty, an inclusion decision was reached after consensus.

5.2.2 Study Selection

Studies were included in the review if they: (1) were a peer-reviewed parallel or crossover randomised controlled trial, (2) delivered a psychological and/or behavioural intervention specifically focused on sleep or circadian rhythms with no restrictions on the type of control arm, (3) participants were adults (≥ 18 years old), and (4) diagnosed with BD.

Records were excluded if: (1) the primary focus of the study was on BD comorbid with any psychiatric or medical condition, apart from sleep disorders, (2) sleep and/or circadian rhythms were not the principal treatment targets but simply additive elements to another proposed intervention, (3) the sleep or circadian intervention was administered to both groups and the randomisation was based on other elements of the study, such as a pharmacological agent, (4) the study compared pre-to-post outcomes in a single group, and (5) the study investigated the effect of the same intervention in two different patient groups. There was no exclusion based on the nature of the control group.

5.2.3 Quality Assessment

The credibility of the conclusions drawn by the included studies was assessed based on the justification of their aims, the rigour of their methodological design, and the transparency of their reporting. Thus, all studies were independently appraised using a modified version of the AXIS tool for risk of bias assessment (Downes et al., 2016). This tool was selected due to its principal focus on the rationale, methods and reporting of the study. It includes 18 questions, each one of which is given a high, low or unclear risk of bias. Discrepancies between the two assessors were resolved based on consensus. Data on safety of the interventions were extracted by the lead author alone.

5.2.4 Data Handling and Analysis Plan

Following the Cochrane Collaboration recommendations, all findings were summarised via narrative synthesis (Higgins et al., 2019). This review only considered differences between the treatment and control arms at post-treatment and follow-up. As such, only data relevant to between-group comparisons were extracted and analysed. The primary outcomes of interest for this review were related to sleep and circadian rhythms, depression, mania, functioning, and quality of life, but all outcomes were extracted.

Hedge's g effect sizes and the corresponding 95% confidence intervals for all extracted outcomes at post-treatment and follow-up were calculated whenever possible. In crossover trials, outcome scores were extracted prior to exposure to the second arm. Hedge's g was the preferred measure of standardised mean difference over Cohen's d, as the latter can be positively biased in studies with small sample sizes. Similar to Cohen's d, Hedge's g effects of 0.00-0.20 were interpreted as small, 0.21-0.80 as moderate and 0.81- onwards as large. The effect sizes were calculated using the published means and standard deviations. In cases where other measures of central tendency, such as medians, or other measures of dispersion, such as 95% confidence intervals (Henriksen et al., 2020) and interquartile ranges were reported, means and standard deviations were estimated as following:

$$sd = \frac{(\mu - CI.lb) * \sqrt{n}}{1.96}$$

$$sd = \sqrt{\frac{1}{12} * \left[\frac{(a - 2m + b)^2}{4} + (b - a)^2\right]}$$

, where μ denotes the mean, CI.lb denotes the lower bound of the confidence interval, and a and b the upper and lower ends of the interquartile end respectively (Hozo et al., 2005).

In instances where there was not enough information to estimate the appropriate effect sizes, the lead or senior author was contacted and asked to provide the necessary statistics from the published papers. Replies were received from Dr Neşe Yorguner-Kupeli, Prof Ellen Frank, Dr Yuichi and Prof David Miklowitz. In cases were a reply was not received, means and standard deviations were extracted using PlotDigitizer, a tool approved by the Cochrane Collaboration (T. Li et al., 2019). Means and standard deviations were extracted for Benedetti et al. (1997) and Dauphinais et al. (2012) using PlotDigitizer. This method has been previously validated for use in psychopathology questionnaires in RCTs (Furukawa et al., 2006). It is worth noting that differences in Steardo et al. (2020) were interpreted as favouring the experimental over the control group, in line with the interpretations in-text. This comes in contrast with the information the authors provide in Table 2 of their paper, but this is probably due to a mix-up in a correction the authors provided regarding a typo in said table. An email was sent to the first author, but no reply was received.

Following the estimation of the Hedge's g effect sizes and the associated 95% confidence intervals, the resulting significance level was calculated. In all instances, "significant" results denote those where the difference in means was associated with a p of less than 0.05. P-values were estimated using the following formula:

$$se = \frac{CI.ub - CI.lb}{2 * 1.96}$$

$$z = \left| \frac{Hedge's\ g\ effect\ size}{se} \right|$$

$$p - value = exp * (-0.7178 * z - 0.416 * z^2)$$

, where CI.ub and CI.lb denote the upper and lower bounds of the confidence interval, respectively, and exp denotes the exponential function (D. G. Altman & Bland, 2011).

Consistent with pre-registered plans, random-effects models were implemented when at least five studies delivered the same intervention and measured the same outcome. Random-effects models estimate the weighted pooled effect sizes, and were preferred over fixed-effects models due to expected heterogeneity in the included studies. Heterogeneity was inspected based on the I2 values and the associated 95% confidence intervals using the Q-profile method (Viechtbauer, 2007). All analyses were performed in the software R, version 3.6.

5.2.5 Registered Clinical Trials

Complementary to the initial search, registered trials in ClinicalTrials.gov, International Standard Randomised Controlled Trial Number, and EU Clinical Trials Register were searched from inception to the 30th of March 2020. The search terms were "sleep" AND "bipolar", with studies in humans and written in English as the only restrictions. The resultant records were assessed against the original screening parameters. The aim of this process was to collate information about prospective studies, and therefore describe in more factual terms the future of this emergent research area.

5.3 Results

After removing duplicate entries (n=1,545), 9,858 title and abstract records were screened. This resulted in the exclusion of 8,174 references, and the retrieval of 138 full-text records. A total of 19 studies reporting on 16 RCTs met the inclusion and exclusion criteria and were subsequently included in this review. Figure 5.1 displays the review PRISMA flowchart. Details of the results, including datasets and analysis scripts, are publicly accessible on the study-specific Open Science Framework page: https://osf.io/gv3pe/.

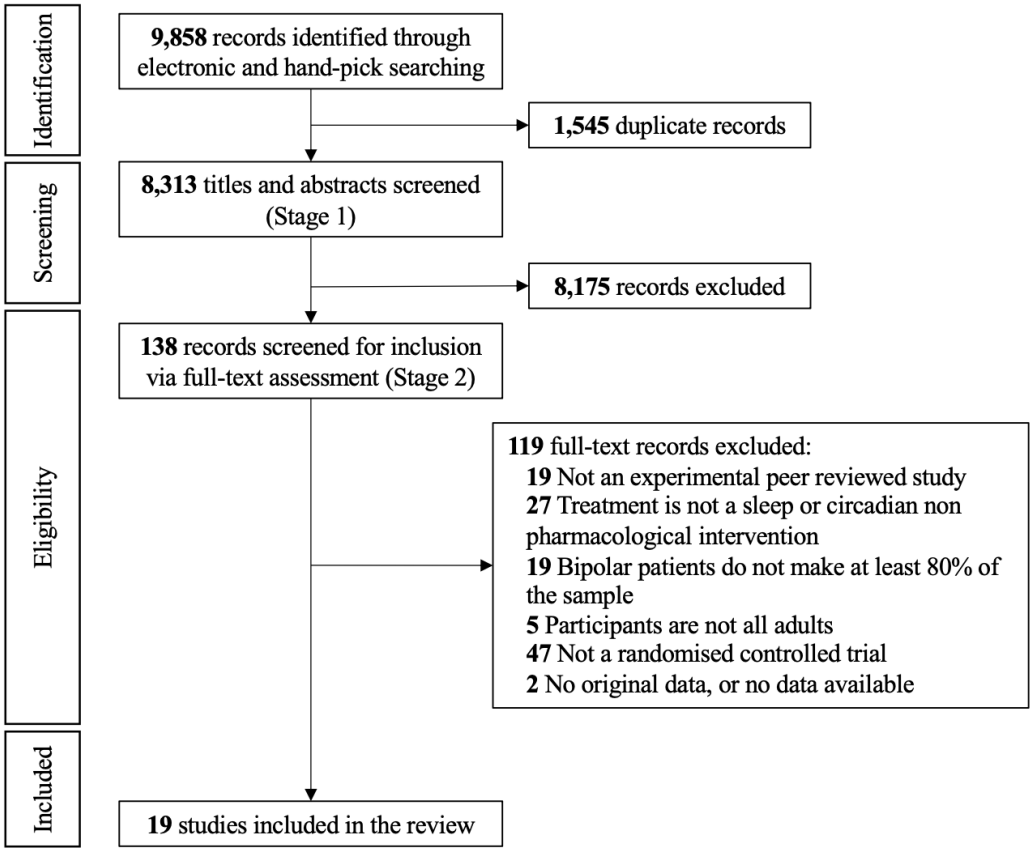


Figure 5.1 PRISMA flowchart of the included studies

5.3.1 Study Characteristics

Key characteristics of all included studies are displayed in Table 5.1. The earliest study was conducted in 1984 and the most recent in 2020, with almost half of all studies (n=9; 47%) published in the last five years. The included studies recruited a total of 1,094 participants, ranging from 9 to 192. Overall, of the 1,094 recruited participants, 852 completed the study protocols and provided post-treatment data (78%). A total of 62% of the sample was female. Four studies recruited inpatients (21%), nine recruited outpatients (47%), four recruited volunteers (21%) and two studies recruited both in- and outpatients (10%). 13 studies (68%) reported on the safety of the administered intervention. None of

these studies reported any serious adverse event and side-effects were rare. Table 5.2 details all the reported adverse events.

Six studies reported on the administration of BLT as a treatment, four on IPSRT, two on blue-light blocking glasses, one on CBT-I, one on TSD, and four on combination treatments. Most studies included both BD-I and II (n=9; 47%), followed by BD-I alone (n=6; 32%), and one study looked specifically at BD-II (5%). Three studies did not specify the BD subtype of their participants (16%). Ten studies recruited people in a depressive phase (53%), three recruited people in a euthymic phase (16%), two recruited people in a manic phase (10%), and two in either a manic, depressed or mixed phase (10%). Two studies did not specify the mood phase of their participants (10%). Following this, 15 studies reported outcomes for depression (79%), ten for mania (53%), nine for sleep and/or circadian rhythms (47%), and four for functioning and/or quality of life (21%). Only three trials specifically recruited participants with sleep or circadian rhythm disruption at baseline, all of which recruited people with BD and a comorbid diagnosis of insomnia (16%).

Table 5.1 Characteristics of included studies

Author year location	Diagnosis (manual), subtype, phase, comorbidities	Randomised *n* (completed *n*), *n* female, mean age (sd), recruitment population	Treatment type: frequency, duration, timing (administrator)	Control type: frequency, duration, timing (administrator)	Medication status	Domains examined (measurement tool)
Bright Light Therapy						
Dauphinais et al., 2012 USA	BD (DSM-IV), I and II, depressed, unclear comorbidities	*BLT:* 18 (10), 13f, 42.9 (12.4), outpatients *Negative Ion Therapy:* 20 (11), 15f, 43.1 (16.0), outpatients	*BLT:* 7,000 lux, daily for 8 weeks, 7.5 min upon waking for the first three days with toleration increasing 2 x 7.5 up to 45 min upon waking (self-administered)	*Negative Ion Therapy:* Daily for 8 weeks, 7.5 min upon waking for the first three days with toleration increasing 7.5 up to 45 min upon waking (self-administered)	Stable psychotropic medication. Benzodiazepines lorazepam-equivalents and zolpidem were allowed for insomnia	Depression (SIGH-ADS and MADRS), mania (YMRS), quality of life (Q-ES-Q)
Franchini et al., 2009 Italy	BD (DSM-IV-TR), unclear, depressed with psychotic symptoms, no other Axis-I diagnosis	*BLT + Fluvoxamine:* 17 (17), 7f, 42.9 (17.9), inpatients *Fluvoxamine:* 10 (10), 7f, 54.0 (12.2), inpatients	*BLT:* 10,000 lux, daily for 40 days, 30 min, between 4.45am- 8.45am (nursing staff) *Fluvoxamine:* Same as in the control condition	*Fluvoxamine:* Titrated at 100mg qid days 1-3, 100mg bid on days 4-7, and 150mg bid on day 8. Participants then remained on 300mg per day for the remaining 5 weeks	As suited fluvoxamine, lithium (prophylactic dose), and/or flurazepam (up to 45mg/day). No other psychotropic medication allowed	Depression (HDRS), delusions (DDERS)
Yorguner Kupeli et al., 2018 Turkey	BD (DSM-IV and HDRS >17), I and II, depressed, no psychotic symptoms	*BLT:* 16 (16), 10f, 42.1 (9.1), outpatients *Dim light:* 16 (16), 16f, 37.1 (8.2), outpatients	*BLT:* 10,000 lux, every morning for 30 minutes for 14 days, between 8 and 10 am (clinician)	*Dim light:* <500 lux, every morning for 30 minutes for 14 days, between 8-10 am (clinician)	Stable medication throughout the study except lorazepam when needed as an add-on treatment	Depression (HDRS and MADRS) and sleep quality (PSQI)
Rosenthal, 1984 USA	Major affective disorder: BD (major affective disorder according to the RDC), I and II, unclear, unclear comorbidities	*BLT:* 4(4), 4f, 31.25(7.63), volunteers *Dim yellow light:* 5 (5), 4f, 44.8 (4.97), volunteers	*BLT:* 2,500 lx, 6 hours a day (3 hours before dawn and 3 hours after dusk) for 2 weeks (unclear)	*Dim yellow light:* 100 lx, 6 hours a day (3 hours before dawn and 3 hours after dusk) for 2 weeks (unclear)	Unclear but most participants were on some form of medication	Depression (HDRS)
Sit et al., 2018 USA	BD (SCID in DSM-IV), I and II, depressed, no OCD	*BLT:* 23 (22), 14f, 45.7 (14.3), outpatients *Dim red light:* 23 (18), 17f, 43.7 (15.0), outpatients	*BLT:* 7,000 lx, start with 15-minute sessions between 12:00 p.m. and 2:30 p.m. Then weekly increase by 15 minutes to attain a target dose of 60 minutes per daily session by week 4 or until remission (research personnel)	*Dim red light:* 50 lx, start with 15-minute sessions between 12:00 p.m. and 2:30 p.m. Then weekly increase by 15 minutes to attain a target dose of 60 minutes per daily session by week 4 or until remission (research personnel)	Anti-manic medication for at least 4 weeks prior to enrolment	Depression (SIGH-ADS and HDRS), functioning (GAF), clinical severity (CGI-BP), anxiety and suicidal thoughts (HDRS), sleep quality (PSQI), psychosis (BPRS)
Zhou et al., 2018 China	BD (DSM-IV), unclear, depressed, no other Axis-I diagnoses	*BLT:* 37 (33), 20f, 35.09 (14.19), volunteers *Dim light:* 37 (30), 14f, 39.73 (13.53), volunteers	*BLT* 5000 lx, 1 hour a day every day for 2 weeks, between 6:30am-9 am (research staff)	*Dim light:* 100 lx, 1 hour a day every day for 2 weeks, between 6:30am-9am (research staff)	Stable psychotropic medication for 2 weeks prior to enrolment	Depression (HDRS) and hypomania (YMRS)
Interpersonal and Social Rhythm Therapy						
Frank et al., 2005 USA	BD (SCID-P for DSM-IV) or schizoaffective disorder manic type (SCID-P DSM-IV or schedule for affective disorders	*IPSRT:* 87 (49), 26f, 36.4 (10.6) in- and outpatients	*IPSRT (acute)/IPSRT (chronic):* Weekly until stabilisation then biweekly for 12 weeks, then monthly, 45-55min, not stated (social worker, nurse, psychologist)	*ICM (acute)/ICM (chronic):* Weekly until stabilisation then biweekly for 12 weeks, then monthly, 20 min, not stated	For manic phases: lithium to serum 0.8/1.0 mEq/L, or sodium divalproex or carbamazepine as required.	Recurrence of acute mania ore depression episodes (clinical evaluation using the

Table 5.1 Characteristics of included studies

Author year location	Diagnosis (manual), subtype, phase, comorbidities	Randomised *n* (completed *n*), *n* female, mean age (sd), recruitment population	Treatment type: frequency, duration, timing (administrator)	Control type: frequency, duration, timing (administrator)	Medication status	Domains examined (measurement tool)
	and schizophrenia), I, manic, depressed or mixed, no BPD, APD, bulimia or anorexia	*ICM:* 88 (44), 22f, 39.4 (10.8), in- and outpatients		(social worker, nurse, psychologist)	For depressive phases: lithium, and tranylcypromine sulphate, imipramine hydrochloride and SSRI as required	RDC), social rhythms (SRM)
Miklowitz et al., 2007 USA	BD (Affective Disorders Evaluation adapted from SCID-P from DSM-IV), I and II, depressed, unclear comorbidities	*IPSRT:* 62 (42), volunteers *CC:* 130 (90), volunteers	*IPSRT*	*CC:* Three 50-minute individual sessions in the six weeks post randomisation, an educational videotape, and workbook	Mood stabiliser (lithium, valproate, or carbamazepine) plus antidepressant in some cases	Mania and depression relapse
Steardo et al., 2020 Italy	BD (SCID-5-CV for DSM-V), I and II, unclear, unclear comorbidities	*IPSRT:* 22 (22), 12f, 49.1 (12.6), outpatients *TAU:* 22 (22), 13f, 46.7 (12.8), outpatients	*IPSRT:* 12 weekly sessions, 90 min (psychiatrist)	*TAU*	Stable treatment with mood stabilizers for at least a year prior to recruitment	Depression (IDSSR and MADRS), anxiety (HAM-A), mania (MRS), functioning (GAF and AMI), and response to mood stabilizers (ALDA)
Swartz et al., 2012 USA	BD (SCID for DSM-IV-clinician-version), II, depressed, no BPD or APD	*IPSRT:* 14 (12), 7f, 40.1 (11.7), volunteers *Quetiapine:* 11 (9), 3f, 32.1 (12.8), volunteers	*IPSRT:* 12 weekly sessions, 45 min (master's level therapists)	*Quetiapine :* Daily for 12 weeks. Start dose of 50 mg a day, increased weekly by 50 mg a day, as tolerated, to a maximum of 300 mg a day.	No psychotropic medication prior to the study, low dose of lorazepam if sleep problems	Depression (HDRS-25, HDRS-17 and MADRS), mania (YMRS), functioning (CGI-BP), and anxiety (BAI)
Blue-Light Blocking Glasses						
Esaki et al., 2020 Japan	BD (DSM-V), and Insomnia (ISI ≥8), I and II, euthymic, unclear comorbidities	*BB glasses:* 21 (19), 9f, 44.1 (11.8), outpatients *Placebo:* 22 (18), 14f, 41.1 (10.4), outpatients	*BB:* Orange-tinted glasses worn every night for 14 consecutive nights, 8pm-bedtime (unclear)	*Placebo:* Clear glasses worn every night for 14 consecutive nights, 6pm-8pm-dedtime (unclear)	Medication as usual (stable throughout the study)	Sleep (actigraphy, sleep diaries, VAS for sleep quality and ISI), chronotype (MEQ), mania (YMRS), depression (MADRS)
Henriksen et al., 2016 Norway	BD (MINI-Plus for DSM-IV-TR), I, manic, unclear comorbidities	*BB glasses:* 18 (12), 5f, 43.0 (11.0), inpatients *Placebo:* 14 (11), 2f, 49.8 (13.8), inpatients	*BB:* Orange-tinted glasses worn every night for 7 consecutive nights, 6pm-8am (nurses)	*Placebo:* Clear glasses worn every night for 7 consecutive nights, 6pm-8am (nurses)	Medication as usual (stable throughout the study)	Mania (YMRS)
Henriksen et al., 2020 Norway	BD (MINI-Plus for DSM-IV-TR), I, manic, unclear comorbidities	*BB glasses:* 18 (10), 4f, 43.9 (11.8), inpatients *Placebo:* 14 (10), 2f, 48.8 (14.1), inpatients	*BB:* Orange-tinted glasses worn every night for 7 consecutive nights, 6pm-8am (nurses)	*Placebo:* Clear glasses worn every night for 7 consecutive nights, 6pm-8am (nurses)	Medication as usual (stable throughout the study)	Rest-activity and sleep (actigraphy)
Cognitive Behaviour Therapy for Insomnia						
Harvey et al., 2015 USA	BD (SCID for DSM-IV-TR, YMRS<12 and IDS-C<24) and	*CBT-I:* 30 (22), 19f, 37.7 (12.4), outpatients	*CBT-I:* 8 weekly sessions, 50-60 min (doctoral or master's level therapists)	*PE*	Medication as usual (stable throughout the study)	Relapse rate and days spent in acute episodes

Table 5.1 Characteristics of included studies

Author year location	Diagnosis (manual), subtype, phase, comorbidities	Randomised *n* (completed *n*), *n* female, mean age (sd), recruitment population	Treatment type: frequency, duration, timing (administrator)	Control type: frequency, duration, timing (administrator)	Medication status	Domains examined (measurement tool)
	Insomnia (general insomnia by ICSD-2 and primary insomnia by DSISD), I, inter-episode, no PTSD, other sleep disorder, or alcohol and substance abuse/dependency over the past 3 months	*PE:* 28 (19), 17f, 35.5 (9.3), outpatients	The behavioural components included: stimulus control, SRT, psychoeducation, relaxation therapy in dim-light conditions, and a wake-up routine. The cognitive components included: targeting unhelpful beliefs about sleep and reducing sleep-anxiety and rumination. The daytime functioning component included: behavioural activities to allow participants to experience the effects of being active, and identification of energy-generating activities in order to tackle daytime tiredness	8 weekly sessions, 50-60 min (doctoral or master's level therapists)		(clinical evaluation using the SCID for DSM-IV-TR), depression (IDS-C), mania (YMRS), insomnia (ISI and clinical evaluation by the DSISD), sleep quality (PSQI), sleep disturbances (PROMIS-SD), and sleep (sleep diaries), functionality (SDS), quality of life (Q-LES-Q-SF), percentage of people taking mood or sleep medications
Total Sleep Deprivation						
Benedetti et al., 1997 Italy	BD (DSM-III-R), I and II, depressed, unclear comorbidities	*TSD & fluoxetine:* 5 (5), 3f, 40.0 (12.1), outpatients *Fluoxetine only:* 5 (5), 4f, 42.0 (9.7), outpatients	*TSD:* 36 hours awake for 3 nights, from 7.00 to 19.00 the following day (nursing staff) *Fluoxetine:* 20mg once daily, 8am (nurses)	*Fluoxetine:* 20mg once daily, 8am (nursing staff)	Free of all psychotropic medication for at least 1 week before admission	Depression (HDRS)
Combination Treatments						
Colombo et al., 2000 Italy	BD (DSM-IV), unclear, depressed, no other axis 1 diagnosis	*TSD + red BLT + lithium:* 14 (14), 9f, 45.6 (14.6), inpatients *TSD + red BLT:* 19 (19), 13f, 41.6 (12.9), inpatients *TSD + white BLT + lithium:* 17 (17), 10f, 42.6 (12.1), inpatients *TSD + white BLT:* 23 (23), 19f, 45.1 (12.8), inpatients *TSD + ambient light + lithium:* 15(15), 10f, 51.1(13.2), inpatients *TSD + ambient light:* 15(15), 11f, 49.5 (10.5), inpatients	*TSD:* 36 hours awake for 3 nights, from 7am to 7pm the following day (unclear) *Red BLT:* 150 lux of red light given for 30 min on each TSD night at 3am (unclear), on the morning after the recovery sleep and half an hour after awakening between 8am and 9am *White BLT:* 2,500 lux of white light given for 30 min on each TSD night at 3am (unclear), on the morning after the recovery sleep and half an hour after awakening between 8am and 9am *Lithium:* Same lithium carbonate dosage as usual	*TSD:* 36 hours awake for 3 nights, from 7am to 7pm the following day (unclear) *Ambient light:* Room monitored at 80 lux with no additional light exposure *Lithium:* Same lithium carbonate dosage as usual	No other long-term medication besides lithium. If treated with benzodiazepines a progressive dose reduction prior to the run-in period was conducted	Subjective mood (VAS from very happy to very sad), and sleepiness (SSS)

Table 5.1 Characteristics of included studies

Author year location	Diagnosis (manual), subtype, phase, comorbidities	Randomised *n* (completed *n*), *n* female, mean age (sd), recruitment population	Treatment type: frequency, duration, timing (administrator)	Control type: frequency, duration, timing (administrator)	Medication status	Domains examined (measurement tool)
Kaplan et al., 2018 USA	BD (SCID for DSM-IV-TR, YMRS<12 and IDS-C<24) and Insomnia (general insomnia by ICSD-2 and primary insomnia by DSISD), I, inter-episode, no PTSD, other sleep disorder, or alcohol and substance abuse over the past 3 months	*RISE-UP:* 20 (19), 14f, 39.3 (14.2), outpatients *PE:* 20 (19), 13f, 35.4 (8.9), outpatients	*RISE-UP:* One 60-minute therapy session at the start of CBT-I (doctoral student). The components included: refraining from snoozing, increasing activity in the first hour upon awakening, showering or washing face with cold water, expose to sunlight, music and phoning a friend	*PE:* One session, 50-60 min (doctoral or master's level therapists)	Medication as usual (stable throughout the study)	Sleep (actigraphy and sleep diaries), sleepiness (SSS)
Miklowitz et al., 2003 USA	BD (SCID-P for DSM-IV), I and II, (hypo)manic, depressed and mixed, no DSM-IVdrug or alcohol disorder	*IFIT:* 31 (24), 18f, 35.7 (9.2), inpatients and outpatients *CM:* 70 (54), 46f, 35.6 (10.6), inpatients and outpatients	*IFIT:* 21 one-hour sessions, 12 of them weekly, then 6 biweekly and finally 3 monthly sessions (trained therapists) One session per week for 12 months, alternating between IPSRT and FT (optimally 25 IPSRT and 25 FT). Flexibility when designing each therapeutic protocol, not all therapists took all 50 sessions available (one therapist for IPSRT and one for FT, therapists were researchers)	*CM:* 2 home-based BD information sessions within 2 months of entry to the study, emergency counselling also available (clinician)	Medication as usual	Survival time, mood disorder symptom severity, depression, and mania (all from SADS-C)
Wu et al., 2009 USA	BD (SCID in DSM-IV), I and II, depressed, unclear comorbidities	*TSD + BLT + Phase Advance:* 32 (27), 10f, 39 (13.31), outpatients *TAU:* 17 (17), 10f, 40 (14.1), outpatients	*TSD:* 33 hours awake, from 9am to 6pm the day after (nursing staff) *BLT:* 5000 lux for 2 hours over 3 days in the morning following a night of TSD, exact timing was calculated based on individual MEQ scores *Phase advance:* 3 nights the evening after the first TSD night	*Medication treatment as usual* (nursing staff)	Everyone on mood stabilizers, antidepressants and sertraline administered on the same time schedule. Lithium (or other mood stabilizers if intolerant) initiated 1 week before the SD night to minimize the risk of switches into hypomania/mania	Depression (HDRS)

Abbreviations: AMI, Attitude to Mental Illness Questionnaire ; APD, Antisocial Personality Disorder; BAI, Beck Anxiety Inventory; BB glasses, Blue-light Blocking glasses; BD, Bipolar Disorder; BLT, Bright Light Therapy; BPD, Borderline Personality Disorder; BPRS, Brief Psychiatric Rating Scale; CBT-I, Cognitive Behavioural Therapy for Insomnia; CC, Collaborative Care; CGI-BP, Clinical Global Impression for use in Bipolar disorder; CI, Confidence Intervals; CM, Clinical Management; DDERS, Dimensions of Delusional Experience Rating Scale; DSISD, Duke Structured Clinical Interview for Sleep Disorders; DSM, Diagnostic and Statistical Manual for mental disorders; FU, Follow-Up (the precipitating number indicates months); GAF, Global Assessment of Functioning; HAM-A, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; ICM, Intensive Clinical Management; ICSD, International Classification of Sleep Disorders; IDS-C, Inventory of Depressive Symptomatology- Clinician version; IFIT, Integrated Family and Individual Therapy; IPSRT, Interpersonal and Social Rhythm Therapy; ISI, Insomnia Severity Index; MADRS, Montgomery–Åsberg Depression Rating Scale; MEQ, Morningness-Eveningness Questionnaire; MRS, Mania Rating Scale; N, number of participants; OCD, Obsessive-Compulsive Disorder; PE, Psychoeducation; PROMIS-SD, Patient-Reported Outcomes Measurement Information System- Sleep Disturbance; PSQI, Pittsburgh Sleep Quality Index; PTSD, Posttraumatic Stress Disorder; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; RDC, Research Diagnostic Criteria; SADS-C, Schedule for Affective Disorders and Schizophrenia- Change in symptomatology; SCID, Structured Clinical Interview for the DSM; SD, Standard Deviations; SE, Sleep Efficiency; SIGH-ADS, Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement; SRM, Social-Rhythm Metric; SSS, Stanford Sleepiness Scale; TAU, Treatment As Usual; TC, Triple Chronotherapy; VAS, Visual Analogue Scale; WASO, Wake After Sleep Onset; YMRS, Young Mania Rating Scale

Table 5.2. Safety assessment reporting of the included studies

Study	Treatment /Control	Safety Assessment
Bright Light Therapy		
Dauphinais et al. 2012	BLT/Negative ion therapy	No SAEs. 2 drop-outs due to hypomania (1 BLT and 1 Negative ion therapy). No significant* differences in AEs between BLT and negative ion therapy as measured by SAFTEE. AEs included headache (11 BLT and 10 Negative ion therapy), hypomania (4 BLT and 2 Negative ion therapy), and irritability (3 BLT and 1 Negative Ion Therapy)
Franchini et al. 2009	BLT/Fluvoxamine	No drop-outs due to AEs or side-effects
Kupeli et al. 2018	BLT/DL	No drop-outs due to AEs or side-effects and no switch to mania or hypomania in either group. Side effects included insomnia (1 BLT), headache (2 BLT 2 DL), and nausea (1 DL). No significant* differences between BLT and DL measures by SERS
Rosenthal et al. 1984	BLT/DL	*"hypomanic irritability and hyperactivity in a few cases with bright lights"*
Sit et al. 2018	BLT/DL	No SAEs. Infrequent worsening of symptoms in both groups, but less excessive sleepiness in BLT compared to DL
Zhou et al. 2018	BLT/DL	No SAEs. No significant* differences in AEs between BLT and DL as measured by SERS. AEs included dizziness (1 BLT), fatigue (1 BLT), and sleep disturbances (2 BLT)
Interpersonal Social Rhythms Therapy		
Frank et al. 2005	IPSRT/ICM	No information provided
Miklowitz et al. 2007	IPSRT/CC	No information provided
Steardo et al. 2020	IPSRT/TAU	No information provided. *"The intervention was well-received by patients…"*
Swartz et al. 2012	IPSRT/Quetiapine	No information provided
Blue-light Blocking Glasses		
Esaki et al. 2020	BB/CL glasses	One drop-out because of the intervention in BB glasses, and 4 AEs recorded in the same group. No information provided about CL glasses group
Henriksen et al. 2016	BB/CL glasses	Side effects included emerging depressive symptoms (2 in BB glasses) but no switch to depressive phase, headache (1 in BB glasses and 3 in CL glasses)
Henriksen et al. 2020	BB/CL glasses	Safety details reported in Henriksen et al. 2016
Cognitive Behavioural Therapy for Insomnia		
Harvey et al. 2015	CBT-I/PE	Side effects included increase in depressive symptoms in the mild to moderate range (5 in CBT-I and 12 in PE) or the severe range (3 in CBT-I and 3 in PE), increase in manic symptoms in the severe range (1 in CBT-I and 1 in PE), voluntarily hospitalisation for a transient amnestic episode (1 in CBT-I), and voluntarily hospitalisation for suicide ideation (1 in PE)
Total Sleep Deprivation		
Benedetti et al. 1997	TSD/Fluoxetine	No information provided
Combination Treatments		
Colombo et al. 2000	TSD + (no) lithium + red/white/ambient light	No information provided but 7 people switched polarity (3 in TSD + lithium + red light, 2 TSD + red, and 2 TSD + white)
Kaplan et al. 2018	RISE-UP/PE	Safety details reported in Harvey et al. 2015
Miklowitz et al. 2003	IFIT/CM	No information provided
Wu et al. 2009	TC/TAU	AEs included brief switches to hypomanic episodes (2 in TC)

** significance as reported by the original paper*

Abbreviations: AEs, Adverse Events; BB glasses, Blue-light Blocking glasses; BLT, Bright Light Therapy; CBT-I, Cognitive Behavioural Therapy for Insomnia; CC, Collaborative Care; CL glasses, Clear Lenses glasses; CM, Clinical Management; DL, Dim Light; ICM, Intensive Clinical Management; IFIT, Integrated Family and Individual Therapy; IPSRT, Interpersonal and Social Rhythm Therapy, PE, Psychoeducation; SAEs, Serious Adverse Events; SAFTEE, Systematic Assessment for Treatment Emergent Effects; SERS, Side Effects Rating Scale; TAU, Treatment as Usual; TC, Triple Chronotherapy; TSD, Total Sleep Deprivation

5.3.2 Quality Assessment

Tables 5.3 and 5.4 present the quality assessment. The mean interrater reliability score for the quality assessment was 92%. Although the appraisal produced mixed results, there is a distinct trend of improvement. Studies published in the last five years were more comprehensive and transparent in their reporting than previous work in the area. Of the four studies (21%) judged to have a low risk of bias in all domains, three explored the treatment effects of blue light-blocking glasses (Esaki et al., 2020; Henriksen et al., 2016, 2020), and the fourth investigated the effects of BLT (Yorguner Kupeli et al., 2018).

Almost all studies (n= 17; 90%) reported clear aims and objectives. Most studies compared treatment to a non-active control (n=15; 79%), three studies (16%) used an active control arm, and one study (5%) included both an active a non-active control arm. Thirteen out of the 19 studies did not report a sample size justification (68%), with the six studies (32%) that reported a sample size justification being published in the last five years. 15 studies (79%) defined their population clearly using well-established diagnostic tools, whereas four studies (21%) did not provide sufficient information regarding the episode polarity of BD. One study (5%) did not provide enough details about the population their sample was selected from, and in another study (5%) there were concerns about the participant selection process. In this last study, there was a notable imbalance of inpatients and outpatients in the two study groups, with 66% inpatients and 34% outpatients in the treatment group, and 20% inpatients and 80% outpatients in the control group (Zhou et al., 2018). Two studies (10%) did not address their drop-out rate at all, and two more studies did not address it sufficiently (10%). In these last two studies, the participants who switched polarity following TSD were defined as drop-outs (Colombo et al., 2000; Dauphinais et al., 2012), while such instances could be additionally handled and interpreted as adverse events potentially related to the treatment (Wu et al., 2009). The scope of the measured outcomes

was limited, with nine studies (47%) not assessing sleep or circadian rhythms in any capacity and one study providing unclear information (5%). However, for the outcomes they did measure, almost all studies (n=18; 95%) used well-validated measures and statistical significance was clearly reported. Methodological reporting was more transparent than analytical reporting, with most studies (n=17; 90%) reporting sufficient information in the methods to allow a replication, but with one third of the included studies (n=6; 32%) not reporting aggregated scores or measures of dispersion for the raw data. In most cases, the results were internally consistent (n=16; 85%), and there were no omissions in the Results section of measures mentioned in the Methods section (n=16; 85%). In all studies (n=19; 100%), the interpretations were justified by the findings, and only one study did not mention any limitations (5%). In 14 studies (74%) there were no perceived conflicts of interest. In two papers there was a potentially strong conflict of interest (10%), and in three studies (16%) there was an unclear conflict of interest. Finally, all studies (n=19; 100%) had ethical approval for their protocol and informed consent from the participants.

Table 5.3 AXIS risk of bias appraisal - total percentage scores

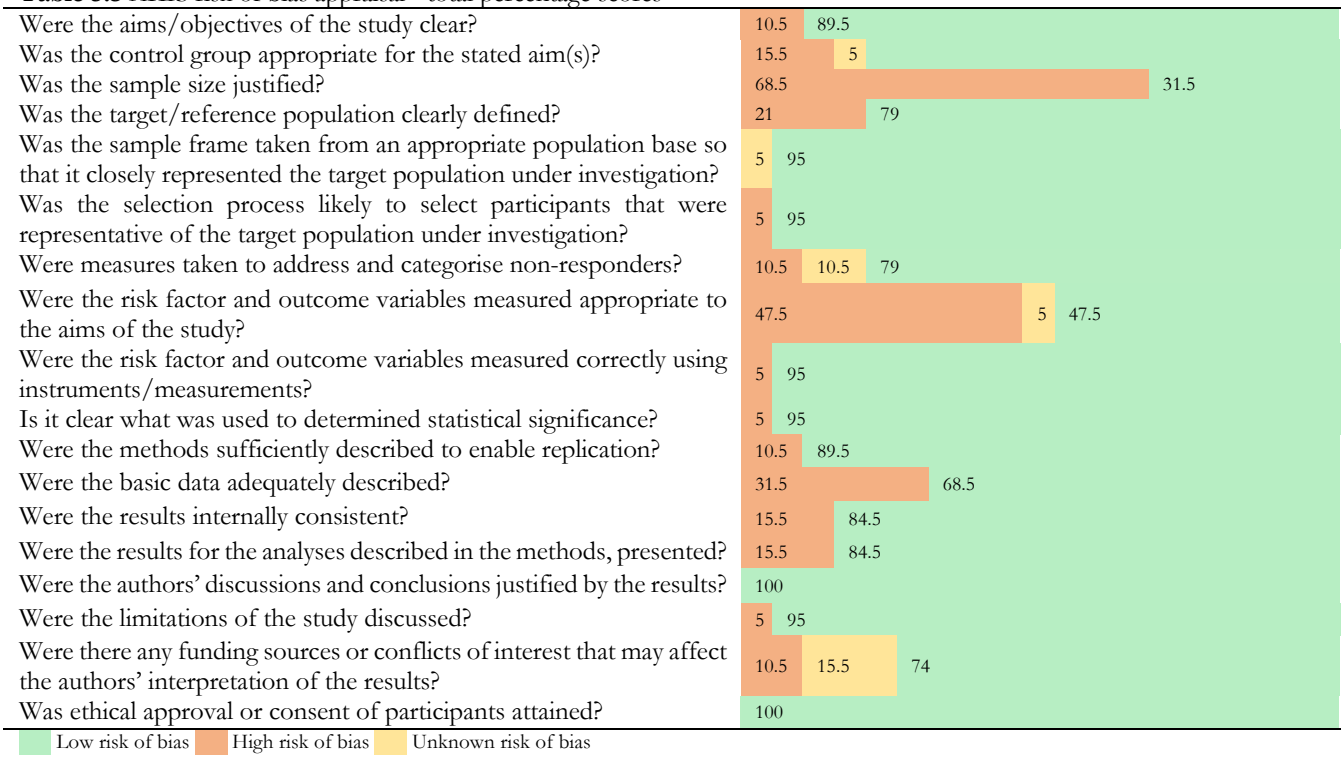
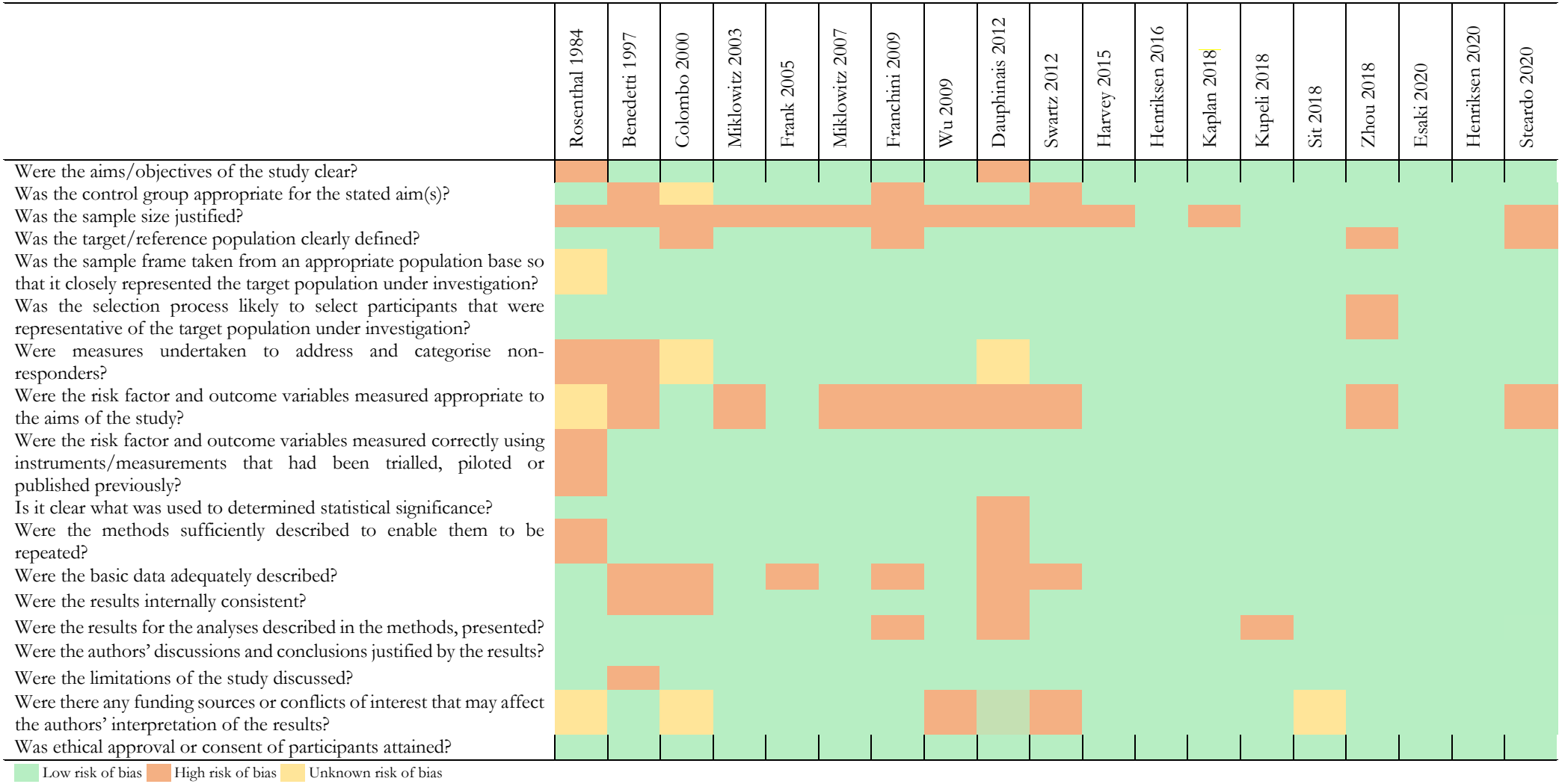


Table 5.4 Quality assessment table using the AXIS tool (Downes et al., 2016)



5.3.3 Data Synthesis

Details of the observed effects of the included studies are provided in Table 5.5.

Bright Light Therapy

Six studies reporting on six RCTs were included. All studies looked at BD-I and BD-II during depressive states. A random-effects model estimated a medium-to-large effect for reduced depression scores in the BLT group versus control at post-treatment (N_c=6; g=-0.74 [95% CI = -1.05 to -0.42], p<0.001; I^2=0.00 [95% CI = 0.00 to 82.85]) (see Figure 5.2). No evidence of publication bias was detected after visual inspection of the associated funnel plot in Figure 5.3 or after conducting an Egger's test (z=-0.075; p=0.941). In one study there was a significant improvement in sleep quality at post-treatment (g=-0.81, p=0.027) (Yorguner Kupeli et al., 2018), while in another study the difference in sleep quality was not significant (g=-.012, p=0.720) (Sit et al., 2018). Finally, in one study there was a large and significant improvement effect in functioning (g=0.71, p=0.031) (Sit et al., 2018). Further details on anxiety and psychosis are presented in Table 5.6.

Interpersonal and Social Rhythm Therapy

Four studies reporting on four RCTs were included. One of those studies did not provide adequate data for independent effect size calculation (Frank et al., 2005). No significant differences in depression (g=-0.15, p=0.435 for Miklowitz et al. 2007; g=0.74, p=0.105 for Swartz et al. 2012) or mania symptoms (g=0.19, p=0.312 for Miklowitz et al. 2007; g=-0.50, p=0.269 for Swartz et al. 2012) were detected in two studies. In one study there was significant improvement in both depression (g=0.94, p=0.003) and mania scores (g=-0.62, p=0.044) (Steardo et al., 2020).

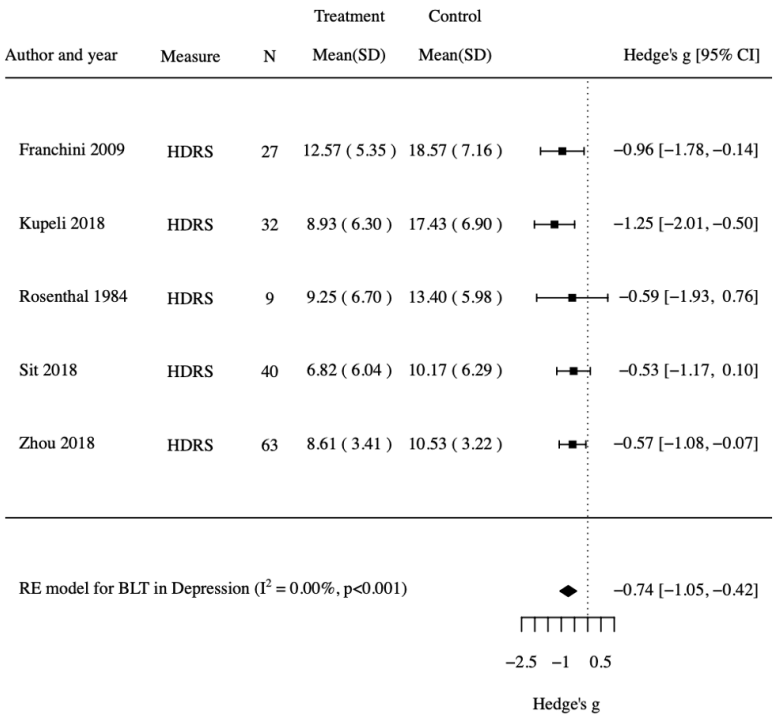


Figure 5.2 Forest plot showing individual study and global effect size estimates for post-treatment comparisons between bright light therapy and control in depression outcomes
Abbreviations: BLT, Bright Light Therapy; CI, Confidence Interval; HDRS, Hamilton Depression Rating Scale; RE, Random Effects; SD, Standard Deviation

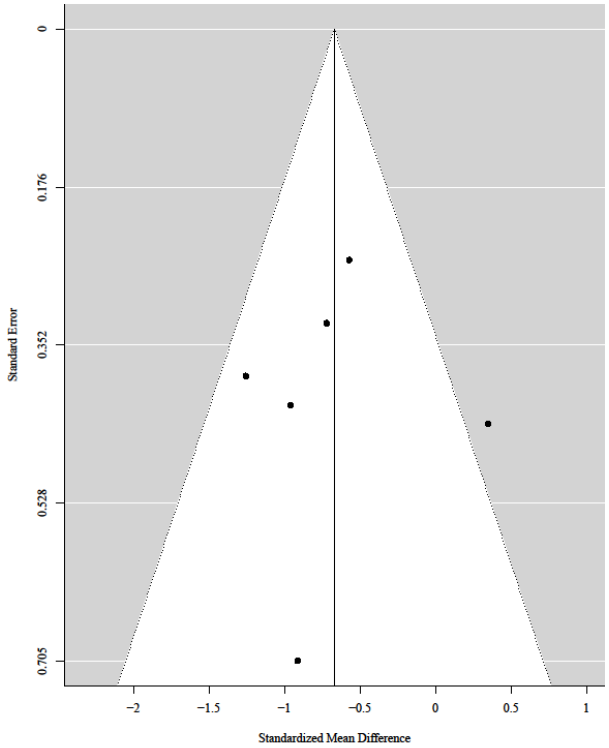


Figure 5.3 Funnel plot for studies examining the effect of Bright Light Therapy in bipolar depression

Interpersonal and Social Rhythm Therapy

Four studies reporting on four RCTs were included. One of the those studies did not provide adequate data for independent effect size calculation (Frank et al., 2005). No significant differences in depression (g=-0.15, p=0.435 for Miklowitz et al. 2007; g=0.74, p=0.105 for Swartz et al. 2012) or mania symptoms (g=0.19, p=0.312 for Miklowitz et al. 2007; g=-0.50, p=0.269 for Swartz et al. 2012) were detected in two studies. In one study there was significant improvement in both depression (g=0.94, p=0.003) and mania scores (g=-0.62, p=0.044) (Steardo et al., 2020).

Blue light-blocking glasses

Three studies reporting two RCTs were included. In Henriksen et al (2016, 2020) there was a large and significant improvement in manic symptoms (g=1.81, p<0.001), sleep efficiency (g=1.00, p=0.035), and wake after sleep onset (g=-1.12, p=0.020). No other studies found any other significant results. Further details on findings from both studies are presented in Table 5.6.

Cognitive Behavioural Therapy

One study reporting one RCT was included. The trial recruited participants who were euthymic. In Harvey et al (2015) between-group differences in mania (g=-0.62, p=0.051) and depression (g=-0.38, p=0.232) following treatment did not reach statistical significance. Differences in mania scores remained moderate and non-significant at follow-up (g=-0.55, p=0.084), whereas reductions in depression scores at 6-month post-treatment follow-up were moderate-to-large and statistically significant (g=-0.67, p=0.037). There was a large and significant improvement in insomnia symptoms following treatment (g=-1.36, p<0.001) which was maintained at follow-up (g=-1.01, p=0.002). Similarly, large and

significant effects for sleep quality (g=-0.80, p=0.014) and sleep disturbances (g=-1.07, p=0001) were observed at post-treatment and only for sleep disturbances at follow-up (g=-0.68, p=0.034). Further details on sleep measures are presented in Table 5.6.

Sleep Deprivation Therapy

One study reporting an RCT in bipolar depression was included. No significant improvements in depression scores between the treatment and control groups were detected at post-treatment (g=-0.94, p=0.159).

Combination Therapies

Four studies reporting on three RCTs were included. One of the included studies did not provide adequate data for independent effect size calculation (Colombo et al., 2000). One study administered TSD, BLT and phase advance to people with BD in depression (Wu et al., 2009), another study administered IPSRT with a family therapy protocol, called Integrated Family and Individual Therapy, to individuals with BD in a manic, depressed, or mixed phase (Miklowitz et al., 2003), and the final study recruited a subsample from Harvey et al (2015) and administered a novel sleep-inertia treatment, called RISE-UP, to people with BD in euthymia (Kaplan et al., 2018). No significant differences in depression were observed in Wu et al (2009), either at post-treatment (g=-0.52, p=0.100) or at a 2-month follow up (g=-0.51, p=.107). In Miklowitz et al (2003) the treatment group showed no significant reductions in mania (g=-0.44, p=0.063) or depression symptoms (g=-0.10, p=0.683) compared to the controls. In Kaplan et al (2018) no measures of sleepiness reached statistical significance in either the first hour (g=-0.39, p=0.238) or the first three hours upon awakening (g=-0.31, p=303). Rest-activity findings using actigraphy are presented in Table 5.6.

Table 5.5 Effect sizes classified by symptom outcome and ordered from improvement to worsening

Author (year)	Treatment /Control	Measure	N analysed	Hedge's g	95% CI	p-value
Depression symptom severity						
Kupeli et al. 2018	BLT/DL	HDRS	32	-1.25	-2.01 to -0.50	**0.001**
Kupeli et al. 2018	BLT/DL	MADRS	32	-1.24	-2.00 to -0.48	**0.001**
Franchini et al. 2009	BLT/Fluvoxamine	HDRS	27	-0.96	-1.78 to -0.14	**0.022**
Steardo et al. 2020	IPSRT/TAU	MADRS	44	-0.94	-1.56 to -0.32	**0.003**
Rosenthal et al. 1984	BLT/DL	HDRS	9	-0.59	-1.93 to 0.76	0.397
Sit et al. 2018	BLT/DL	SIGH-ADS	40	-0.72	-1.36 to -0.08	**0.027**
Harvey et al. 2015	CBT-I/PE	IDS-C; *6FU*	41	-0.67	-1.30 to -0.04	**0.037**
Zhou et al. 2018	BLT/DL	HDRS	63	-0.57	-1.08 to -0.07	**0.027**
Sit et al. 2018	BLT/DL	HDRS	40	-0.53	-1.17 to 0.10	0.102
Wu et al. 2009	TC/TAU	HDRS	44	-0.52	-1.14 to 0.10	0.100
Benedetti et al. 1997	TSD/Fluoxetine	HDRS	10	-0.51	-1.77 to 0.75	0.436
Wu et al. 2009	TC/TAU	HDRS; *2FU*	44	-0.51	-1.13 to 0.11	0.107
Esaki et al. 2020	BB/CL glasses	MADRS	37	-0.50	-1.16 to 0.15	0.135
Harvey et al. 2015	CBT-I/PE	IDS-C	41	-0.38	-1.00 to 0.24	0.232
Miklowitz et al. 2007	IPSRT/CC	MADRS	132	-0.15	-0.52 to 0.22	0.435
Miklowitz et al. 2003	IFIT/CM	SADS-C	82	-0.10	-0.56 to 0.36	0.683
Dauphinais et al. 2012	BLT/Negative ion therapy	SIGH-ADS	21	0.35	-0.51 to 1.21	0.433
Swartz et al. 2012	IPSRT/Quetiapine	MADRS	21	0.74	-0.16 to 1.63	0.105
Mania symptom severity						
Henriksen et al. 2016	BB/CL glasses	YMRS	23	-1.81	-2.78 to -0.84	**<0.001**
Harvey et al. 2015	CBT-I/PE	YMRS	41	-0.62	-1.24 to 0.01	0.051
Steardo et al. 2020	IPSRT/TAU	YMRS	44	-0.60	-1.26 to 0.05	0.072
Harvey et al. 2015	CBT-I/PE	YMRS; *6FU*	41	-0.55	-1.17 to 0.08	0.084
Swartz et al. 2012	IPSRT/Quetiapine	YMRS	21	-0.50	-1.38 to 0.38	0.269
Miklowitz et al. 2003	IFIT/CM	SADS-C	82	-0.44	-0.90 to 0.03	0.063
Esaki et al. 2020	BB/CL glasses	YMRS	37	0.04	-0.60 to 0.69	0.911
Dauphinais et al 2012	BLT/negative ion therapy	YMRS	21	0.17	-0.69 to 1.03	0.712
Miklowitz et al. 2007	IPSRT/CC	YMRS	132	0.19	-0.18 to 0.55	0.312
Insomnia symptom severity						
Harvey et al. 2015	CBT-I/PE	ISI	41	-1.35	-2.03 to -0.67	**<0.001**
Harvey et al. 2015	CBT-I/PE	ISI; *6FU*	41	-1.00	-1.65 to -0.35	**0.003**
Esaki et al. 2020	BB/CL glasses	ISI	37	-0.14	-0.79 to 0.50	0.684
Chronotype						
Esaki et al. 2020	BB/CL glasses	MEQ	37	0.41	-0.24 to 1.06	0.218
Sleep quality and disturbances						
Harvey et al. 2015	CBT-I/PE	PROMIS-SD	41	-1.07	-1.72 to -0.41	**0.001**
Kupeli et al. 2018	BLT/DL	PSQI	32	-0.81	-1.53 to -0.09	**0.027**
Harvey et al. 2015	CBT-I/PE	PSQI	41	-0.80	-1.44 to -0.16	**0.014**
Harvey et al. 2015	CBT-I/PE	PROMIS-SD; *6FU*	41	-0.68	-1.31 to -0.05	**0.034**
Esaki et al. 2020	BB/CL glasses	VAS	37	-0.45	-1.10 to 0.20	0.176
Harvey et al. 2015	CBT-I/PE	PSQI; *6FU*	41	-0.33	-0.94 to 0.29	0.297
Sit et al. 2018	BLT/DL	PSQI	40	-0.12	-0.74 to 0.51	0.720
Sleepiness						
Kaplan et al. 2018	RISE-UP/PE	Sleepiness in the first hour upon awakening	38	-0.39	-1.04 to 0.25	0.238
Kaplan et al. 2018	RISE-UP/PE	Sleepiness in the first three hours upon awakening	38	-0.31	-0.95 to 0.33	0.348

Quality of life and Functioning						
Sit et al. 2018	BLT/DL	GAF	40	0.71	0.07 to 1.36	**0.031**
Harvey et al. 2015	CBT-I/PE	Q-LES-Q-SF; *6FU*	41	0.24	-0.38 to 0.85	0.453
Harvey et al. 2015	CBT-I/PE	Q-LES-Q-SF	41	0.001	-0.61 to 0.62	0.998

Abbreviations: BB glasses, Blue-light Blocking glasses; BLT, Bright Light Therapy; CBT-I, Cognitive Behavioural Therapy for Insomnia; CC, Collaborative Care; CI, Confidence Intervals; CL glasses, Clear Lenses glasses; CL, Clinical Management; DL, Dim Light; FU, Follow-Up (the precipitating number indicates months); HDRS, Hamilton Depression Rating Scale; IDS-C, Inventory of Depressive Symptomatology- Clinician version; IFIT, Integrated Family and Individual Therapy; IPSRT, Interpersonal Social Rhythm Therapy; ISI, Insomnia Severity Index; MADRS, Montgomery–Åsberg Depression Rating Scale; MEQ, Morningness-Eveningness Questionnaire; N, number of participants; PE, Psychoeducation; PROMIS-SD, Patient-Reported Outcomes Measurement Information System-Sleep Disturbance; PSQI, Pittsburgh Sleep Quality Index; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SADS-C, Schedule for Affective Disorders and Schizophrenia- Change in symptomatology; SIGH-ADS, Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement; TC, Triple Chronotherapy; VAS, Visual Analogue Scale; YMRS, Young Mania Rating Scale

Table 5.6 Effect sizes classified by symptom outcome and ordered from improvement to worsening

Author (year)	Treatment /Control	Measure	N analysed	Hedge's g	95% CI	p
Activity levels						
Henriksen et al. 2020	BB/CL glasses	Activity counts	20	-0.98	-1.91 to -0.05	**0.039**
Kaplan et al. 2018	RISE-UP/PE	Activity in the first hour upon awakening	38	0.66	0.01 to 1.32	**0.048**
Sleep Onset Latency						
Harvey et al. 2015	CBT-I/PE	Sleep diaries	41	-0.47	-1.09 to 0.15	0.138
Harvey et al. 2015	CBT-I/PE	Sleep diaries; *6FU*	41	-0.14	-0.76 to 0.47	0.668
Esaki et al. 2020	BB/CL glasses	Actigraphy	37	0.27	-0.38 to 0.91	0.420
Wake After Sleep Onset						
Henriksen et al. 2020	BB/CL glasses	Actigraphy	20	c	-2.06 to -0.17	**0.020**
Harvey et al. 2015	CBT-I/PE	Sleep diaries; *6FU*	41	-0.26	-0.87 to 0.36	0.415
Harvey et al. 2015	CBT-I/PE	Sleep diaries	41	0.03	-0.58 to 0.65	0.930
Esaki et al. 2020	BB/CL glasses	Actigraphy	37	0.18	-0.47 to 0.83	0.599
Sleep Efficiency						
Henriksen et al. 2020	BB/CL glasses	Actigraphy	20	1.00	0.07 to 1.93	**0.035**
Harvey et al. 2015	CBT-I/PE	Sleep diaries; *6FU*	41	0.66	0.03 to 1.29	**0.040**
Harvey et al. 2015	CBT-I/PE	Sleep diaries	41	0.34	-0.28 to 0.96	0.286
Esaki et al. 2020	BB/CL glasses	Sleep diaries	37	-0.45	-1.10 to 0.20	0.176
Total Sleep Time						
Henriksen et al. 2020	BB/CL glasses	Actigraphy	20	0.68	-0.22 to 1.58	0.139
Harvey et al. 2015	CBT-I/PE	Sleep diaries; 6*FU*	41	0.08	-0.54 to 0.69	0.811
Harvey et al. 2015	CBT-I/PE	Sleep diaries	41	-0.06	-0.68 to 0.55	0.859
Esaki et al. 2020	BB/CL glasses	Actigraphy	37	-0.04	-0.69 to 0.60	0.911
Total Wake Time						
Harvey et al. 2015	CBT-I/PE	Sleep diaries	41	-0.48	-1.11 to 0.14	0.132
Harvey et al. 2015	CBT-I/PE	Sleep diaries; *6FU*	41	-0.48	-1.10 to 0.15	0.132
Time in bed						
Harvey et al. 2015	CBT-I/PE	Sleep diaries	41	-0.33	-0.95 to 0.28	0.297
Harvey et al. 2015	CBT-I/PE	Sleep diaries; *6FU*	41	-0.21	-0.83 to 0.40	0.514
Sleep inertia						
Kaplan et al. 2018	RISE-UP/PE	Sleep diaries	38	0.22	-0.42 to 0.86	0.511
Psychosis						
Sit et al. 2018	BLT/DL	BPRS	40	-0.85	-1.50 to -0.20	**0.010**
Anxiety						
Sit et al. 2018	BLT/DL	HDRS-anxiety	40	-0.49	-1.13 to 0.14	0.131

Abbreviations: BB glasses, Blue-light Blocking glasses; BLT, Bright Light Therapy; BPRS, Brief Psychiatric Rating Scale; CBT-I, Cognitive Behavioural Therapy for Insomnia; CI, Confidence Intervals; CL glasses, Clear Lenses glasses; DL, Dim Light; FU, Follow-Up (the precipitating number indicates months); HDRS, Hamilton Depression Rating Scale; N, number of participants; PE, Psychoeducation

5.3.4 Registered Clinical Trials

Following the screening of 131 original registration records, five RCT registrations, all from clinicaltrials.gov, were included in this review (Beaulieu, NCT00590265; Jernelöv, NCT04130529; Morken, NCT01704352; Deckersbach, NCT01764035; Olie, NCT02936466). Overall, three out of the five trials plan to investigate euthymia, and recruit participants with a baseline insomnia comorbidity. Two of those trials also plan to administer CBT-I. Future literature in the area might also see the first RCT including polysomnography (one of the five trials), and the wider use of actigraphy (two of the five trials).

5.4 Discussion

This review constitutes the first comprehensive appraisal of the effects of psychological and behavioural interventions in BD for sleep and circadian rhythms, as observed in RCTs. Overall, there was limited evidence for the therapeutic capacity of such interventions. This was primarily due to the small number of studies and sample sizes, as well as the inconsistency in assessed outcomes, diagnostic characterisation, and treatment protocols.

According to the quality appraisal, all studies assessed mood symptoms, while only 48% assessed sleep or circadian rhythms. However, it is essential that sleep and circadian outcomes are adequately measured in BD research at large and especially in this research area. First, as a proof of concept, given that the interventions reviewed here are assumed to exert their treatment effects on mood via sleep and circadian pathways. Second, due to the importance of sleep and circadian outcomes on their own right. Sleep, activity, and energy levels are domains particularly salient to people for the self-monitoring of BD symptoms (Gordon-Smith et al., 2021), and to clinicians given their persistence to standard care (Ng et

al., 2015). Finally, sleep and circadian rhythms are presumed mediators of improved psychiatric and functional outcomes in BD. Their integration as endpoints in intervention RCTs will allow researchers to delineate the involvement of sleep and circadian rhythms in the multifactorial causation of BD.

The only therapeutic modality with enough data to meta-analyse was BLT, revealing a medium-to-large difference at post-treatment in depression symptoms (n_c=6; g=-0.74; p<0.001). A review of RCTs in non-seasonal depression showed a similar effect size (n_c= 7; standardised mean difference=-0.71; p<0.001) in favour of BLT as a single-component treatment (Al-Karawi & Jubair, 2016). Both of these findings contrast with the moderate and non-significant effect of -0.25 reported by a review of RCTs on BLT in bipolar depression (Takeshima et al., 2020). This discrepancy is possibly due to Takeshima et al (2020) choice to extract follow-up as opposed to post-treatment values for one study (Franchini et al., 2009) and to exclude another trial (Yorguner Kupeli et al., 2018) that we included. Findings for blue-light blocking glasses and CBT-I were mostly positive for sleep, morningness, and mood. Only mood symptoms were assessed in IPSRT trials, and results were conflicting. No individual trial containing a TSD element showed any significant effects on any domain examined. This finding is contrary to recent claims in support of the effectiveness of TSD for bipolar depression (Gottlieb et al., 2019; Ramirez-Mahaluf et al., 2020). However, those claims were based on a literature dominated by non-controlled studies or RCTs that compare TSD plus medication against TSD alone. This inconsistency in findings between RCTs and studies without comparators has previously been highlighted. In a recent review, the significant antidepressant effect of TSD in unipolar depression (Boland et al., 2017) disappears when non-controlled trials are excluded from the analysis (Freeman et al., 2020; Stewart, 2018). Our review of clinical trial registries suggests that future research might take into account the omission of sleep and circadian outcomes. Recently completed or ongoing trials contain self-report assessments of sleep disruption, and measures of circadian rest-

activity rhythms and sleep architecture, with the aim of elucidating the mechanistic role of sleep – and its treatment - in BD. Additionally, there is evidence of a plan to include more comprehensive assessments of functioning and quality of life.

Furthermore, there were several limitations in terms of the clinical characterisation of the BD groups in the included studies. First, no study investigated the differential effects of treatment on BD subtypes. This is particularly salient given that BD-I and BD-II differ in their response to sleep loss (Lewis et al., 2017) and their genetic liability to insomnia and hypersomnia (Lewis et al., 2020). Second, most of the included studies recruited people with BD in an acute illness phase (82%), usually depression (71%). This is expected due to the higher frequency, duration, and burden associated with bipolar depression compared to mania (Judd et al., 2002), as well as practical challenges with recruitment during a manic episode. However, this leads to a limited understanding of the efficacy of behavioural sleep and circadian treatments in acute mania, and their role in the maintenance of euthymic (more stable) mood and relapse prevention. Finally, only three studies (16%) recruited people with BD based on sleep or circadian disruption at baseline, rendering it possible that there was limited scope for improvement to begin with. Future RCTs might apply more rigid clinical characterisation, as the majority of registered trials report the recruitment of participants experiencing euthymia and a significant sleep disturbance at baseline.

Consensus on the features of the treatment protocols differed depending on intervention type. There were marked differences in the duration and intensity of BLT and the timing of treatment with blue-light blocking glasses. Interestingly, BLT was delivered mostly in the morning, with the only trial delivering BLT at mid-day not yielding significant improvements in depression or sleep quality (Sit et al., 2018). Although there is arguably no scientific consensus on the protocols of these interventions, recent findings about the neurobiological effects of light are likely to inform future literature in BD. For example,

there is suggestive evidence that low intensity or blue-enriched light might be equally effective as bright light in alleviating depressive symptoms (Gordijn et al., 2012; Maruani & Geoffroy, 2019; Meesters et al., 2011; Smith et al., 2009). Regarding other treatment modalities, studies including a TSD element adopted the recommendations of Benedetti et al (1997). All studies in the IPSRT literature followed a standardised treatment protocol. On some occasions, treatment development was informed by advances in experimental work, as evidenced by: the integration of IPSRT components in CBT-I (Harvey et al., 2015), a shift to personalised wake and sleep times for BLT (Wu et al., 2009), and the combination of single treatments to form the triple-chronotherapy intervention (Wu et al., 2009). According to the trial registries, two RCTs will look into the effects of CBT-I in BD, so the evidence base for this intervention might change in the near future. While there was inconsistency in monitoring and reporting of side-effect, no serious adverse events were reported, and side-effects were rare. Future trials would benefit from standardised and comparable reporting of safety (Condon et al., 2021), as well as from direct and prospective safety comparisons between the included interventions and pharmacological treatments. This is important because the interventions reviewed here appear to have minimal side effect burden, contrasting with pharmacological treatments for BD which show notable rates of discontinuation due to adverse events (Bai et al., 2020). As the field develops and interventions are examined through more trials, systematic appraisal through tools like GRADE can aid more conclusive observations regarding the quality of the evidence base. The primary strength of this review is the comprehensive appraisal of all outcomes, diagnostic features, and treatment parameters in RCTs of psychological and behavioural interventions in BD targeting sleep and circadian rhythms. However, inferences in this review are based on a limited number of studies. Only one meta-analytic model was computed, with all other interpretations in this review being based on single-trial effect sizes. Additionally, the included studies contain a small number of participants, with the median

number of recruited participants being 44. This observation is likely linked to the lack of a sample size justification in the included studies, as only 31.5% reported a power analysis. The small number of participants has implications in terms of the findings observed, as trials with low number of participants are only powered enough to detect the largest of effects. Moreover, studies on pharmacological sleep and circadian rhythm interventions, such as melatonin and other hypnotics, were excluded, limiting the inferences that can be made about the general therapeutic modulation of sleep and circadian rhythms in BD. Since only RCTs were included, the evidence base of this review looks notably different to that of other published reviews in the same research area (D'Agostino et al., 2020; Dallaspezia & Benedetti, 2020; Gottlieb et al., 2019, 2021; Humpston et al., 2020; Ramirez-Mahaluf et al., 2020; Takeshima et al., 2020). Finally, the inclusion of active control groups in four studies (Benedetti et al., 1997; C. Colombo et al., 2000; Franchini et al., 2009; Swartz et al., 2012) limits the extent to which the effects observed can be solely attributed to the action of the intervention under investigation.

6

Digital Sleep Intervention for Bipolar Disorder, the DIGIT-B Study

Contents

6.1 Background and Rationale

As covered in previous chapters, sleep and circadian disruptions are highly prevalent across all phases of BD, and are the most salient symptoms used by individuals to self-monitor their condition (Chevance et al., 2020; Gordon-Smith et al., 2021). Amongst these sleep and circadian disruptions, insomnia is the most prevalent disorder, with insomnia symptoms being ubiquitous in episodic phases, and with up to 55% of people in euthymic phases meeting the diagnostic criteria for a comorbid diagnosis of insomnia disorder (Harvey et al., 2005).

CBT-I is the recommended first line of treatment for insomnia either as a standalone condition or comorbid with other mental health diagnoses (Riemann et al., 2023). Nevertheless, hypnotic medication remains the most common clinical response to insomnia

(Crescenzo et al., 2022; Siriwardena et al., 2010), with lack of trained therapists, limited resources, accessibility constraints, and low awareness among healthcare professionals being some of the proposed factors driving this phenomenon (Crescenzo et al., 2022; Soh et al., 2020).

There is only one published pilot RCT of CBT-I in BD (Harvey et al., 2015), and an uncontrolled feasibility trial of group-delivered CBT-I (Jernelöv et al., 2022). Both studies recruited people in euthymia and found CBT-I to be safe, feasible and effective in reducing insomnia symptoms both at post-treatment and 3-month follow up. Despite the positive findings, establishing scalable sleep and circadian interventions in BD remains a challenge, given current treatment modalities involve extensive face-to-face treatment protocols. As such, this present study aims to investigate the potential benefits of a digital CBT-I delivered to people with BD.

In insomnia research, digital CBT-I has been found to be efficacious in reducing night-time and day-time symptoms of insomnia (Espie et al., 2019; Gao et al., 2022; Soh et al., 2020) and improving depression symptoms (Cheng et al., 2019; Henry et al., 2021). The most updated clinical guidelines for the treatment of insomnia recommended CBT-I for the treatment of insomnia (Riemann et al., 2023). In the UK, a digital CBT-I treatment, Sleepio, was the first digital therapeutic to be ever receive accreditation by NICE in 2022, establishing Sleepio as a cost-saving option for treating insomnia (National Institute for Health and Care Excellence, 2022).

The aim of our study was to examine the feasibility, acceptability and safety of a digital CBT-I in BD, and provide preliminary evidence on potential efficacy. We focused specifically on people with BD-II reporting symptoms of probable depression and insomnia, while our study was also the first investigation of CBT-I in BD to integrate a mixed methods approach, presenting both quantitative and qualitative findings.

6.2 Methodology

6.2.1 Study Design and Setting

The DIGIT-B study was a single arm mixed-methods trial, designed to pilot a digital CBT-I intervention for people with BD-II. The study contained a single treatment arm, so all reported comparisons are within subjects. Both quantitative and qualitative assessments were employed. The study was conducted fully remotely in 2022-2023, recruiting participants across the United Kingdom. Ethical approval was obtained by the University of Oxford Medical Sciences Interdivisional Research Ethics Committee (Ref: R81156/RE002).

6.2.1 Participant Information

The intended sample size was pre-defined at 25 people. The number was decided based on the work of Whitehead et al. (2016) on the use of pilot studies. For main trials designed with 90% power, two-sided 5% significance and expecting to yield small effect sizes ($0.1 \leq d < 0.3$), the recommended size of the pilot study was 25 participants. This number was also deemed appropriate to get a sufficient level of engagement with the intervention and study procedures and, allow for enough participants in the semi-structured interviews

The inclusion criteria included: (1) self-reported diagnosis of BD-II that would later be confirmed by the researcher using the Structured Clinical Interview for the DSM-5; (2) a positive screen for depressive phase as indexed by a score of 6 and above in the Quick Inventory for Depressive Symptomatology (QIDS≥6), and a score of 5 and lower in the Altman Self Rating Mania Scale (ASRM≤5); (3) endorsement of symptoms of insomnia disorder as indexed by a score of 10 and above in the Insomnia Severity Index (ISI≥10); (4) for assessment of hypomania, symptoms to remain stable at week 2 prior to the participant accessing the treatment; (5) access to a laptop or desktop computer and a phone and reliable

internet access either at home or work; (6) being able to read and understand English; and (g) living in the UK.

The exclusion criteria included: (1) engaged in psychotherapy for insomnia; (2) previous or current participation in online sleep treatments; (3) psychiatric comorbidity with psychosis; (4) diagnosis of epilepsy or other neurological disorder, (5) diagnosis of mild cognitive impairment or dementia; (6) meeting the threshold of a probable sleep related movement disorder or sleep related breathing disorder in the Brief Sleep Disorders Screen; (7) reported diagnosis of a sleep related movement disorder or sleep related breathing disorder, central disorder of hypersomnolence or parasomnia; (8) serious physical health concerns necessitating surgery or with a survival prognosis of < 6 months; (9) habitual night shift, evening, or rotating shift-workers; (10) suicidal thoughts as established by the Columbia Suicide Severity Rating Scale item or history of recent suicide attempt in the past 12 months; (11) psychiatric hospital admission in the past year, or crisis team support within the past year; (12) clinically concerning alcohol misuse and dependence, operationalised a score of 20 or above in the Alcohol Use Disorders Identification Test (AUDIT≥20); (13) illicit drug use.

6.2.3 Outcomes

Table 6.1 describes the schedule for all assessments in the DIGIT-B study.

Feasibility. The study was registered during data collection, but after our pre-specified sample size was achieved. As such, feasibility was primarily assessed on the basis of retention and adherence. Retention was defined as the percentage of participants providing post-treatment data for the insomnia outcome. When applicable, the reason for drop-outs and discontinuations was reported. Adherence was defined as the percentage of participants completing at least 4 out of 6 treatment sessions.

Acceptability. Acceptability was assessed using a modified theory informed acceptability measure developed for use in healthcare interventions (Sekhon et al., 2022). The questionnaire utilises a 5-point Likert scale to measures eight domains of acceptability, namely: affective attitude, burden, ethicality, perceived effectiveness, intervention coherence, self-efficacy, opportunity costs and general acceptability. Our modified version did not include a question on ethicality and the questions on perceived effectiveness and self-efficacy were modified. As opposed to the original version where 'no opinion' is scored as 5, in our modified version this answer was coded as 0 to avoid a positive bias. Following scaling, total scores on the questionnaire ranged from 1 to 10, with higher scores reflecting higher acceptability.

Safety. Adverse events were recorded at pre-treatment (i.e. for the two weeks prior to the start of treatment), mid-treatment and post-treatment. There is no evidence that digital CBT-I causes serious harm, so the likelihood of a serious adverse event occurring in our study was deemed as low. Following agreed guidelines, all serious adverse events were assessed on their seriousness, expectedness and relatedness. Planned hospital visits and changes unrelated to participants' clinical state were not reported. Serious adverse events were defined as (a) any medical occurrence that results in death, (b) any suicide attempts, and (c) any admission to secure units.

Safety was also assessed through symptom monitoring of suicide and hypomania at mid-treatment and post-treatment. Suicidality was measured using item 12 on the QIDS-16, thoughts on death and suicide. Any new reports of daily suicidal thoughts with potential plan (i.e. a score of 3) were reported as an adverse event. Hypomania was measured using the ASRMS. An adverse event here was defined as any score higher than 5, interpreted as high probability of a hypomanic episode.

Questionnaires. We also measured several other domains related to sleep, mental health and functioning using a range of questionnaires. Table 6.1 contains a list with all questionnaires that we employed and the timepoint at which they were administered. Details on the ISI, PSQI, MEQ and GAD-7 are included in Chapter 4.

Quick Inventory for Depressive Symptomatology (Rush et al., 2003). This measure is a shortened version of the 30-item Inventory of Depressive Symptomatology, and it includes nine domains of depression, measured across 16 items. Each one of these domains can be attributed a score between zero and three, providing a total score of 0-27. In terms of their clinical utility, scores of less than five denote typical symptomatology, 6-10 signify mild depression, 11-15 moderate depression, 16-20 severe depression, and 21-27 very severe depression. Meta-analytic studies have shown QIDS to have good internal consistency (Cronbach's α: 0.69-0.89) (Reilly et al., 2015), and be an appropriate depression measure for trials recruiting focused on people with BD (Bernstein et al., 2009).

Altman Self-Rating Mania Scale (Altman et al., 1997). The ASRM is a five-item measure of manic symptomatology, with questions on the domains of mood, self-confidence, sleep, speech and activity levels. The questions concern the past week and are scored on a scale between 0 (absence of symptomatology) and 4 (symptoms present nearly every day), with total scores ranging from 0 to 23. A score of 6 or higher indicates possible (hypo)mania. A meta-analysis of studies using the ASRMS reported good internal consistency (Cronbach's α: 0.57-0.84) (Meyer et al., 2020).

Behavioral Activation for Depression, Short Form (Manos et al., 2011). The BAD is a 9-item scale measuring the degree of behavioural activation related to depression. Each item is scored on a 7-point scale ranging from 0 (not at all) to 6 (completely), resulting in a total possible score of 0-54. Higher scores indicate greater levels of activation. The scale has good internal consistency (Cronbach's α: 0.82) (Manos et al., 2011).

British Columbia Cognitive Complaints Inventory (Iverson & Lam, 2013). This is a scale aimed at measuring subjective cognitive functioning, covering concentration, memory, trouble expressing thoughts, word finding, and problem-solving. The 6 included items are rated on a 4-point scale ranging from 0 (not at all) to 3 (very much). Total scores range from 0 to 18, with higher scores indicating greater severity of cognitive complaints. The measure has good internal consistency for people with depression (Cronbach's α: 0.86) (Iverson & Lam, 2013).

Warwick-Edinburgh Mental Wellbeing Scale (Tennant et al., 2007). The WEMWS consists of 14 items measuring mental wellbeing, probing elements of affective-emotional aspects, cognitive-evaluative dimensions and psychological functioning. The included items are scored from 1 (none of the time) to 5 (all of the time), resulting in total scores of 14-70, with higher scores reflecting better mental wellbeing. WEMWS shows good internal consistency (Cronbach's α: 0.89-0.91) (Tennant et al., 2007).

Work and Social Adjustment Scale (Mundt et al., 2002). The WSAS assesses the extent to which an individual's mental health condition impedes their ability to work, manage home responsibilities, engage in social activities, maintain close relationships, and pursue leisure activities. It includes 5 items rated on a 9-point scale ranging from 0 (not at all) to 8 (very severely impaired). Total scores range from 0 to 40 and higher scores denote higher dysfunction. WSAS has good internal consistency outcomes when administered both to people with depression (Cronbach's α: 0.81-0.94) (Mundt et al., 2002) and insomnia (Cronbach's α: 0.91) (Jansson-Fröjmark, 2014).

Sleep Diary. Participants kept two types of diaries throughout the study, between baseline (week 0) and post-treatment (week 12). To compare sleep diary measures across timepoints, all measures were averaged across three 14-day periods, namely: baseline (weeks0-2), mid-treatment (weeks 5-7), and post-treatment (weeks 10-12). The meeting for

each respective timepoint (baseline, mid- and post-treatment) reflected the endpoint of this 14-day period. Based on previous published literature (Kyle et al., 2023), if fewer than 4 days of a sleep diary were completed for a timepoint, then the diary scores for that participant for the corresponding timepoint were treated as missing.

In the first two weeks, between baseline (week 0) and pre-treatment (week 2), participants completed a modified version of the consensus sleep diary (Carney et al., 2012). This diary was completed twice daily, in the morning and evening. In the morning, participants reported their SOL, WASO, TST and SE for the preceding night, rated their sleepiness level on a visual analogue scale, and answered a 5-point Likert scale about their sleep quality, restfulness, dreaming and cognitive arousal while in bed. In the evening, they rated their sleepiness level on another visual analogue scale, and answered questions on napping, caffeine and alcohol consumption during the day. They also rated on a 5-point Likert scale the extent to which 6 mood items described their mood throughout the day. These items were included based on published literature on prospective mood monitoring in BD (Tsanas et al., 2016), and included feeling: sad, anxious, irritable, happy, energetic and relaxed.

The second diary was embedded within Sleepio. It was completed once a day and participants were asked to report their SOL, WASO, TST and SE for the preceding night, and rate the quality of their sleep on a 5-point Likert scale.

Actigraphy. Concurrently with the sleep diary, between baseline (week 0) and post-treatment (week 12), participants wore an actigraph watch (MotionWatch 8, CamNTech Ltd.) on their dominant wrist. In line with recording settings from previous studies in clinical populations (Maurer et al., 2020), the watches were set to record activity in tri-axial mode and light over 60-second epochs. Participants were instructed to press an event marker button on the watch when initiating sleep and upon their final awakening. Prior to actigraphy

scoring, a guideline manual was written up and reviewed by members of the research team. Herein, events markers were used to demarcate the start and end of a sleep episode. In the absence of these markers, a sleep period was defined based on bed and rise time specified in the sleep diary or by indicators of light and activity measures. All corresponding rest-activity variables calculated by the validated build-in algorithm of the MotionWare software 1.4.20. Similar to sleep diaries, rest-activity measures were averaged across 14-day periods to define the baseline, mid- and post-treatment timepoints, with each respective meeting indicating the endpoint of this period. Again, similar to sleep diaries, a minimum of 4 days per assessment timepoint was required to be included in the actigraphy analysis.

Semi-structured interviews. A semi-structured interview schedule was developed through an iterative process which involved: preparing a preliminary schedule based on existing published literature on sleep and BD, reviewing the preliminary schedule with clinicians in our research team specialising in BD and/or insomnia, and finally consulting with people with BD from the Patient and Public Involvement group of the NIHR Oxford Biomedical Research Centre, to establish a final interview schedule. The final schedule focused on 4 key topics: (a) personal experience of sleep problems and their impact on mood and daily life, (b) contentment with the clinical response, if any, to reported sleep problems, (c) overall experience in the study and with the Sleepio app, and (d) perceived benefits and barriers around the use of digital interventions for mental health. The schedule was used flexibly, with additional prompts employed to encourage elaboration and stimulate discussion. Appendix 5 in the Supplementary Materials includes the semi-structured interview schedule. The participants' own vocabulary was used by the interviewer in relation to reported symptoms and disruptions. All interviews were conducted virtually. Interviews were audio-recorded and transcribed verbatim.

Table 6.1 Schedule for quantitative and qualitative assessments in the DIGIT-B study

Assessments	Domain	Baseline (week 0)	Pre-treatment (week 2)	Mid-treatment (week 7)	Post-treatment (week 12)	Follow-up (week 24)
Questionnaires						
Demographic questionnaire	Demographics	✓				
Insomnia Severity Index	Insomnia	✓	✓	✓	✓	✓
Pittsburgh Sleep Quality Index	Sleep Quality	✓		✓	✓	✓
Morningness-Eveningness Questionnaire	Chronotype	✓			✓	✓
Quick Inventory for Depressive Symptomatology	Depression	✓	✓	✓	✓	✓
Behavioural Activation for Depression	Depression activating behaviours	✓			✓	✓
Altman Self-Rating Mania Scale	Hypomania	✓	✓	✓	✓	✓
Generalised Anxiety Disorder-7	Anxiety	✓		✓	✓	✓
British Columbia Cognitive Complaints Inventory	Cognition	✓			✓	✓
Warwick-Edinburgh Mental Wellbeing Scale	Mental Wellbeing	✓			✓	✓
Work and Social Adjustment Scale	Work and Social Functioning	✓			✓	✓
Sleep Diary	Sleep behaviours	✓	✓	✓	✓	✓
Actigraphy	Rest-Activity rhythms	✓	✓	✓	✓	✓
Sem-structured Interview	Lived experience perspective				✓	

6.2.4 Intervention

The digital CBT-I was delivered through the Sleepio programme from Big Health Ltd. Sleepio can be accessed via a laptop or computer on the associated website (www.sleepio.com), or via a phone or tablet device using the Sleepio app. The program is fully automated, and its underlying algorithm feeds the delivery of information, support, and advice in a personally tailored manner.

The intervention is delivered in 6 sessions lasting approximately 20 minutes each. Table 6.2 summarises the basic elements of each treatment session. The content of the

intervention is based on CBT manuals for insomnia and includes behavioural (i.e. sleep restriction, stimulus control, and relaxation), cognitive (i.e. paradoxical intention, cognitive restructuring, mindfulness, positive imagery, and putting the day to rest), and educational (i.e. psychoeducation and sleep hygiene) components. The programme is interactive, and content is presented by an animated virtual therapist. Prior to the start of the treatment, participants are asked to complete a questionnaire regarding their sleep and mental health. In the DIGIT-B study, we asked participants in our study to declare their BD diagnosis at this stage. This is because the Sleepio programme and treatment goals are tailored based on the answers to this questionnaire. Following a declaration of a mental health related diagnosis, the sleep restriction therapy window is set to 6 hours minimum.

During Sleepio, participants complete a daily sleep diary, which is used by the programme to provide tailored, personalised advice. Participants are also able to set daily phone notifications on the Sleepio app to prompt them to fill their sleep diary. An option is also provided for the reminders to be sent via email or text message. Additionally, participants gain access to an online community forum, and a library of information on sleep and sleep disorders. They can also access their case file, containing a progress review, a reminder of strategies to try out between sessions, an agreed sleep schedule, and a list of further readings. Sleepio also provides online analytics which can be used to monitor adherence by assessing how many sessions were completed and the number of weeks to complete the course. Participants were able to maintain unrestricted access to Sleepio for 12 months after signing up.

Table 6.2 Summary of Sleepio treatment components

Session	Summary presented to participants	Focus of each treatment session
1	*Learn about the causes of poor sleep and set your goals for the programme*	• Formulation • Goal setting • Diary keeping • Motivational contract
2	*Address lifestyle barriers to sleep and learn how to improve your bedroom*	• Sleep hygiene (lifestyle and bedroom)

3	*Boost your bed-sleep connection through sleep restriction*	• Progressive relaxation • Thought checker • Sleep hygiene (schedule) • Stimulus control • Sleep restriction
4	*Learn a range of cognitive techniques that help you clear your mind for sleep*	Depending on priorities: • Cognitive restructure • Cognitive shuffle • Autogenic training • Imagery • Mindfulness • Paradoxical intention
5	*Grow your toolkit with some final sleep techniques tailored to what you need*	• Review goals • Reinforce motivation
6	*Review important topics and plan for the future*	• Review goals • Plan for the future

6.2.5 Procedure

Figure 6.1 illustrates the DIGIT-B study procedure.

Following positive screening based on the inclusion and exclusion criteria, participants were invited for an online meeting where the diagnosis was confirmed using the Structured Clinical Interview for the DSM-5. If eligibility was established, then they progressed to the baseline meeting (week 0). Following the baseline meeting, participants entered a 2-week monitoring period where they were offered two meetings with a member of the study team. At the end of this period, people were invited to another meeting, where eligibility was re-assessed to ensure the maintenance of low hypomania scores, and if met, they were given access to the treatment.

The treatment phase lasted 10 weeks and was delivered through Sleepio. The treatment contained 6 sessions that became available to participants weekly. Participants were contacted again for a 'mid-treatment' assessment on week 7, and a post-treatment assessment on week 12. During all assessments participants completed a series of questionnaires, and during the post-treatment assessment the participants were also invited

to a semi-structured interview. From baseline to post-treatment, participants also wore an actiwatch and completed daily sleep diaries.

Three months post-treatment (week 24) participants were sent a link to complete a final series of online questionnaires as part of the follow-up assessment. All meetings took place on Microsoft Teams.

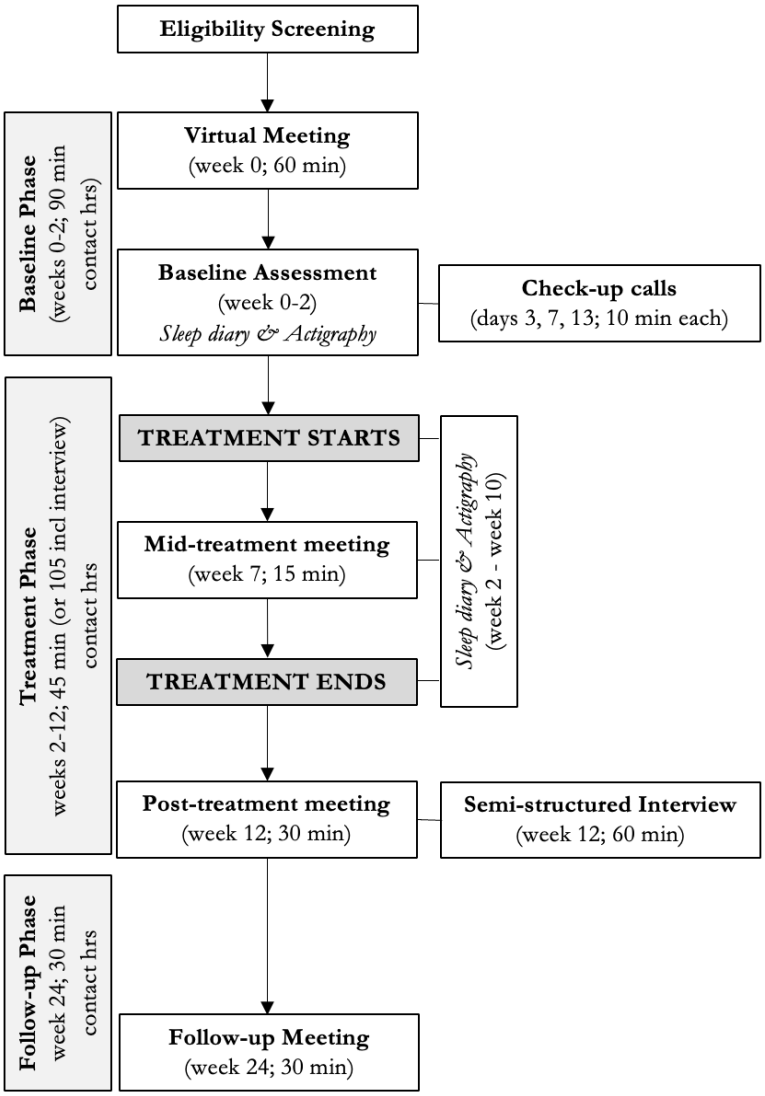


Figure 6.1 The DIGIT-B Study Procedure

6.2.6 Analysis Plan

All quantitative analyses were conducted in the statistical software R 4.3.1 (16/06/2023), and, unless otherwise specified, were registered during recruitment. The

qualitative analysis was performed in the software NVivo v14, and the use of a thematic analysis was registered.

Missing values and descriptive analyses. Although a full dataset was sought, missing data were expected. Single missing items from otherwise complete questionnaires were replaced using mean imputation. Means and standard deviations were estimated for continuous variables; while frequencies and percentages were estimated for binary and categorical variables. For all values 95% confidence intervals were also estimated.

Questionnaire and Sleep Diary data. A linear mixed model was fitted on all questionnaire measures. The analysis focused on descriptive statistics, effect sizes and 95% confidence intervals, following published recommendations that this should be the focus of pilot trials (Lancaster et al 2004). Timepoint was the fixed covariate, and a participant-specific random covariate was added to account for repeated measures. Effect sizes were defined as the standardised mean change between baseline (week 0) and each subsequent timepoint. We followed conventional benchmarks of referring to effect sizes as small for d=0.20, moderate for d=0.50 and large for d=0.80 (Cohen, 2013). However, we are also aware of the arbitrary nature of such conventions (Funder & Ozer, 2019), and our inferences bases on these effect sizes are contextualised throughout the discussion. All questionnaire outcomes were modelled following the same principles. Sleep diary outcomes, namely SOL, WASO, TST and SE, were also modelled following the same principles.

Actigraphy data. Sleep periods were scored based on a standard operating procedure established and maintained by the research team. Parametric sleep outcomes, namely SOL, WASO, TST and SE were derived via the validated build-in algorithm of the MotionWare software 1.4.20. They were then included as outcomes in linear mixed linear, similar to questionnaires and sleep diary data.

Post-hoc quantitative analyses. Following the registered analyses, we carried out two post-hoc sensitivity analyses.

First, we sought to conduct a sensitivity analysis to control for the effect of entering a study but not accessing treatment immediately. Consequently, for the outcomes ISI, QIDS and ASRMS that were assessed twice before the start of treatment, once at baseline (week 0) and again at pre-treatment (week 2), we averaged the scores of these two timepoints and entered them as one timepoint in our linear mixed models.

Second, instead of a single imputation model for missing values in our questionnaire data (like the mean imputation method that we had registered), we applied a multiple imputation model to account for missing values. Single imputations of missing values can lead to biased results given that we are uncertain of the nature of missing data (Sterne et al., 2009). Multiple imputation models deal with this uncertainty by creating several unique yet plausible imputed datasets, and then combining results obtained from each one of these imputations (Sterne et al., 2009). There are two widely used approaches to multiple imputation modelling: multiple imputation based on the multivariate normal distribution (Schafer, 1997), and multivariate imputations based on fully conditional specifications, implemented through chained equations modelling (Van Buuren et al., 1999). Although both approaches rely on missing data occurring in nonmonotone patterns, and although in stimulation studies they typically produce comparable results (Lee & Carlin, 2010), they are based on distinct theoretical frameworks. Out of the two, fully conditional/chained equations modelling is more flexible as it does not rely on the assumption of multivariate normality. As such, it was the method we chose to use for our missing data sensitivity analysis.

In chained equations modelling, conditional distributions are estimated for each variable that contains missing values, conditional on all the other variables in the imputation

model (Lee & Carlin, 2010). Imputations are generated by calculating each distribution in turn. Observed cases are used for the variables being considered, and imputed values are used for the other variables at that iteration and imputing missing values (Lee & Carlin, 2010). As mentioned above, conditional distributions are not restricted to being normal. Although the more imputations, the more precise the final model, the chosen number of imputations in a chained equations model is arbitrary. Published guidance for chained equation models indicates producing as many imputations as the rate of missingness for each variable (White et al., 2011). For example, if 23% of the cases of a variable are missing, then at least 23 imputations should be generated to estimate missing data. As such, our chained equation modelling contained as many iterations as the rate of missing values for each variable. After complete datasets were acquired through this missing data imputation method, new mixed-effects models were fit on all questionnaire data.

Qualitative analysis. Qualitative data acquired through the semi-structured were analysed using thematic analysis as outlined by Braun and Clarke (2006). Our qualitative approach was descriptive in nature and focused on learning from the participants' perspective rather than generate theory. In line with other descriptive qualitative studies in health interventions (Astbury et al., 2020), our ontological framework was relativism, and our epistemological endeavour was grounded in subjectivity. This approach is suitable for novel interventions in areas where there is limited qualitative information (Astbury et al., 2020).

The analysis followed six phases: familiarisation, generation of initial codes, searching for relevant themes, review of themes, definition and naming of such themes, production of report. First, all transcripts were read concurrently with the audio recording to ensure accuracy and familiarity with the data. Then, transcripts were uploaded to NVivo and conducted an iterative line-by-line coding of each transcript. The resulting codes were

then grouped in broader categories. In turn, these categories were organised in candidate themes and a draft thematic map was developed. The resulting themes and categories were shared with the broader research group for review, and were adjusted when necessary. Once the themes were refined, the team reflectively reviewed the entire analysis until consensus was reached.

6.2.7 Registration, Data and Code Availability

The methods and analysis plan were both registered and are publicly available on a study dedicated Open Science Framework page: https://osf.io/yhcd3/. The registration was submitted during data collection but after recruitment had already concluded, thus we do not refer to a pre-registration. The methodology (including the power analysis to support sample size calculation) was established prior to recruitment, and can be seen in our ethics protocol, also available on Open Science Framework. The analysis plan was first devised for the registration document. At the point of registration, no participant had provided complete data, and no preliminary analyses had taken place. The only deviation from our registered protocol was the fact that we did not use the GGIR package in R to analyse our actigraphy data, given the sufficiency of the outcomes provided directly from the Motioware software. Appendix 4 in the Supplementary Materials contains the study registration.

The source code will become available upon peer-reviewed publication of our study. All participants provided consent for their de-identified data to become publicly accessible, and our research team will seek to do this upon peer-reviewed publication of the study results.

6.2.8 Out of Scope Data

Although the greatest proportion of collected data in the DIGIT-B study were included in this thesis, some of the data are outside the scope of my doctoral work due to time and word limitations. These data are not included in the analysis plan of my study

registration, and are not discussed further in this chapter. These data include the mood, nightmare, sleepiness and sleep quality items of the baseline sleep diary questionnaires, as well as the Sleepio diaries and actigraphy during treatment but outside the predetermined 14-day timepoints of mid- and post-treatment. They also include non-parametric circadian outcomes of actigraphy, such as L5, M10, intradaily stability, interdaily variability, and relative amplitude, as well as light data captured by actigraphy. Although these outcomes are outside the scope of my doctoral work, our team intends to use them for future publications.

6.3 Quantitative Results

In terms of recruitment, 128 people completed the screening questionnaire Of those, 31 people (24%) screened positive. Table 6.3 illustrates the primary reasons for exclusion. The total here does not equal 100% given that participant could be ineligible for more than one reason. The two primary reasons for exclusion were probable sleep-related breathing or movement disorders, based on reported scores from the Brief Sleep Disorders Screen. Notably, symptom self-report is not adequate for the diagnosis of either type of disorder, so these percentages are likely to overestimate the number of people that would be otherwise diagnosed in a clinical setting.

Table 6.3 Reasons for exclusion from the DIGIT-B study for participants that completed initial screen

No diagnosis of Bipolar Disorder-II	9 (9.29%)
Younger than 18 or older than 65	3 (3.09%)
No reliable internet connection	1 (1.03%)
No English language proficiency	0 (0.00%)
Residing outside the UK	0 (0.00%)
Typical shift workers	3 (3.09%)
Comorbid diagnosis of schizophrenia	10 (10.30%)

Hospitalisation in mental health facility in the last 12 months	14 (14.43%)
Ill physical health	0 (0.00%)
Comorbid diagnosis of dementia or mild cognitive impairment	2 (2.06%)
Comorbid diagnosis of a severe neurological disorder	0 (0.00%)
Illicit drug use	3 (3.09%)
Low insomnia score, based on the Insomnia Severity Index	4 (4.12%)
Probable sleep-related breathing disorder, based on the Brief Sleep Disorders Screen	33 (34.02%)
Probable sleep-related movement disorder, based on the Brief Sleep Disorders Screen	27 (27.83%)
Comorbid diagnosis of a sleep-related movement disorder	1 (1.03%)
Low depression score, based on the Quick Inventory for Depression Symptomatology	5 (5.15%)
Severe suicide ideation, based on the Columbia Suicide Severity Rating Scale	8 (8.25%)
High hypomania score, based on the Altman Self Rating Mania Scale	0 (0.00%)
High alcohol use score, based on the Alcohol Use Disorders Identification Test	3 (3.09%)

Of the 31 people that screened positive, 26 met up with the research team and completed the full screening assessment. Two cases did not meet the criteria for a BD-II diagnosis based on the subsequent Structured Clinical Interview for the DSM-5 conducted by our team. So, 24 people were recruited out of our intended sample size of 25. These 24 people all completed the 2-week baseline to pre-treatment phase. At the end of this phase, two people screened positive for possible hypomania in the ASRMS and were subsequently excluded and did not progress to the treatment phase. Two people indicated that they would not like to progress to the treatment phase due to personal reasons, but were interested in providing data at their pre-allocated timepoints, and two more stopped responding to the research team and never entered the treatment phase. In the end, 18 people accessed treatment.

The demographic characteristics of the recruited sample are presented in Table 6.4. More than 80% of our sample was female and all participants were white. The age of our participants ranged from 20 to 63, with a mean of 41.64 years (sd=11.15). Most people in our sample were not in full time employment, with 45.45% reporting being in full-time employment. About 41% of the sample did not attend higher education, but 59% had obtained at least an undergraduate degree. About 41% did not report any physical health problems, and of those that did asthma was the most frequent diagnosis (22.73%). Over 95% of the sample was receiving prescribed medication, with the mean number of concurrent medications being 2.50. Antidepressant medication was the most common medication class, with 59% of participants reporting currently being prescribed antidepressants. Half of the sample was receiving anticonvulsant medication, 31.82% was receiving lithium and 27.27% antipsychotic medication. Over a third of the sample (36.36%) was receiving hypnotic medication, although is all cases this was on an as-needed basis with self-monitoring by the participants themselves. The majority of people were not using a sleep-tracking device at the time of recruitment. Mean scores of alcohol use were also low at screening (3.56 [sd=4.99]).

Table 6.4 Baseline characteristics of the DIGIT-B sample

Age in years, mean (sd)	41.64 (11.15); 20.00-63.00
Gender, no (%)	
Male	4 (18.80%)
Female	18 (81.82%)
Ethnicity, no (%)	
White	22 (100.00%)
Employment type, no (%)	
Full-time occupation	10 (45.45)
Part-time occupation	4 (18.18)
University student	1 (4.55%)
Unemployed	7 (31.82)
Education level, no (%)	
Completed secondary education or equivalent	1 (4.55%)
Apprenticeship, trades certificate or equivalent	1 (4.55%)
Completed A levels, International Baccalaureate or equivalent	7 (31.82%)
Undergraduate degree	5 (22.73%)
Postgraduate degree	8 (36.36%)

Physical health comorbidity	
None	9 (40.91%)
Asthma	5 (22.73%)
Cardiovascular disorder	3 (13.64%)
Diabetes	1 (4.55%)
Gastrointestinal disorder	3 (13.64%)
Dermatological disorder	1 (4.55%)
Current prescribed psychotropic medication, no (%)	
None	1 (4.55%)
Lithium	7 (31.82%)
Antipsychotic medication	6 (27.27%)
Anticonvulsant medication	11 (50.00%)
Antidepressant medication	13 (59.10%)
Hypnotic medication	8 (36.36%)
Anxiolytic medication	1 (4.55%)
Wakefulness promoting agents	1 (4.55%)
Mean number of prescribed psychotropic medication, no (%)	2.50 (1.24); 1.00-5.00
Non-prescription medication for sleep, no (%)	
None	22 (100.00%)
Sleep tracking device, no (%)	
None	16 (72.73%)
Motion detection device	6 (27.27%)
Alcohol Use Disorders Identification Test, mean (sd)	3.56 (4.99); 0-19

Abbreviations: SD, Standard Deviations

6.3.1Feasibility, Acceptability and Safety

Of the 20 people that were scheduled to provide post-treatment data, i.e. 18 that accessed treatment and 2 that did not but kept contact with the research team, 18 (90%) provided data for the ISI, which was our registered determinant of retention. Table 6.5 provides the number of people who completed each of the 6 Sleepio sessions. Our registered measure of adherence was the completion of at least 4 out of 6 sessions, which 83.33% of the eligible participants did.

Table 6.5 Sleepio treatment completion rate

Completed sessions	n	Percentage
1	18	100.00%
2	18	100.00%
3	16	88.89%
4	15	83.33%
5	11	61.11%
6	10	55.56%

Table 6.6 indicates the acceptability ratings for the nine items of our modified theory informed acceptability measures. One participant was excluded from these estimates as they never entered the treatment phase, and the majority of their responses in this questionnaire were 'no opinion'. Overall, scores were comparable across all items, with the lowest mean derived for the domain of functioning 'Sleepio has improved my daily functioning' (2.29 [1.45]), and the highest for the domain of importance 'Improving my sleep is important to me' (3.76 [0.44]). The total mean score was 7.42 (sd=1.01) out of 10, indicating a high level of acceptability of the Sleepio intervention in our sample.

Table 6.6 Sleepio acceptability based on the modified theory informed acceptability measure

	n	**Minimum rating by participants***	**Maximum rating by participants**	**Mean (SD)**
Did you like or dislike Sleepio?	17	2	4	3.35 (0.61)
How much effort did it take to engage with Sleepio?	17	3	4	3.06 (1.52)
Improving my sleep is important to me	17	3	4	3.76 (0.44)
Sleepio has improved my sleep	17	2	4	3.12 (0.99)
Sleepio has improved my mood	17	2	4	2.47 (1.33)
Sleepio has improved my daily functioning	17	2	4	2.29 (1.45)
At the time, it was clear to me how Sleepio would improve my sleep	17	2	4	2.47 (1.07)
Engaging with Sleepio interfered with my other priorities	17	1	4	2.65 (1.90)
How acceptable was Sleepio to you?	17	3	4	3.53 (0.51)
TOTAL MEAN SCORE	17	5.00/10	8.61/10	7.42 (1.01)

** These ratings exclude 0 which was given when the 'no opinion' option was selected. They also do not include one participant that never entered the treatment phase, as so the majority of their answers in this questionnaire were 'no opinion'.*
Abbreviations: SD, Standard Deviations

In terms of safety, no serious adverse events were reported. Additionally, no participant at any timepoint reported any daily suicidal thoughts with potential plan as measured using the QIDS. Regarding hypomania, 2 participants reported a high ASRMS score at mid-treatment, and 4 at post-treatment. These scores were no higher than 7, and as it can be seen on Table 6.7, they were predominantly driven by high ratings on the items corresponding to talkativeness and activity.

Table 6.7 Item based unadjusted means and standard deviations for the Altman Self Rating Mania Scale

	Timepoints				
	Baseline	**Pre-treatment**	**Mid-treatment**	**Post-treatment**	**Follow-up**
Symptoms	**n=22**	**n=21**	**n=20**	**n=18**	**n=19**
1. Happiness	0.23 (0.43)	0.38 (0.50)	0.60 (0.60)	0.67 (0.69)	0.53 (0.70)
2. Confidence	0.18 (0.39)	0.19 (0.40)	0.40 (0.50)	0.39 (0.61)	0.37 (0.68)
3. Sleep	0.45 (0.96)	0.10 (0.30)	0.25 (0.55)	0.06 (0.24)	0.53 (0.77)
4. Talkativeness	0.55 (0.80)	0.29 (0.46)	0.50 (0.61)	1.89 (0.96)	2.21 (0.85)
5. Activity	0.14 (0.47)	0.29 (0.46)	0.50 (0.83)	0.94 (1.00)	1.16 (0.76)
Total Score	1.55 (1.90)	1.24 (1.37)	2.25 (2.05)	3.94 (1.80)	4.79 (2.10)

6.3.2 Questionnaire Results

Table 6.8 presents the unadjusted mean score for all questionnaires at each timepoint, accompanied by the standard deviation and number of participants who provided usable data. The table also displays the adjusted mean difference between baseline (week 0) and each subsequent timepoint, and the standardised effect size, each accompanied by 95% CIs. Figure 6.2 illustrates the effect size and 95% CIs for all outcomes at post-treatment and follow-up. Figure 6.3 illustrates the unadjusted scores across timepoints. Table 6.10 illustrates the proportion of people meeting cut-off points for a possible diagnosis according to the respective questionnaire used.

Our registered primary clinical outcome was the baseline to post-treatment difference in insomnia scores on the ISI. As shown in both Table 6.6 and Figure 6.3, there was a large improvement in insomnia scores at post-treatment, when compared to baseline (d=-1.87; 95%CI: -2.77 to -0.98) that was maintained at follow-up (d=-1.67; 95%CI: -2.72 to -0.62). A large improvement was observed as early as mid-treatment (d=-1.36; 95%CI: -1.98 to -0.74), but with only a moderate improvement in the pre-treatment period between weeks 0-2 (d=-0.55 95%CI: -0.90 to -0.20). At baseline, the mean insomnia scores indicated that the average participant was showing signs of clinical insomnia with moderate severity. At follow-up this was reduced to no clinically significant insomnia, and subthreshold

insomnia at follow-up. According to the ISI cut-off scores on Table 6.10, all participants were meeting the criteria for possible insomnia at baseline (week 0), 80.95% at pre-treatment (week 2), 60% at mid-treatment (week 7), 27.78% at post-treatment, and 42.11% at follow-up (week 24). These improvements were also reflected on the PSQI as the sleep quality outcome. More specifically, there was a large post-treatment improvement (d=-1.18; 95%CI: -1.77 to -0.58) that was maintained at follow-up (d=-0.91; 95%CI: -1.48 to -0.33), and could be observed as a moderate effect since mid-treatment (d=-0.52; 95%CI=-0.88 to -0.16).

There was also a large improvement on the QIDS depression scores at post-treatment (d=-1.91; 95%CI: -2.95 to -0.88) that was maintained at follow-up (d=-1.67; 95%CI: -2.57 to -0.77). Contrary to the observable pattern in insomnia, a large improvement in depression scores was already observable prior to the start of treatment (d=-1.07 95%CI: -1.59 to -0.56) and slightly increased at mid-treatment (d=-1.41; 95%CI: -1.96 to -0.85). At baseline, the mean QIDS scores indicated that the average participant was experiencing moderate depression which was reduced to mild at post-treatment and follow-up. According to the QIDS cut-off scores on Table 6.10, all participants were meeting the criteria for possible depression at baseline (week 0), 85% at pre-treatment (week 2), 80% at mid-treatment (week 7), 55.56% at post-treatment, and 63.16% at follow-up (week 24). The large improvement in QIDS depression scores at post-treatment are also reflected improvements in avoidance and activation as measured using the BADS. At post-treatment there was a large improvement in behavioural activation (d=1.02; 95%CI: 0.30 to 1.75) that was maintained at follow-up (d=0.84; 95CI: 0.15 to 1.54).

Hypomania as measured with the ASRMS also increased at post-treatment, with a large effect size (d=1.20; 95%CI: 0.50 to 1.89) that was maintained at follow-up (d=1.57; 95%CI: 0.58 to 2.56). There was also a small hypomania increase at mid-treatment (d=0.35; 95%CI: -0.29 to 0.99), and a small decrease during the pre-treatment phase (d=-0.19; 95%CI:

-0.56 to 0.18). According to the ASRMS cut-off scores on Table 6.10, no participants were meeting the criteria for possible hypomania at baseline (week 0) or pre-treatment (week 2), 10% were meeting the criteria at mid-treatment (week 7), 22.22% at post-treatment, and 21.05% at follow-up (week 24). An important caveat here is that two participants who scored higher than 5 at the end of the pre-treatment phase were subsequently excluded, as indicated in our ethics application. Nonetheless, across all timepoints the average ASRMS score remained low, showing that the average participant had low probability of experiencing hypomania. Figure 6.4 presents individual level data on the ASRMS.

There was a moderate improvement in the GAD-7 anxiety scores at post-treatment (d=-0.69 95%CI: -1.13 to -0.25) that decreased to a small effect at follow-up (d=-0.35; 95%CI: -0.75 to 0.06). The improvement in anxiety at mid-treatment was very small (d=-0.06; 95%CI: -0.45 to 0.33).

There were no changes in chronotype following the intervention, with a very small effect towards eveningness at post-treatment (d=0.13; 95%CI: -0.2 to 0.48) and a very small effect towards morningness at follow up (d=0.14; 95%CI: -0.21 to 0.49). Across baseline, post-treatment and follow-up, the unadjusted mean MEQ score indicated that participants are between evening and intermediate chronotypes, given that the cut-off score is 12.

Cognitive complaints were reduced following the intervention, with a large post-treatment effect for the BCCCI (d=-0.97; 95%CI: -1.58 to -0.36) that was slightly decreased but remained large at follow-up (d=-0.90; 95%CI: -1.42 to -0.38).

Mental wellbeing as measured using the WEMWS showed a large improvement at post-treatment (d=0.97; 95CI: 0.18 to 1.77) that was reduced to a moderate effect at follow-up (d=0.50; 95CI: -0.21 to 1.20). Social and occupational functioning also improved. There was a large effect size for WSAS at post-treatment (d=-0.94; 95%CI -1.49 to -0.39) that was maintained as a moderate effect at follow-up (d=-0.69; 95%CI: -1.23 to -0.14).

Table 6.8 Summary statistics of questionnaire outcomes

	Unadjusted mean score (sd); n	Adjusted mean difference (95% CI)	Cohen's d (95% CI)
Insomnia Severity Index (0-28)			
Baseline	16.86 (4.45); n=22		
Pre-treatment	14.67 (4.13); n=21	2.36 (-0.70 to 5.41)	-0.55 (-0.90 to -0.20)
Mid-treatment	10.45 (4.65); n=20	6.30 (3.19 to 9.41)	-1.36 (-1.98 to -0.74)
Post-treatment	7.50 (5.43); n=18	9.32 (6.10 to 12.53)	-1.87 (-2.77 to -0.98)
Follow-up	8.11 (6.05); n=19	8.77 (5.61 to 11.93)	-1.67 (-2.72 to -0.62)
Quick Inventory for Depressive Symptomatology (0-27)			
Baseline	14.55 (4.01); n=22		
Pre-treatment	9.75 (4.14); n=20	4.66 (2.15 to 7.17)	-1.07 (-1.59 to -0.56)
Mid-treatment	8.90 (3.37); n=20	5.49 (2.98 to 8.01)	-1.41 (-1.96 to -0.85)
Post-treatment	6.50 (4.85); n=18	8.22 (5.62 to 10.82)	-1.91 (-2.95 to -0.88)
Follow-up	8.21 (4.26); n=19	6.68 (4.13 to 9.24)	-1.67 (-2.57 to -0.77)
Behavioural Activation for Depression Scale (0-54)			
Baseline	21.94 (6.97); n=22		
Post-treatment	30.70 (10.00); n=21	-8.71 (-14.04 to -3.38)	1.02 (0.30 to 1.75)
Follow-up	28.39 (9.52); n=20	-6.72 (-11.95 to -1.49)	0.84 (0.15 to 1.54)
Altman Self-Rating Mania Scale (0-20)			
Baseline	1.55 (1.90); n=22		
Pre-treatment	1.24 (1.37); n=21	0.30 (-1.03 to 1.63)	-0.19 (-0.56 to 0.18)
Mid-treatment	2.25 (2.05); n=20	-0.69 (-2.04 to 0.66)	0.35 (-0.29 to 0.99)
Post-treatment	3.94 (1.80); n=18	-2.34 (-3.74 to -0.94)	1.20 (0.50 to 1.89)
Follow-up	4.79 (2.10); n=19	-3.23 (-4.60 to -1.86)	1.57 (0.58 to 2.56)
Pittsburgh Sleep Quality Index (0-21)			
Baseline	9.81 (3.25); n=21		
Mid-treatment	7.85 (3.45); n=20	1.75 (0.17 to 3.34)	-0.52 (-0.88 to -0.16)
Post-treatment	5.72 (2.67); n=18	3.50 (1.85 to 5.15)	-1.18 (-1.77 to -0.58)
Follow-up	6.42 (3.02); n=19	2.92 (1.30 to 4.54)	-0.91 (-1.48 to -0.33)
Generalised Anxiety Disorder (0-21)			
Baseline	7.41 (4.47); n=22		
Mid-treatment	6.68 (4.55); n=20	0.35 (-1.97 to 2.67)	-0.06 (-0.45 to 0.33)
Post-treatment	4.28 (3.97); n=18	3.03 (0.63 to 5.44)	-0.69 (-1.13 to -0.25)
Follow-up	5.82 (5.58); n=19	1.91 (-0.45 to 4.27)	-0.35 (-0.75 to 0.06)
Morningness Eveningness Questionnaire (4-26)			
Baseline	12.45 (3.90); n=22		
Post-treatment	12.44 (3.22); n=18	-0.39 (-1.99 to 1.22)	0.13 (-0.22 to 0.48)
Follow-up	12.74 (3.97); n=19	-0.49 (-2.06 to 1.08)	0.14 (-0.21 to 0.49)
British Columbia Cognitive Complaints Inventory (0-18)			
Baseline	8.18 (4.90); n=22		
Post-treatment	4.22 (3.47); n=18	4.15 (1.88 to 6.42)	-0.97 (-1.58 to -0.36)
Follow-up	4.72 (3.89); n=18	3.90 (1.63 to 6.16)	-0.90 (-1.42 to -0.38)
Warwick Edinburgh Mental Wellbeing Scale (14-70)			
Baseline	36.36 (9.43); n=22		
Post-treatment	45.67 (7.93); n=18	-9.18 (-15.42 to -2.95)	0.97 (0.18 to 1.77)
Follow-up	41.05 (9.02); n= 19	-4.71 (-10.83 to 1.42)	0.50 (-0.21 to 1.20)
Work and Social Adjustment Scale (0-40)			
Baseline	21.68 (8.02); n=22		
Post-treatment	13.17 (9.64); n=18	8.50 (3.70 to 13.30)	-0.94 (-1.49 to -0.39)

Follow-up	15.63 (10.37); n=19	6.32 (1.61 to 11.03)	-0.69 (-1.23 to -0.14)

Abbreviations: CI, confidence intervals; SD, standard deviations

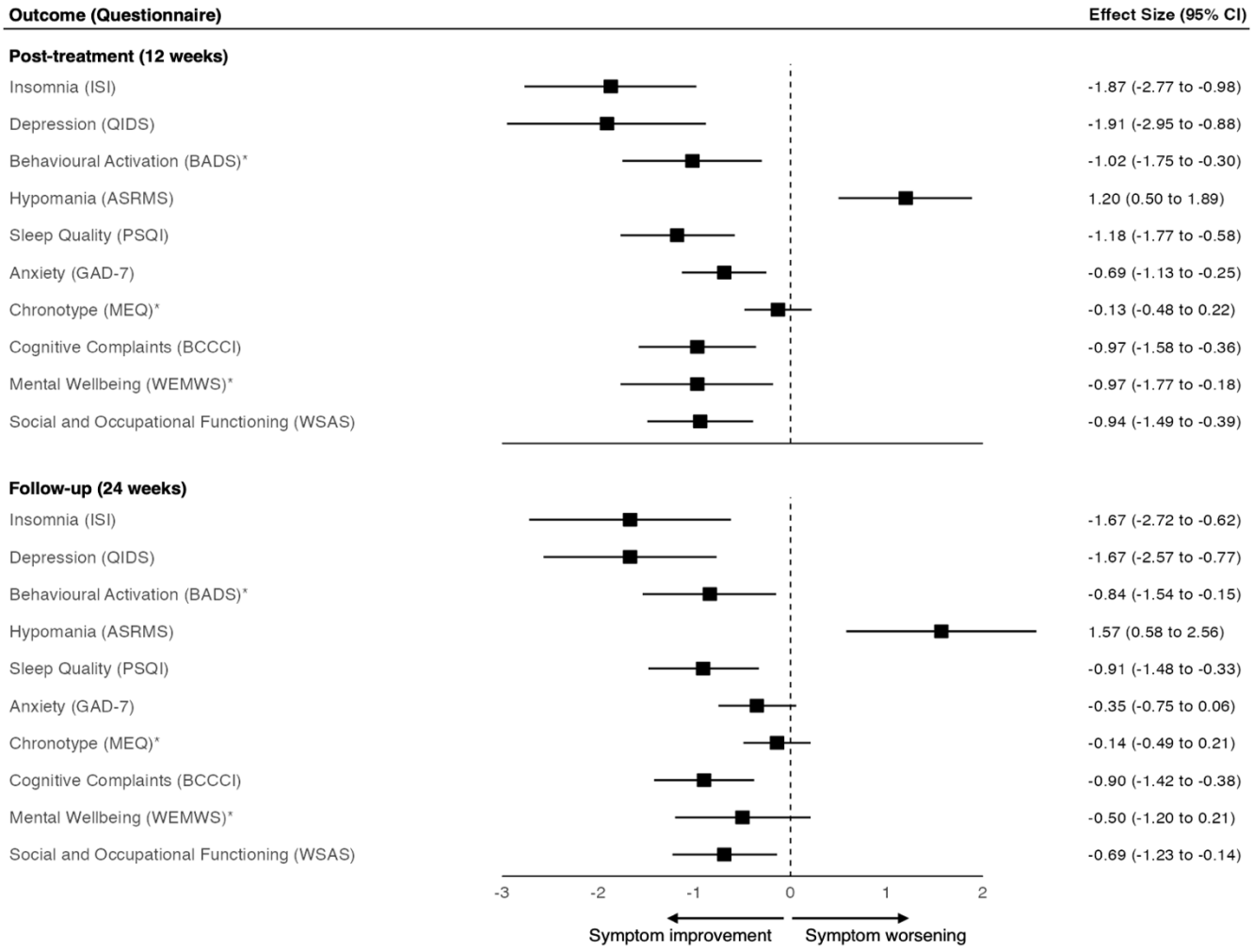


Figure 6.2. Forest plot of post-treatment and follow-up questionnaire outcomes

** Effect size and CI direction changed to match the rest of the outcomes. In the case of chronotype, although this is not necessarily therapeutic, an improvement denotes an increase in morningness*

Abbreviations: ASRMS, Altman Self-Rating Mania Scale; BADS, Behavioural Activation for Depression Scale; BCCCI, British Columbia Cognitive Complaints Inventory; GAD, Generalised Anxiety Disorder; ISI, Insomnia Severity Index; PSQI, MEQ, Morningness Eveningness Questionnaire; Pittsburgh Sleep Quality Index; QUIDS, Quick Inventory for Depressive Symptomatology, WEMWS, Warwick-Edinburgh Mental Wellbeing Scale; WSAS, Work and Social Adjustment Scale

Table 6.9 Participants meeting the threshold for insomnia, depression and hypomania according to the administered questionnaires

	n (%) ISI criteria for possible insomnia: ISI≥10	**n (%) QIDS criteria for possible depression: QIDS≥6**	**n (%) ASRMS criteria for possible hypomania: ASRMS>5**
Baseline	22 (100.00%); n=22	22 (100.00%); n=22	0.00 (0.00%); n=22
Pre-treatment	17 (80.95%); n=21	17 (85.00%); n=20	0.00 (0.00%); n=21
Mid-treatment	12 (60.00%); n=20	16 (80.00%); n=20	2 (10.00%); n=20
Post-treatment	5 (27.78%); n=18	10 (55.56%); n=18	4 (22.22%); n=18
Follow-up	8 (42.11%); n=19	12 (63.16%); n=19	4 (21.05%); n=19

Abbreviations: ASRMS, Altman Self Rating Mania Scale; ISI, Insomnia Severity Index, QIDS, Quick Inventory for Depressive Symtomatology

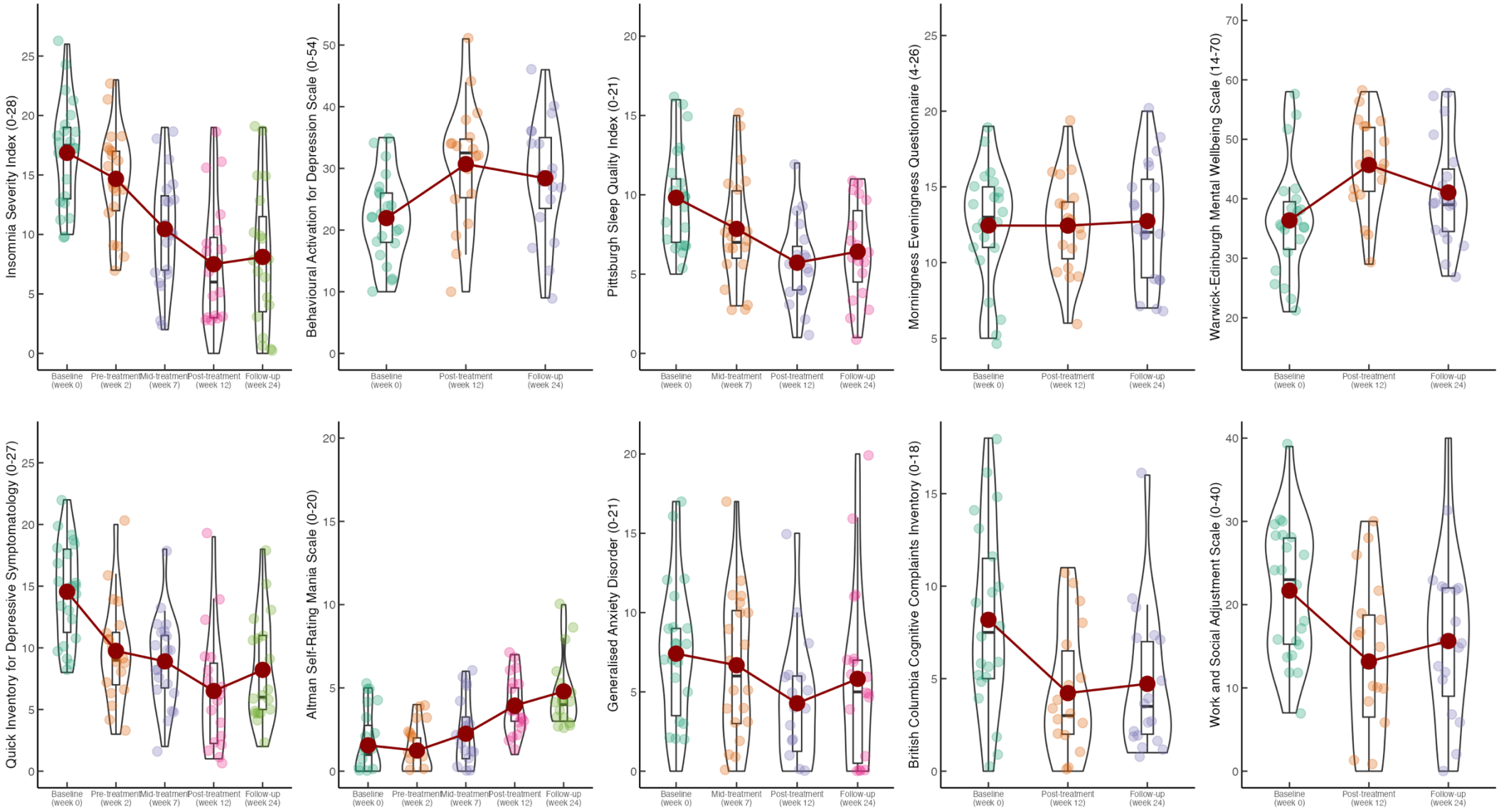


Figure 6.3 Questionnaire outcomes for all timepoints in the DIGIT-B study. The red points indicate mean scores

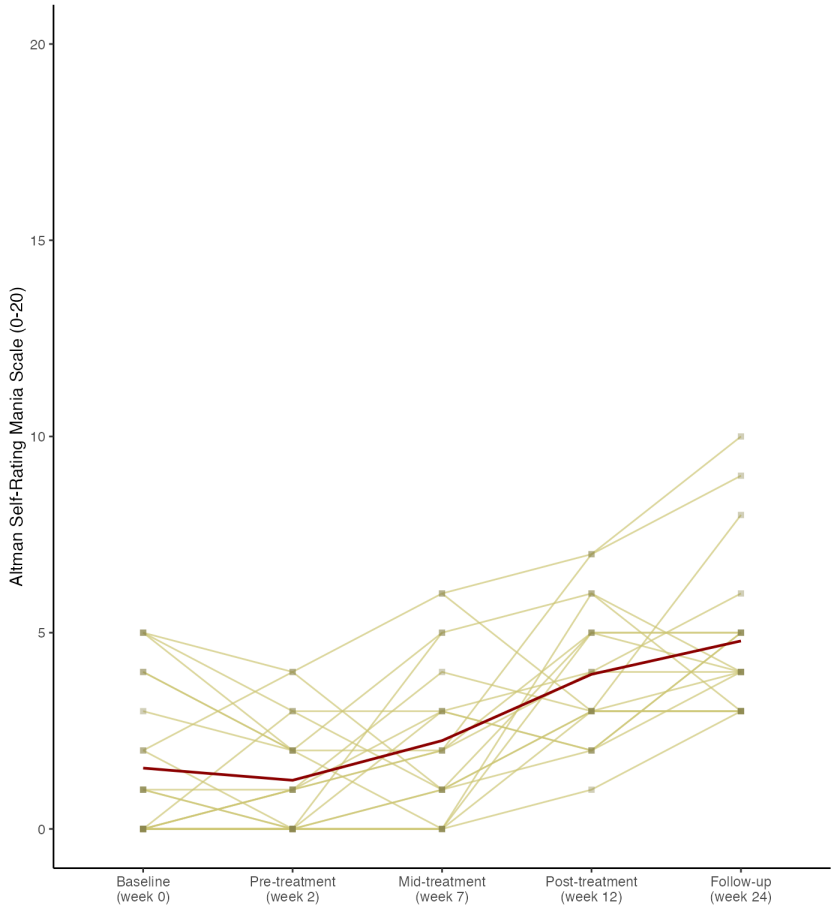


Figure 6.4 Individual-level data of hypomania scores. The red points indicates mean scores

6.3.4 Post-hoc Sensitivity Analysis

In the first sensitivity analysis we averaged the values for the timepoints before treatment started, i.e. baseline (week 0) and pre-treatment (week 2), and entered them as one timepoint in our mixed level models. This was only relevant to the three questionnaires that we administered twice before treatment started, namely: the ISI, QIDS and ASRMS. Table 6.10 mirrors Table 6.8 and presents the estimates with the newly calculated average baseline (weeks 0-2) as the comparison arm. Figure 6.5 mirrors Figure 6.3 and displays the outcomes for all timepoints for the relevant outcomes. Overall, the new model showed more mild improvements, with decreased effect sizes for insomnia and depression and increased effect sizes for hypomania. Nevertheless,

the direction and magnitude classification remained the same for all outcome throughout each timepoint.

Table 6.10 Summary statistics of questionnaire outcomes for the newly calculated timepoint

	Unadjusted mean score (sd); n	Adjusted mean difference (95% CI)	Cohen's d (95% CI)
Insomnia Severity Index (0-28)			
Average Baseline	15.86 (4.00); n=22		
Mid-treatment	10.45 (4.65); n=20	5.15 (2.20 to 8.10)	-1.13 (-1.66 to -0.61)
Post-treatment	7.50 (5.43); n=18	8.11 (5.04 to 11.17)	-1.68 (-2.48 to -0.87)
Follow-up	8.11 (6.05); n=19	7.56 (4.56 to 10.57)	-1.49 (-2.45 to -0.53)
Quick Inventory for Depressive Symptomatology (0-27)			
Average Baseline	11.88 (3.51); n=22		
Mid-treatment	8.90 (3.37); n=20	2.81 (0.61 to 5.02)	-0.86 (-1.30 to -0.42)
Post-treatment	6.50 (4.85); n=18	5.50 (3.21 to 7.78)	-1.21 (-1.87 to -0.55)
Follow-up	8.21 (4.26); n=19	3.99 (1.75 to 6.24)	-1.05 (-1.71 to -0.40)
Altman Self-Rating Mania Scale (0-20)			
Average Baseline	1.40 (1.51); n=22		
Mid-treatment	2.25 (2.05); n=20	-0.82 (-2.14 to 0.51)	0.36 (-0.24 to 0.97)
Post-treatment	3.94 (1.80); n=18	-2.49 (-3.86 to -1.11)	1.42 (0.70 to 2.14)
Follow-up	4.79 (2.10); n=19	-3.37 (-4.72 to -2.02)	1.82 (0.87 to 2.78)

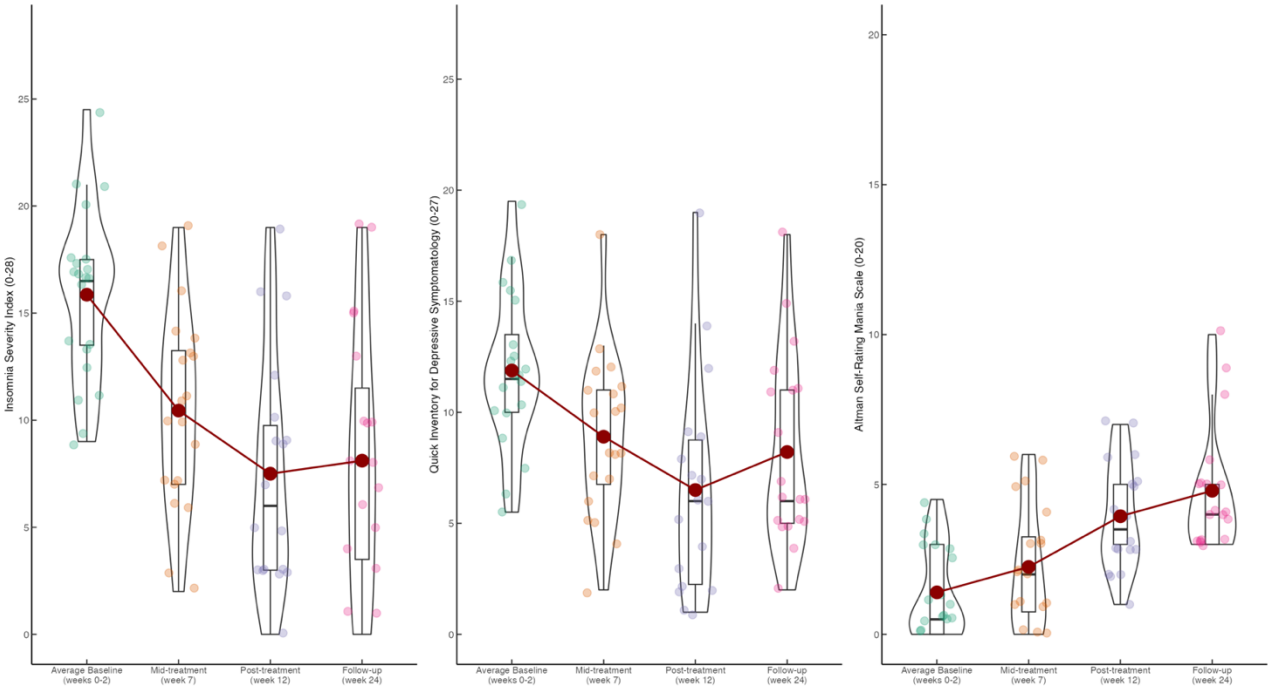


Figure 6.5 Questionnaire items using the newly calculated average baseline timepoint (weeks 0-2). The red line points mean scores

In the second sensitivity analysis we implemented multiple imputations via chained equation modelling to derive complete datasets. On average, 10.5% of the data for each questionnaire outcome were missing, with the rate ranging between 9-12%. Following our imputation, complete data were retrieved for each outcome (n=22). Table 6.11 mirrors Table 6.8 which presented the same estimates for the original dataset. Figure 6.6 displays the unadjusted means of both the original and completed data retrieved through our multiple imputations models. Overall, there are minimal differences between the original and completed datasets. Scores in the MEQ remained very small but their direction changed, and the post-treatment effect on anxiety in the GAD-7 increased from a moderate (d=-0.69; 95%CI: -1.13 to -0.25) to a large effect size (d=-0.89; 95%CI: -1.40 to -0.39). Otherwise, all effects remained in the same direction and magnitude.

Table 6.11 Summary statistics of questionnaire outcomes for full datasets using multiple imputations via chained equations modelling

	Unadjusted mean score (sd); n	**Adjusted mean difference (95% CI)**	**Cohen's d (95% CI)**
Insomnia Severity Index (0-28); 9% missing data			
Baseline	16.86 (4.45); n=22		
Pre-treatment	14.36 (4.27); n-22	2.50 (-0.69 to 5.69)	-0.52 (-0.86 to -0.18)
Mid-treatment	10.41 (4.52); n=22	6.45 (3.27 to 9.64)	-1.33 (-1.92 to -0.75)
Post-treatment	7.68 (5.11); n=22	9.18 (6.00 to 12.37)	-1.97 (-2.80 to -1.15)
Follow-up	8.91 (6.21); n =22	7.95 (4.77 to 11.14)	-1.69 (-2.68 to -0.71)
Quick Inventory for Depressive Symptomatology (0-27); 10%missing data			
Baseline	14.55 (4.01); n=22		
Pre-treatment	10.41 (4.57); n=22	4.14 (1.52 to 6.75)	-1.17 (-1.73 to -0.60)
Mid-treatment	9.09 (3.54); n=22	5.45 (2.84 to 8.07)	-1.49 (-2.03 to -0.94)
Post-treatment	6.91 (4.68); n=22	7.64 (5.02 to 10.25)	-1.93 (-2.58 to -1.01)
Follow-up	8.55 (4.53); n=22	6.00 (3.39 to 8.61)	-1.60 (-2.42 to -0.77)
Behavioural Activation for Depression Scale (0-54); 11% missing data			
Baseline	21.94 (6.97); n=22		
Post-treatment	30.85 (9.16); n=22	-8.91 (-13.58 to -4.24)	1.00 (0.37 to 1.63)
Follow-up	28.30 (8.85); n=22	-6.36 (-11.03 to -1.69)	0.87 (0.25 to 1.50)
Altman Self-Rating Mania Scale (0-20); 9% missing data			
Baseline	1.55 (1.90); n=22		
Pre-treatment	1.18 (1.37); n=22	0.36 (-0.91 to 1.63)	-0.18 (-0.54 to 0.17)
Mid-treatment	2.14 (2.01); n=22	-0.59 (-1.86 to 0.68)	0.35 (-0.27 to 0.97)
Post-treatment	3.86 (1.67); n=22	-2.32 (-3.59 to -1.05)	1.16 (0.57 to 1.75)
Follow-up	4.77 (1.97); n=22	-3.23 (-4.50 to -1.96)	1.68 (0.73 to 2.62)
Pittsburgh Sleep Quality Index (0-21); 11% missing data			
Baseline	9.86 (3.18); n=22		
Mid-treatment	8.09 (3.54); n=22	1.77 (0.25 to 3.29)	-0.46 (-0.79 to -0.12)
Post-treatment	6.05 (2.61); n=22	3.82 (2.30 to 5.34)	-1.18 (-1.65 to -0.71)
Follow-up	6.95 (3.12); n=22	2.91 (1.39 to 4.43)	-1.10 (-1.70 to -0.50)
Generalised Anxiety Disorder (0-21); 10% missing data			
Baseline	7.41 (4.47); n=22		

Mid-treatment	6.75 (4.41); n=22	0.66 (-1.58 to 2.90)	-0.18 (-0.59 to 0.23)
Post-treatment	4.05 (3.84); n=22	3.36 (1.12 to 5.60)	-0.89 (-1.40 to -0.39)
Follow-up	5.48 (5.33); n=22	1.92 (-0.32 to 4.16)	-0.41 (-0.78 to -0.04)
Morningness Eveningness Questionnaire (4-26); 11% missing data			
Baseline	12.45 (3.90); n=22		
Post-treatment	12.55 (2.96); n=22	-0.09 (-1.59 to 1.41)	0.12 (-0.18 to 0.42)
Follow-up	12.41 (3.87); n=22	0.05 (-1.45 to 1.54)	0.21 (-0.11 to 0.53)
British Columbia Cognitive Complaints Inventory (0-18); 12% missing data			
Baseline	8.18 (4.90); n=22		
Post-treatment	4.27 (3.51); n=22	3.91 (1.88 to 5.93)	-0.81 (-1.37 to -0.26)
Follow-up	4.55 (3.67); n=22	3.64 (1.61 to 5.66)	-0.86 (-1.31 to -0.41)
Warwick Edinburgh Mental Wellbeing Scale (14-70); 11% missing data			
Baseline	36.36 (9.43); n=22		
Post-treatment	45.59 (7.68); n=22	-9.23 (-14.97 to -3.48)	0.90 (0.23 to 1.58)
Follow-up	41.23 (9.35); n=22	-4.86 (-10.61 to 0.88)	0.43 (-0.21 to 1.07)
Work and Social Adjustment Scale (0-40); 11% missing data			
Baseline	21.68 (8.02); n=22		
Post-treatment	14.09 (9.30); n=22	7.59 (3.20 to 11.98)	-0.95 (-1.42 to -0.47)
Follow-up	15.50 (9.81); n=22	6.18 (1.79 to 10.57)	-0.61 (-1.11 to -0.10)

Abbreviations: CI, Confidence Intervals; SD, Standard Deviations

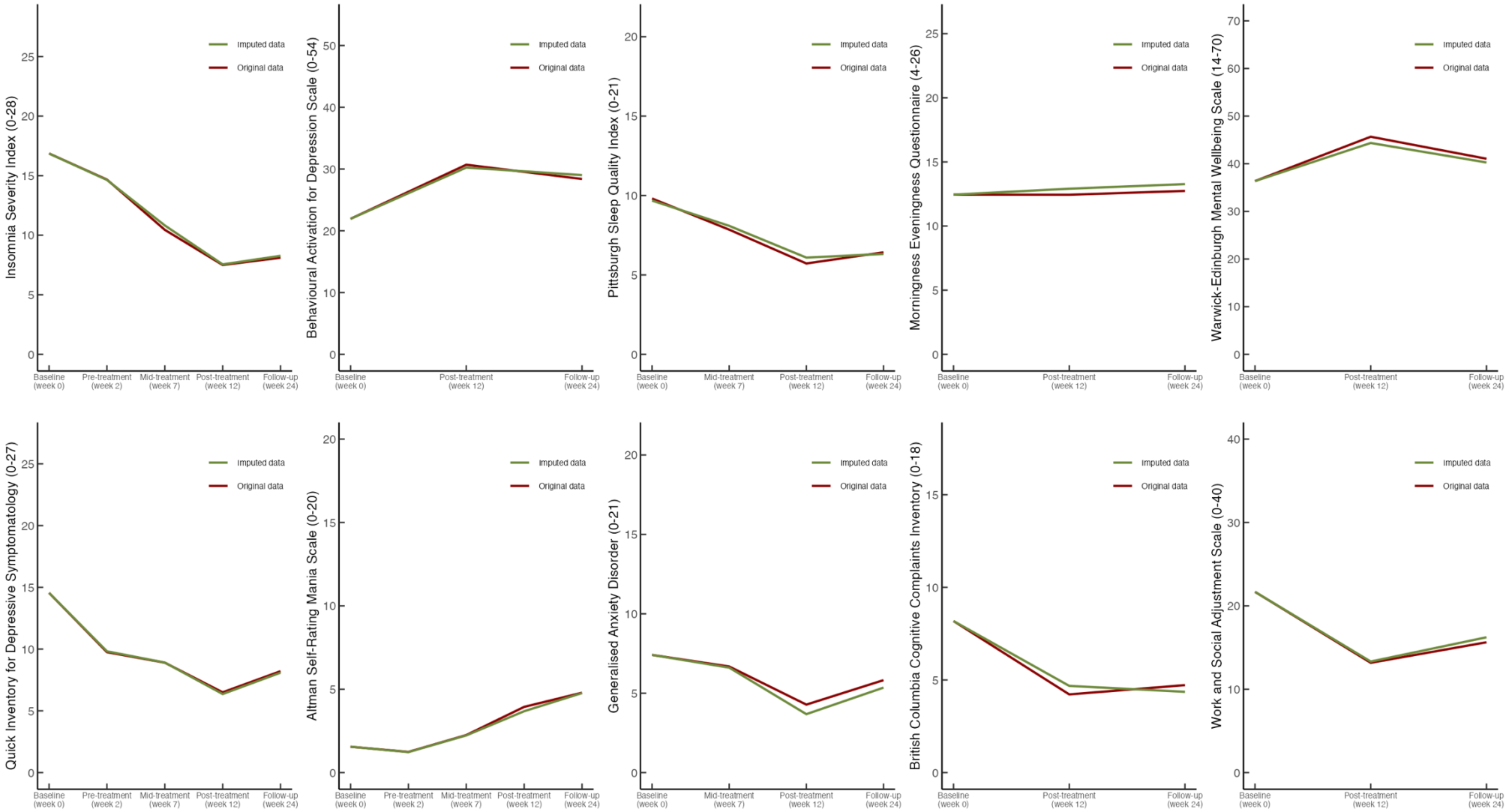


Figure 6.6 Comparison between the mean unadjusted scores for all timepoints according to the original dataset and imputed complete dataset through multiple imputations via chained equation modelling

6.3.5 Sleep Diary Results

Table 6.12 presents the unadjusted mean score for all registered sleep diary outcomes, SOL, WASO, TST and SE, at each timepoint, accompanied by the standard deviation and number of participants who provided usable sleep diary data. The table also displays the adjusted mean difference between baseline and each subsequent timepoint, and the standardised effect size, each accompanied by 95% CIs. Figure 6.7 illustrates the unadjusted scores across timepoints.

There was a moderate reduction of SOL at mid-treatment (d=-0.67; 95%CI: -1.55 to 0.21), and a large effect at post-treatment (d=-1.10; 95%CI: -1.95 to -0.24). When compared the average baseline SOL of 34.97 (22.45) minutes, the average SOL at mid-treatment was 21.71 (16.78) minutes, and 14.61 (11.07) minutes at post-treatment.

There was a small effect size indicating an increase in WASO at mid-treatment (d=0.17; 95%CI: -0.40 to 0.74), and another small effect size indicating a decrease in WASO at post-treatment (d=-0.23; 95%CI: -1.15 to 0.68). Unadjusted mean values at each timepoint reflect these changes. At baseline, the average WASO was 35.21 (28.11) minutes, increasing to 40.42 (28.36) minutes at mid-treatment and then decreasing to 30.81 (29.00) minutes at post-treatment.

There was a small decrease in sleep duration at mid-treatment (d=-0.06; 95%CI: -0.61 to 0.49), and a small increase at post-treatment (d=0.08 95%CI: -0.68 to 0.84). When compared to the average baseline TST of 423.62 (71.17) minutes, the average TST at mid-treatment was 409.46 (79.28) minutes and average TST at post-treatment was 427.62 (67.50) minutes.

SE increased throughout the intervention, with a small effect at mid-treatment (d=0.27; 95%CI: -0.37 to 0.91), and a moderate-to-large effect at post-treatment (d=0.76;

95%CI: 0.01 to 1.51). This reflected a change from an average 75.43% (9.49) baseline SE score, to an average 78.44% (6.77) at mid-treatment, and 81.95% (6.95) at post-treatment.

Table 6.12 Summary statistics for sleep diary outcomes

	Unadjusted mean score (sd); n	Adjusted mean difference (95% CI)	Standardised effect size (95% CI)
Sleep Onset Latency (minutes)			
Baseline	34.97 (22.45); n=19		
Mid-treatment	21.71 (16.78); n=18	14.50 (3.79 to 25.20)	-0.67 (-1.55 to 0.21)
Post-treatment	14.61 (11.07); n=16	18.58 (7.56 to 29.60)	-1.10 (-1.95 to -0.24)
Wake after Sleep Onset (minutes)			
Baseline	35.21 (28.11); n=19		
Mid-treatment	40.42 (28.36); n=19	-3.98 (-19.64 to 11.67)	0.17 (-0.40 to 0.74)
Post-treatment	30.81 (29.00); n=16	5.57 (-10.54 to 21.68)	-0.23 (-1.15 to 0.68)
Total Sleep Time (minutes)			
Baseline	423.62 (71.17); n=19		
Mid-treatment	409.46 (79.28); n=18	-1.12 (-35.33 to 33.10)	-0.06 (-0.61 to 0.49)
Post-treatment	427.62 (67.50); n=16	-12.08 (-47.23 to 23.07)	0.08 (-0.68 to 0.84)
Sleep Efficiency (0-100)			
Baseline	75.43 (9.49); n=19		
Mid-treatment	78.44 (6.77); n=18	-3.74 (-8.62 to 1.15)	0.27 (-0.37 to 0.91)
Post-treatment	81.95 (6.95); n=16	-6.70 (-11.73 to -1.67)	0.76 (0.01 to 1.51)

Abbreviations: CI, confidence intervals; SD, standard deviations

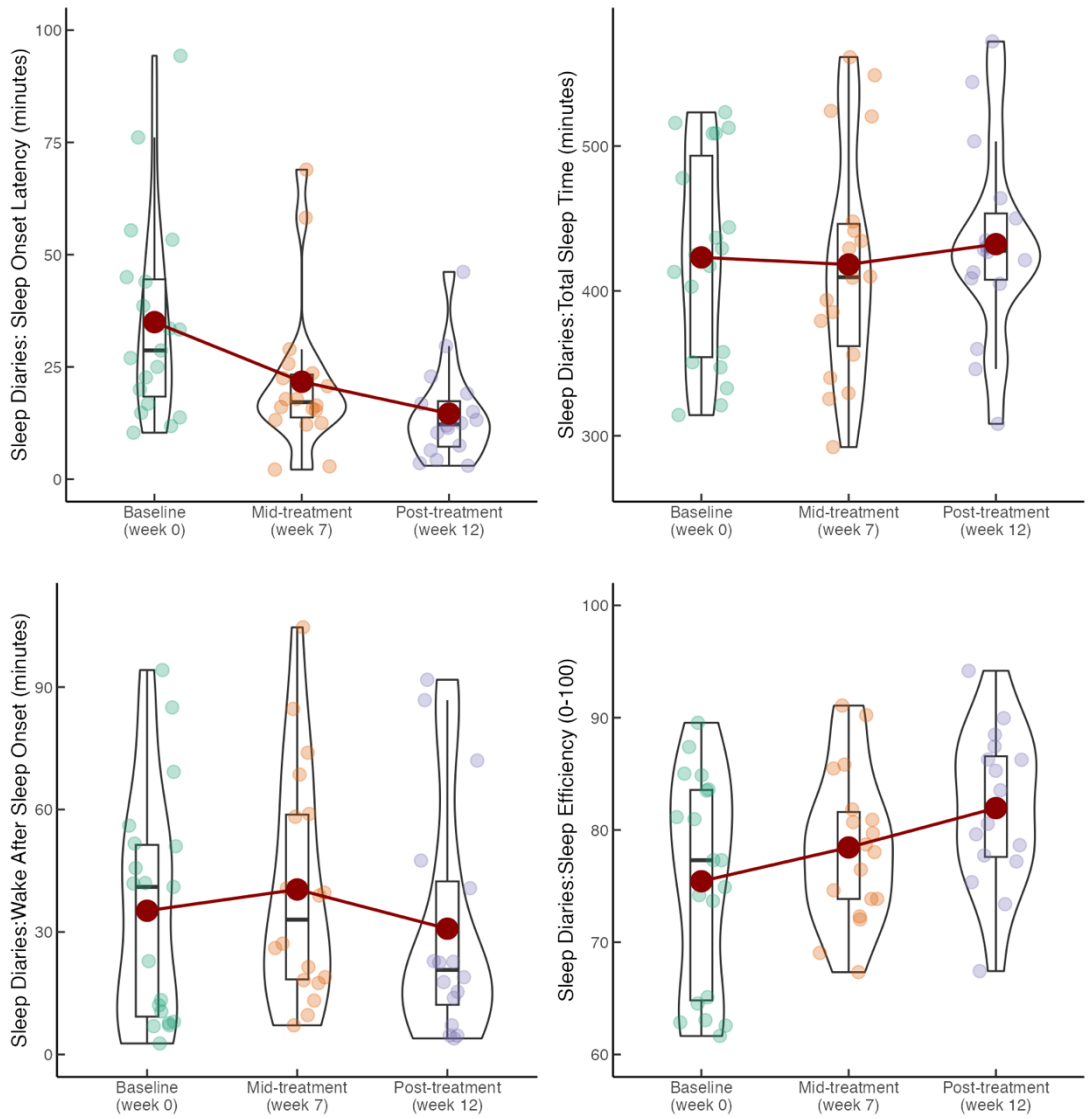


Figure 6.7 Diary outcomes for all timepoints in the DIGIT-B study. The red line indicates mean scores

6.3.6 Actigraphy Results

Table 6.13 presents the unadjusted mean score for all registered actigraphy outcomes, SOL, WASO, TST and SE, at each timepoint, accompanied by the standard deviation and number of participants who provided usable sleep diary data. The table also displays the adjusted mean difference between baseline and each subsequent timepoint, and the standardised effect size, each accompanied by 95% CIs. Figure 6.8 illustrates the unadjusted scores across timepoints.

There was a small decrease of SOL at post-treatment (d=-0.23; 95%CI: -0.75 to 0.28), reflecting a decrease from 8.14 (8.19) minutes at baseline to 6.88 (5.68) minutes at post-treatment. There was a small increase in WASO at post-treatment (d=0.22; 95%CI: -0.59 to 1.03), reflecting an increase from 78.70 (39.45) minutes at baseline to 85.32 (43.65) minutes at post-treatment. There was a very small decrease in TST (d=-0.08; 95%CI: -0.60 to 0.44), reflecting a change from 422.22 (51.68) minutes at baseline to 417.65 (76.60) minutes at post-treatment. There was also a small decrease in SE at post-treatment (d=-0.30; 95%CI: -1.11 to 0.51), reflecting an increase from 83.14% (6.11) at baseline to 81.59% (6.82) at post-treatment.

Table 6.13 Summary statistics for actigraphy outcomes

	Unadjusted mean score (sd); n	**Adjusted mean difference (95% CI)**	**Standardised effect size (95% CI)**
Sleep Onset Latency (minutes)			
Baseline	8.14 (8.19); n=18		
Post-treatment	6.88 (5.68); n=15	1.21 (-2.20 to 4.61)	-0.23 (-0.75 to 0.28)
Wake after Sleep Onset (minutes)			
Baseline	78.70 (39.45); n=18		
Post-treatment	85.32 (43.65); n=15	-3.87 (-21.56 to 13.82)	0.22 (-0.59 to 1.03)
Total Sleep Time (minutes)			
Baseline	422.22 (51.68); n=18		
Post-treatment	417.65 (76.60); n=15	2.45 (-22.66 to 27.56)	-0.08 (-0.60 to 0.44)
Sleep Efficiency (0-100)			
Baseline	83.14 (6.11); n=18		
Post-treatment	81.59 (6.82); n=15	1.07 (-1.59 to 3.72)	-0.30 (-1.11 to 0.51)

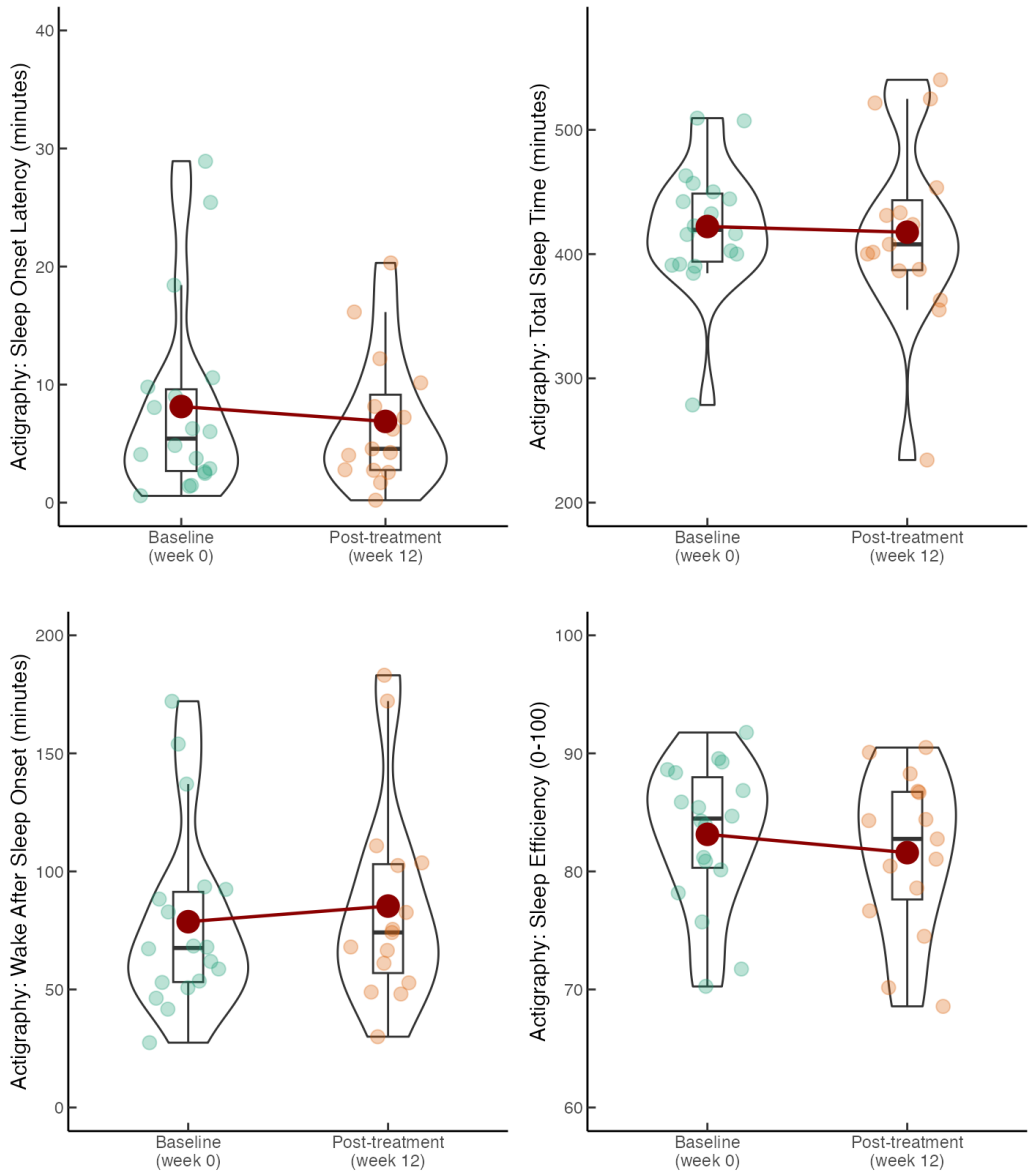


Figure 6.8 Actigraphy outcomes for baseline and post-treatment. The red points indicate mean scores

6.4 Qualitative Results

Interviews were conducted with 18 participants (2 male and 16 female). Given the nature of our sample, providing individual-based characteristics, such as gender, medication and session completion rate, would violate the anonymity of our participants, but aggregated baseline characteristics are provided on Table 6.4. Interviews ranged in duration between 15.22 and 72.73 minutes, with an average duration of 36.33 (13.71) minutes. The names

given to participants here were assigned at random and regardless of gender. The names represent characters from James Baldwin's novels.

Five key themes were developed, each with several subordinate categories that encompass the shared and contrasting experience of our participants. Table 6.14 represents the overall structure of the themes and sub-categories, and displays characteristic examples of each case.

Table 6.14 Themes and sub-categories of the post-treatment semi-structure interview

T1. Manifestation of sleep disruptions	
Symptom presentation of sleep disruptions	*I used to wake up quite often through the night. Going to bed is fine. I can go to bed quite quickly, but I'll definitely wake up sometime through the night. And then wake up really early.* [Isaac]
Timing of sleep disruptions	*I think so much of what I have tends to be seasonable… my anxiety and insomnia would tend to occur more in winter time… so in summer time although I was sleeping less, I would feel like I had plenty of energy and life was good and ah things are manageable* [Daniel]
Effects of sleep disruptions	
Mood	*I always think that I need to have regular sleep to maintain my mood so if it goes off for any reason then I notice it quite quickly because… I know that if I don't sleep properly then it can trigger me to become higher or lower* [Florence]
Cognition	*If I wasn't sleeping, the next day my concertation would be very poor* [Leona]
Daily life	*At times I feel sleepy when I'm driving; sometimes I have to stop driving and pull over* [Hattie]
Onset of sleep disruptions	*Life-long sleep issues* [John]
Situations exacerbating sleep disruptions	*The socio-political climate* [David]
Sleep disruptions as pre-cursors to other symptoms of BD	*That's normally a good indicator for me that something's not quite right you know… I got the bipolar diagnosis about 20 years ago and I know my body pretty well now, so I would totally say sleep [is] a really accurate indicator* [Sonny]
Self-management of sleep disruptions	*It's hard to know because [the sleep problems have] been going on for so long I don't know what I would feel like if I had really good sleep anymore. I just don't know what it's like so. But I know it's a lot better* [Rufus] *In my worst episodes my partner and I used to [have]… a system on paper to try and look [into my sleep and mood]… It wasn't very easy to do. We used to just try and grade mood and sleep from 1 to 10* [Hattie]
T2. Clinical response to sleep disruptions	
Enquiries from clinicians about sleep	*When I got diagnosed with bipolar… it was a little more frequent* [Tish]
Response to reported sleep disruptions	*You don't really get much response because the psychiatrists I've spoken to thought [sleep problems are] part of the symptoms of bipolar so they would give you the different medications like your*

	mood stabilizes and [expect] that would help. They don't address sleep as an issue on its own… [they are] often resistant to address it as a standalone. In my experience [Elisha]
Perception of clinical response	
Positive	*Very good access to mental health services and I think certainly if I bring up anything that's been an issue including sleep, then they do take that very seriously* [Richard]
Negative	*This wasn't a long-term solution, so I wasn't massively pleased* [Giovanni]
Mixed	*I don't think there is a quick solution to it; like there isn't a bad solution, you can't wave a magic wand and go back to a normal sleeping pattern* [Milan]
Medications to help with sleep	*Antidepressants* [Isaac] *Antihistamines* [Richard] *Mood stabilisers* [Elisha; Richard].
Perception of usefulness of medication	*Drugged up* [Fonny] *Foggy and drowsy the next day* [Florence]
T3. Experience with CBT-I treatment	
Motivation for participating	*Look for things beyond medication* [Clara] *I try to participate in research whenever I can* [Richard]
Expectations from the study	*I'm not sure I've had very like big expectations. I think there was a slight bias that I didn't think it was going to help, because I've been struggling with my sleep for such a long time, I think everything I was doing was the thing that worked best… so I think I was a little biased for it not going well* [Tish]
Sleep improvements after treatment	
Sleep behaviours	*Now when I get into bed, I typically fall asleep pretty quickly* [Giovanni]
Sleep-related thinking	*I'm spending less time in bed, I'm spending less time asleep, but my sleep quality is better. So, I feel much more awake during the day and feel like I've got two or three hours back in the day. Because I'm not spending time in bed… it's made quite a big difference to the quality of my sleep rather than the quantity* [Roy]
Other improvements after treatment	
Mood	*More able to let things go… my tendency to ruminate has really decreased quite significantly* [David]
Daily life	*I actually feel safer now driving… like 90% of the time I do feel more safe now doing basic driving and stuff like that* [Leona]
Caveats to improvement	*I live in a very cramped premises for financial reasons so it's very hard to declutter and move things around* [John] *I thought the sleep restriction was quite good because I think it took away the pressure to fall asleep, and because I'd like had that designated time to be like oh this is when you go to sleep* [Tish]
Pros and cons of specific sessions and elements	*I think if someone was quite new to the diagnosis or hadn't quite worked out their [sleep] patterns and they follow this really rigidly, I think there is a danger that it would make them ill… I think it obviously it depends on how much a person understands about their condition. It also depends on how it's monitored* [Richard]
Using CBT-I in the future	*My overall takeaway on the app is that when I feel like I'm going into a bad episode again… [I can] sign up to the app and use it* [Daniel]
T4. Experience with the Sleepio app	

Positives of the Sleepio app	*I mean despite being really cynical about it, I think it was pitched at the right level. So even though it was telling me stuff I already knew, I was like actually you know it was kind of treating me like an adult, and talking about kind of real life situations and stuff* [Clara]
Negatives of the Sleepio app	*I think it was more focused on people with insomnia rather than people who oversleep like myself. It can get one way or the other quite quickly. It can change from week to week, but I feel like the emphasis was more on insomnia* [Milan]
Recommendations for improving Sleepio	*More of a community element to kind of engage with other people that are going through this and share experiences* [Roy]
T5. Digital element of the study and intervention	
Past experiences with digital interventions	*More than happy to take part in [another] digital intervention* [John]
Preference for digital or in-person	*No [I would not have preferred digital meetings], because then you'd be tied to a time, and you might not be in a position to be receptive to learning. Like this is what I like. This way you can choose, set aside time when you can properly focus on it* [Hattie]

6.4.1 Theme 1: Manifestation of Sleep Disruptions

Symptom presentation and timing of sleep disruptions

The first subordinate theme captures the participants' experience of sleep disruptions prior to entering the DIGIT-B study. Participants reported typical symptoms of insomnia, such as difficulty initiating or maintaining sleep, and waking up too early. While all participants reported problems with their sleep, the nature of these disruptions varied among individuals. For the majority of participants, the primary sleep complaint was related to sleep maintenance, as *I generally get off to sleep fairly quickly* [Fonny].

- *I would fall asleep very quickly, probably within 10 or 15 minutes of going to bed, but I would wake up very often in the night. I didn't look at a clock, but it almost felt like I was awake a few minutes every hour. And at its worst, which probably coincides with the worst of my depression, I would wake up after maybe an hour or an hour and a half of sleep and then just not be able to get back to sleep at all despite everything that I tried. And obviously you know this sleep problems had a really big impact on my life* [Roy]

- *I used to wake up quite often through the night. Going to bed is fine. I can go to bed quite quickly, but I'll definitely wake up sometime through the night. And then wake up really early.* [Isaac]
- *I can have really bad insomnia… it could go on for months. So, if I was unwell, mainly, I wouldn't have any problem getting to sleep; staying asleep would be the problem. Waking up numerous times at night and then just lying awake* [Leona]

Other problems included difficulties *getting out of bed in the morning* [Giovanni], *bad dreams* [Hattie], and *not sleeping very much most of the time* [Elisha]. Even though insufficient sleep was a common complaint, participants mentioned that *however much I sleep at night it doesn't seem to make a difference* [Hattie]. They often referred to their sleep schedule as *erratic* [Fonny; Milan] or *sporadic* [Elisha], and complained about *poor sleep scheduling* [David]. For some people this might be a consequence of circadian misalignment, explaining that *my body clock seems to be slightly out… [feeling] more awake at midnight than I am perhaps at lunch time* [Fonny] and elaborating that *I obviously sleep later into the morning… to make up for the fact that I had taken ages to go to sleep* [Giovanni].

Participants also reported problems *oversleeping* [Richard; Gabriel; Leona], recalling periods like *sleep marathons* [David] where they *could sleep up to 16 hours* [Milan] a day, and *sleepiness was affecting my day-to-day life* [John]. These appear to be more frequent during depression episodes; *If I'm in a low, it's very very difficult to stay awake through the day. Cause I'll tend to want to sleep through the day* [Isaac]. As expected, the opposite effect was observed in periods of hypomania, with participants *not wanting to go to bed* [Tish]; *If I'm on a high then nothing really helps you sleep. You just, you're just wired, you're just constantly on the go* [Fonny]; and generally, *if I was in the hypomanic phase, I would sleep a lot less, be getting up a lot earlier, be going to bed later* [Gabriel]. Overall, people said that even though *sleep varies depending on my mood* [Richard] and *some nights were more difficult than other* [David], *sleep problems are always there* [John] and *to be honest it's every*

night [Isaac]. Two participants highlighted that their sleep and mood are seasonally dependent:

- *I think so much of what I have tends to be seasonable… my anxiety and insomnia would tend to occur more in winter time… so in summer time although I was sleeping less, I would feel like I had plenty of energy and life was good and ah things are manageable. But then my sleep got disrupted [again] during the winter. Low, you know awake through sort of dark nights. And it was dark when I was supposed to get up again. I think that was really challenging* [Daniel]

Effects of sleep disruptions on mood and daily life

Participants highlighted several areas affected by their poor sleep. Several people reported problems with their *memory* [Rufus; Gabriel], *judgment* [John], and said that *If I wasn't sleeping, the next day my concertation would be very poor* [Leona]. In terms of mood, participants talked about feeling *completely worn out and exhausted* [Rufus], *groggy* [Leona], *irritable* [Leona] and *frustrated* [Tish; Sonny]. Participants acknowledged the effects of poor sleep on their mental health as being *massive* [Gabriel; Hattie] and *detrimental* [Richard], and highlighted being hypervigilant of this association.

- *I always think that I need to have regular sleep to maintain my mood so if it goes off for any reason then I notice it quite quickly because… I know that if I don't sleep properly then it can trigger me to become higher or lower. So, it's always on the back of your mind. Like oh I've got to [pay attention to my] sleep patterns to stay well* [Florence]

Sleep disruptions have also had an impact on participants' daily life. People explained that sleep problems *have had in the past had an impact on my professional life. I've had to take sick leave* [Milan], *not being able to work at the moment because I sleep in the mornings* [Hattie], and *not [being] able to stay on top of those aspects enough to be able to maintain employment* [Clara]. Sleep loss further interferes with tasks like *driving* [David; Rufus; John; Leona], with participants saying that *at times I feel sleepy when I'm driving; sometimes I have to stop driving and pull over* [Hattie]. There

were also comments on the effects on interpersonal relationships, with participants *feeling quite isolated. Because I would avoid going out because I didn't want to have a late night. Or just be feeling tired.. So, it would impact, you know, both my kind of personal and home life* [Roy], with others adding that *my sleep has always quite disrupted… my relationships. And this… struggle to selfcare… maintain my exercise and keep a routine and everything because I feel like I was always trying to keep on top of my sleep* [Clara].

Onset of sleep disruptions and situations exacerbating them

Almost every participant referred to *life-long sleep issues* [John], and although the nature of these *problems would change* through their diagnosis [Hattie], *there were issues before then* [David]. Some people recalled sleep issues *since I was a child really* [David], or for *years and years* [Isaac] or simply *never been a very good sleeper* [Fonny]. One participant only started experiencing sleep disruptions around the time *when I was diagnosed with bipolar in a manic episode* [Milan]. Two of the participants that reported lifelong sleep disruptions shared that these disruptions got worse post-partum [David; Rufus]. Other factor exacerbating existing sleep problems include anxiety over *the socio-political climate* [David], physical health comorbidities, travelling, or work stress.

Sleep disruptions as precursors of other BD symptoms

Sleep disruptions were often described as *precursors* [Elisha] to other BD symptoms, and several participants elaborated on how they use sleep to monitor their own diagnosis:

- *That's normally a good indicator for me that something's not quite right you know… I got the bipolar diagnosis about 20 years ago and I know my body pretty well now, so I would totally say sleep [is] a really accurate indicator* [Sonny]
- *With the depressive episodes, it's often one of the things that I notice first or my partner would notice first. It's needing to sleep more. That can often be one of the early kind of signs. And then when I'm*

in a high, that's probably one of the early things as well. It's just not sleeping, [having a] very over-active mind, not feeling like I need to sleep but finding it really difficult to get to sleep when I try to. Yeah, so sleep is early thing in both types of episodes. It's an early indicator I guess [Hattie]

- *I would say I notice a change in my sleep maybe about a week or two before I would have an episode of high* [Leona]

One participant reported sleep problems *starting a bit later* [Rufus] than other symptoms, and one more participant said that all symptoms start *around the same time* [Tish]. Despite noticing sleep disruptions earlier and using them for self-monitoring, participants clarified that *it's hard to unpick the causality; whether the sleep affects my depression or depression affect my sleep, but I know that they are really interlinked* [Roy]. The bidirectional relationship between sleep and mood was often described as a *chicken and egg* [Richard; Milan; Clara] issue. *I think certainly… poor sleep influences mental health but then you know it's chicken and egg isn't it?* [David]. Other people preferred to refer to this relationship as *self-reinforcing problem* [David]:

- *I've have had periods where I worry about going to sleep.. that's sort of what I would call insomnia. When I go into these phases, it can be quite difficult to get out. Becomes a bit self-reinforcing… I try… to exercise a bit more, try to have a hot bath in the evening, try to do yoga, things like that. But then comes a point where I can remember… just thinking I really hope this makes me go to sleep rather than actually just [doing the activity] for the pleasure of the activity itself* [Daniel]

Regardless of the nature of the relationship, the importance of sleep for people with BD was emphasised repeatedly: *I feel like… it gets treated as just this sort of side thing. Whereas with bipolar, I find… sleep is just a massive, massive factor. It's just really important. And at times when I haven't had enough sleep for whatever reason, not for being in a high, but just for whatever reason, that can be a real trigger for episodes. Yeah, I just find sleep and bipolar are like massively intertwined for me. It's one of the most important things* [Hattie]

Self-management of sleep disruptions

Even prior to participating in our study people had developed ways to manage their sleep problems. These approaches included *herbal supplements* [John], *listening* [Tish] or *reading to go to sleep* [Giovanni], *having hot showers* [Daniel], practising *mindfulness* [DGB0026]. Some people said they already knew some elements of CBT-I, especially around sleep hygiene, and were trying to adopt them. For example, a participant mentioned that *in my worst episodes my partner and I used to [have]… a system on paper to try and look [into my sleep and mood]… It wasn't very easy to do. We used to just try and grade mood and sleep from 1 to 10* [Hattie]. Others reported trying to maintain a consistent sleep and wake schedule [Sonny], and coincidentally practising stimulus control therapy: *I'm fortunate enough to be able to have another room that I can go to. And so, I can kind of break that connection if I got a bad connection with the bed in that room I can [go] somewhere else and break it up a bit. My anxiety just gets harder and harder if I stay in the same bed and try to get to sleep* [Clara].

Some individuals also viewed sleep as a pathway to directly influence their mood, with reports that they *shortened my sleep to improve my mood* [David], and u*se sleep as kind of a self-harm strategy sometimes when I'm not feeling well or feeling quite low, I will intentionally disrupt my sleep or over sleep* [Clara]. However, the most common approach towards sleep problems, was accepting them as natural. *It is what it is* [Milan]

- *It's hard to know because [the sleep problems have] been going on for so long I don't know what I would feel like if I had really good sleep anymore. I just don't know what it's like so. But I know it's a lot better* [Rufus]
- *Because I've had it all lifelong, well, that's just me, it's natural for me. And there is nothing really to cure because I'm just the way that I am naturally. Uh so that was the reason why I didn't go to see a doctor. Had I however slept perfectly all my life and all of a sudden gone through a period of sleeping badly perhaps due to a redundancy or a divorce then I might say look I'm sleeping badly, it's out of character for me, can you help me. But, for me it's never been out of character* [John]

This behaviour partly resulted from participants knowing how prevalent sleep problems are in BD. *It's not just me who's struggling with something. It's actually something that lots of people with bipolar struggle with* [Hattie], *but I always thought to myself well, not everybody sleeps well. Some people sleep badly* [John]. Sometimes people would talk *about it to other friends and see what thoughts or recommendations they might have* [John] but often people resorted to doing their *own digging around all this* [David], and *never thought of seeing a doctor* [John].

6.4.2 Theme 2: Clinical Response to Sleep Disruptions

Clinicians enquiring and responding to sleep disruptions

Almost all participants recalled being asked about their sleep during a clinical appointment, particularly *when I got diagnosed with bipolar… it was a little more frequent* [Tish]. There was an equal split between general practitioners and psychiatrists asking about people's sleep. One of the three participants that had never talked to a clinician about their sleep had *discussed it once with a pharmacist…* [who] *recommended I try some herbal supplements* [John].

In most cases, clinicians responded by prescribing medication, such as *zopiclone* [David; Gabriel] or other *sleeping tables* [Fonny; Leona; Milan], *clozapine* [Isaac], *quetiapine* [Fonny], *antidepressants* [Isaac], *antihistamines* [Richard] or *mood stabilisers* [Elisha; Richard]. There were instances where clinicians recommended non-pharmacological approaches too, including *breathing exercises* [Richard; Florence], *self-help tips* [Tish], and *psychoeducation* [Roy]. In general, participants shared a feeling that sleep problems were underappreciated by clinicians, and often *treated as just this sort of side thing* [Hattie].

- *You don't really get much response because the psychiatrists I've spoken to thought [sleep problems are] part of the symptoms of bipolar so they would give you the different medications like your mood stabilizes and [expect] that would help. They don't address sleep as an issue on its own… [they are] often resistant to address it as a standalone. In my experience* [Elisha]

Perception of clinical response to sleep disruptions

Participants were mostly unhappy with the clinical response when they reported problems with their sleep. They felt that their complaints *were not taken very seriously* [Rufus], and the situation was *badly handled* [David]. The dissatisfaction often originated from the improvidence of the choice to respond to sleep complaints with short-term medication. People acknowledged that *this wasn't a long-term solution, so I wasn't massively pleased* [Giovanni], and were frustrated that despite the frequency of these complaints, the approach of the attending clinician did not change: *every time I went to the doctor, he just gave me antidepressants, not connecting the fact that it was every few months. So yeah, that wasn't very understanding* [Leona]. Participants believed that the lack of a targeted long-term solution is partly the reason why their mental health got worse during some episodes: *I don't know if I was expecting much more but I wasn't satisfied I didn't get any extra help because this made things worse* [Elisha] and *I don't think it was taken very seriously. And I just. Well, I juts ploughed on with it. And it just. As I say it just got worse and worse and worse* [Rufus].

On the other hand, participants also acknowledged the complexity of the situation, and explained how a lot of their frustration is due to the fact that in mental health there is not *a clear cause, a clear issue, and a clear treatment; as simple as when you break a bone, that would be the ideal thing* [Clara]. Even people that were dissatisfied with the clinical response to their sleep complaints mentioned that although the response was n*ot ideal, but I don't think there is a quick solution to it; like there isn't a bad solution, you can't wave a magic wand and go back to a normal sleeping pattern* [Milan].

There are two participants that were satisfied with the response to their sleep complaints, explaining that they are grateful for having *very good access to mental health services and I think certainly if I bring up anything that's been an issue including sleep, then they do take that very seriously* [Richard].

– *I remember when I was first diagnosed, the psychiatrist that I always spoke to, the first thing that she would ask me about was my sleep, cause she realised how important that is -I guess for everybody- but you know she obviously picked up that sleep is really important for me… From a medication perspective, like in an ideal world I think they would probably do a little bit more to address the causes of my problems rather than using medication. But I'm really aware that actually not everybody would be offered sleeping medication. It's often seen as the last resort. So, the fact that they will give me a small amount of medication without asking too many questions, which means that they trust me to use it responsibly* [Roy]

Medication to alleviate sleep disruptions

Although it was not a focus of our pre-defined schedule for the semi-structured interviews, participants emphasised their experiences with various medications that were prescribed to them to alleviate their sleep disruptions. These included promethazine, diazepine, zopiclone, melatonin, chlorpromazine, chlorphenamine, quetiapine and other non-specified antidepressants and mood stabilisers. Participants felt that their medication made them feel *drugged up* [Fonny], *foggy and drowsy the next day* [Florence], and prohibiting them from *functioning… and getting on with life* [Fonny]. As such, many participants were *interested to look at ways to sleep better other than drugging myself to sleep* [John], and wanted to be able to manage their sleep problems autonomously and without the use of medication: *[I am looking for] other ways I could manage my own sleep patterns, so I don't have to use any type of medication in the future. You know so that I could manage it myself a bit better* [Leona].

It is worth noting that some participants were at least partly satisfied with the medication for their sleep, as *I felt the only thing that was improving my sleep was taking medication every now and again… taking some medication after two or three bad night's sleep is a bit of a reset button* [Roy]. For many it was the only thing that *would make me sleep solidly through the night* [John] and

although *I do feel even if a bit groggy in the morning… I do find that I feel refreshed because I, it has enabled me to get some sleep* [John].

6.4.3 Theme 3: Experience with CBT-I Treatment

Motivation and expectations from the DIGIT-B study

Compounding on the need to *look for things beyond medication* [Clara], every participant joined the DIGIT-B study looking for ways to understand and improve their sleep. Almost every participant was also motivated by a need to *help other people with bipolar as well; to try and not solve the problem, but try and help other people that, that do suffer with bipolar and sleep disorders* [Fonny]. People were also *interested in research* [Tish] and highlighted that *medical research is so important* [Sonny] that *I try to participate in research whenever I can because to be honest anything that can try and advance the you know the knowledge of this condition and try and advance the treatment and understanding it's a good thing* [Richard]. Generally, people wanted to *be able to help… in any of the bipolar research studies* [Hattie], and felt that you know I can't lose anything [Isaac] as *there is no downside to doing something like this* [Daniel].

People admitted to having *good intentions* [David], but *not very big expectations* [Tish] from the study prior to participating, *but also I was really keen to try a different approach to improving my sleep and get a bit of support from someone or something else other than medication and kind of my own knowledge I guess* [Roy]

- *I'm not sure I've had very like big expectations. I think there was a slight bias that I didn't think it was going to help, because I've been struggling with my sleep for such a long time, I think everything I was doing was the thing that worked best… so I think I was a little biased for it not going well* [Tish]

Sleep improvements after treatment

For many people, the treatment led to a *huge difference* [Giovanni] and *big changes that have been really positive* [Isaac], and *only really been since I started the app that things started to gradually improve* [David].

For many people, one of the most notable improvements after treatment was *not sleeping throughout the day, whereas when I was depressed before I just slept all day because it was easier than having to face, you know, the bad mood, the bad days* [Isaac]. It was reiterated that *I'm not actually napping as much during the day. Now that I think of it, even when I do have a nap, it's maybe for 20 max you know, and that's what the app said* [Leona]. Post-treatment sleep was also more *consolidated* [Daniel], and participants reported *waking up throughout the night a lot less than I used to… and I've just noticed that instead of my head running, it's clear. So, I can get back to sleep a lot quicker so I know that even though I don't time it, I know that it's been less because I'm less tired* [Isaac]. Awakenings did not completely dissipate for most people, *but it's calmed down a lot* [Leona], and participants acknowledged that although *it's fewer awakenings, I also think it's because my mood's been lifted a bit* [Isaac]. Fewer people mentioned *sleeping more hours* [John] and *getting out of bed as soon as I wake up* [Isaac]. The frequency of nightmares was also reduced [Isaac], and so was sleep onset latency.

- *Now when I get into bed, I typically fall asleep pretty quickly… I'm used to sleep within 10 minutes maximum. Sometimes I fall asleep straight away, sometimes it takes a few minutes but that is compared to it taking up to several hours sometimes before taking part in this study so that's a huge difference for me* [Giovanni]

CBT-I also enabled participants to establish and maintain a regular sleep routine: *I'm trying to keep the same bedtime and awake time. I'm probably not quite as consistent at the weekend, because it needs to be sustainable, but I'm definitely not lying in too late* [Roy]. The discussion focused on *activating activities and activities that aren't activating* [Giovanni], such as *exercise* [Milan] and *seeing friends* [Giovanni], or *having a bath and put a face pack on* [Florence]. Participants noted that

some of their habits diverge from the recommended activities. *I've started to read before bed, which wasn't part of the app, but I find it relaxing. So, I probably find that more relaxing than watching television, so that's one sort of change that I've made. But it's still keeping with the principles* [Roy]. People also started *not drinking caffeine after a certain time* [Fonny], *not smoking for hours before bed* [Elisha], and *switched to decaf tea in the evening* [Roy]. A few participants also referred to the benefits of *tidying up your bedroom* [John] and *clearing your room of [clutter]* [Sonny].

In terms of the psychoeducation element of the treatment, participants *already knew* [Fonny] some of the guidelines included in Sleepio, yet the app *reinforced* [Fonny; Richard] and *cemented* [John] this existing knowledge, and *just knowing that sleep disruptions are very common… I think it's, it's quite reassuring* [Richard].

- *I think that what is good about it is the fact that even if you knew most of those points either instinctively or by being told about them in the past, it reiterated those points to you so it reminded you of things you might have perhaps been told in the past. But also, it often explained the reason why such a thing was a good idea… and they gave you the logic behind some of the approaches. And that I felt was useful in cementing the ideas in my mind and explaining to me why it makes sense to follow them* [John].

Most importantly, participants said although *it might take a while to change the way that I think about sleep and my habits and stuff, I feel like I got the tools in my head now to start working on it* [Hattie]. Sleepio helped people *feel a bit more maybe empowered… and it's just helpful knowing that I've got other tools in my toolbox for sleep as a whole. There's things that I might help might build on those too… Knowing that I have more tools I feel less helpless around it. And less kind of wanting someone else to fix it. I know that it's going to take time. There are things that I just need to practice* [DGB0026].

On the other hand, some participants *didn't know whether anything [regarding my sleep behaviours] has really changed that much* [Fonny]. They admitted that they are *not sure if I'm sleeping any more than I used to* [Elisha] and they believe that their sleep is *probably about the same really*

[Florence]. They reported *frustration* [Tish] due to the small changes in sleep, and clearly seeing *room for improvement* [David]. However, even though behavioural sleep outcomes might have remained stable for some participants, the same individuals explained that what is most important to them is that CBT-I *has taken away a stressor in my life. It might be that I'm still tired but it's not a big a deal. I don't get annoyed with myself for not being able to sleep which I would do sometimes. So yeah, it's taken the stressor away from sleep* [Elisha]. All participants shared that they *don't feel so stressed about it now* [Rufus], and they are *much happier about my sleep… there's not sort of this source of cause of stress for me anymore* [Giovanni]. Participants also felt empowered and *a little bit more in control of it rather than letting it control me* [Hattie].

- *I'm spending less time in bed, I'm spending less time asleep, but my sleep quality is better. So, I feel much more awake during the day and feel like I've got two or three hours back in the day. Because I'm not spending time in bed… it's made quite a big difference to the quality of my sleep rather than the quantity. I'm more relaxed about sleep… because I'm reassured that I'm getting better quality sleep. There is also learning from the app that actually it's okay to have a bad night sleep… I can still see that having better quality sleep really does impact my mood and my productivity the next day, because on the occasional nights where I've not had a very good sleep… I still sort of feel a bit sluggish, but I'm not worried about it* [Roy]
- *I don't think I'm as anxious about sleep. I'm not as, I'm not as like worried that if I don't get sleep you know it's not going to be the end of the world type of thing* [Leona]
- *I would say that it's very much like a kind of cognitive change in that I don't feel that pressure to go to sleep and I know it sounds kind of weird, like, I know that I can cope without sleep… it kind of takes [away] that anxiety* [Tish]

Mood and daily life improvements after treatment

In addition to sleep related improvements, CBT-I helped participants have *more energy that enables me to sustain myself through the day* [John], are *a lot more alert* [David], have fewer

anxious thoughts [Tish], and they *feel more hopeful* [Hattie] and *not as negative about things* [David]. They also *feel more empowered* [Clara] and are *more able to let things go… my tendency to ruminate has really decreased quite significantly* [David]. There was a shared sentiment of generally *feeling better* [Sonny] after treatment, and although some participants were certain that they *feel less depressed as a result of sleeping better* [John], others believed that *my mood is a lot better… and some of that could be attributed to sleep as well, but It's hard to tell. I definitely feel more confident in my ability to sleep now* [Roy]. One participant specifically indicated that *I think using an app like that could help you understand patterns and maybe sometimes see early warning signs, I think it is a brilliant idea in that sense* [Hattie]. For many people it was *hard to unpick* [Roy] *whether it's really the intervention that's really made a difference* [Fonny], or improvements in other areas such as university/work [David; Tish; Richard], or naturally coming out of a depression episode during the study [Roy]. This was seen as a potential shortcoming of the treatment and the study recruitment strategy:

- *In bipolar your sleeping pattern is not always the same. It goes in cycles, [this is] the nature of bipolar. So, I think this was very much focused on the depressive/anxiety stage. And I think that's what you recruited people for. But also, like you can't say yes, I'm going to be depressed for the next 8 weeks of your intervention. Cause I think at the beginning I was experiencing depressive episodes, and I had just increased my antidepressants. But coming out of that, my sleep has changed. It changes. The mood also changes. That's what I'm trying to say* [Milan]

Regardless, the change in mood enabled people to improve their daily lives: *I'm a lot more positive than I was. I don't feel as worn out all day and it has lifted my mood. I feel more interested in doing things. Like I've got more energy now. Had very little energy before. So I'm engaging in a lot more like with my children and my grandchildren and things like that, which is good* [Isaac]. Additional daily life improvements include people feeling that they have *more brain capacity* [Richard] and are *more able to do the things that I want to do* [David]. Participants also reported that *I think the biggest thing*

has been… that when I'm driving I'm a lot more alert than I was [David], *I actually feel safer now driving… like 90% of the time I do feel more safe now doing basic driving and stuff like that* [Leona].

Caveats to seeing improvement

The most frequently reported caveats to improvement were financial difficulties. A participant reported that they *live in a very cramped premises for financial reasons so it's very hard to declutter and move things around* [John]. Some other treatment recommendations were impractical specifically for people in house-shares. For example, *I live in a house-share… so if I want my peace and quiet before bed, I would go lay on my bed, not necessarily sleep, and the app says what time you get into bed, but I'm just there resting. So, in a way that might have skewed slightly the result I put in there. Made me look less efficient in sleeping* [Milan]. Stimulus control was another treatment element that was hard to follow. This is either because they did not want to *make noise* [Rufus] and wake up their housemates, or because their *house is very cold in the winter* [Rufus] and are unable to heat more than one room. One participant also mentioned that the *sociopolitical climate… over the last three years… and living alone* [David] also influence their *mood and levels of energy* [David], so there is limited capacity for sleep improvements to affect their mood and energy to a greater extent.

Pros and cons of specific treatment sessions and elements

A lot of the discussion around specific treatment sessions focused on sleep restriction therapy. People admitted that *it was very difficult, it was very challenging to do. I think that it was very prescriptive, again, because it was like you got to do this and then try and keep up with that, as well as keep up with the sleep diaries. It was really challenging. That was probably the most challenging part* [Gabriel]. Participants struggled *not sleeping through the day* [Isaac] and *being disciplined with it* [Clara]. It was also suggested that some *needed more sleep than what it was suggested* [Fonny] and were feeling *too tired when I was doing the sleep restriction* [Fonny]. As a result, two participants

chose to minimise their engagement with the restriction element and *made the decision because I know that about my sleep already. I made the decision to not follow that exactly* [Richard].

Nevertheless, the majority of participants found that *sleep restriction was quite interesting* [Sonny] and *it did work* [Leona], despite their initial reservations. *The fact that it wasn't asking you to only sleep 4 hours was really good. The fact that it was more. Well for me anyway. It worked out that it was only kinda taking 15 minutes off at the start and at the end of my sleep in the morning. That worked really well. It wasn't kind of triggering me into hypomania. It just yeah, it was fine* [Giovanni]. The most important benefit of the restriction therapy appeared to be relieving the pressure to follow perceived norms around bedtime and encouraging participants to go to bed when they are tired.

- *I went into the sleep restriction thinking, not sure it's really going to help my particular problem, mainly because the app seemed to be geared towards people that struggled to get to sleep or that maybe woke up early… So, I was presently surprised how effective [it was]. It works and I think the app made the sleep restriction a bit easier. Cause it was quite upfront about that it was going to be difficult and, you know, you'd have to stay awake or you'd have to get up early and you have to consistent with it… but now I'm surprised about how much difference that has made* [Roy]
- *I thought the sleep restriction was quite good because I think it took away the pressure to fall asleep, and because I'd like had that designated time to be like oh this is when you go to sleep. It wasn't like me going to bed early cause I think I was always forcing myself to be like you need to be in bed early, you need to be trying to sleep. And I found that really helpful because I was actually going to bed when I was tired, instead of being like the norm is you have to go to sleep now. So I found that really beneficial and just like easing off that pressure* [Tish]

One participant was critical of sleep restriction therapy, and suggested that the session might not be suitable for people who are new to the BD diagnosis

- *I think if someone was quite new to the diagnosis or hadn't quite worked out their [sleep] patterns and they follow this really rigidly, I think there is a danger that it would make them ill… I think it obviously it depends on how much a person understands about their condition. It also depends on how it's monitored. Whether it's monitored by health professionals or whether there is someone they can turn to for advice when they are using it… I think that would work. I think that might be fine… it is always difficult when you're talking about people, or involving people who are potentially quite vulnerable. And especially if they don't have a good understanding of their condition.. I think [sleep restriction therapy] would probably work with insomnia but maybe not with people with bipolar* [Richard]

Participants enjoyed filling the diaries and actually some found this to be the most therapeutic phase of the treatment: *the most effective part for me was actually the baseline phase, cause it just got me thinking about my sleep in a different way and made me question some of my habits and how effective my sleep hygiene really was* [Roy]. Filling in the diaries helped them be more conscious [Fonny], and *concentrate* on their sleep [David]. Additionally, *purely from a sort of data point of view* [Richard], participants appreciated the ability to *look through the diary because I could definitely see the sleep I would get* [Sonny]. Although thought that the sleep diary was really easy to complete [Roy], others believed that the expectation to fill it daily could become overwhelming.

- *For me I know, I mean I know this is the same for some other people with bipolar, if you have a very low mood and you are told you that have to do certain things, it can exacerbate that condition… And although there's nothing about the sleep diary which is actually onerous, it's really really quick, it doesn't take very long, I think sometimes having that pressure, oh I've got to do this, it's just another little burden that's kind of put on you* [Richard]

Additionally, even in the pre-treatment phase, participants were encouraged to fill in the diary with their best time estimation and avoid clock watching. However, some people still struggled avoiding clock watching: *I just remember thinking like when I'm going to sleep, I'm not*

focused on checking the clock. What time [it is]. And actually, when I first started doing the diary, I got very like hocked up on it, making sure I was doing it properly. Later I just guessed the time [Clara].

Finally, many participants said that they particularly enjoyed the cognitive shuffle and restructuring techniques, emphasising how much they helped them relax around bedtime: *the one where it says repeat a neutral word like 'the'. It really helped… I can go back to sleep a lot quicker now than I did before, because my mind is not racing nearly as much as it used to* [Isaac]. Contrarily, one participant reported that *this was the only one [session] I would have said I had major issues with* [Sonny]. Other participants said the enjoyed *progressive relaxation and tense and release* [Clara] or stimulus control therapy [David] the most. Participants also liked the psychoeducation elements of the intervention, *the background behind why sleep problems occur, the fact that it is regular within a lot of the population* [Gabriel].

Using CBT-I in the future

Participants indicated a general interest to continue engaging with the intervention, especially during acute episodes: *my overall takeaway on the app is that when I feel like I'm going into a bad episode again… [I can] sign up to the app and use it* [Daniel]. Some participants said that the app would be useful both when feeling *higher or lower* [Leona], whereas others specified that they believe the intervention would be most helpful in hypomania. I *haven't had a high while I've been learning about Sleepio, but I can see how it can would really help with that. Because in the past all I've done when I try to get to sleep when I'm high is just lie there and then it's even more frustrating because it doesn't happen. Whereas I can imagine now with some of the sort of techniques, that would give something kind of constructive to work through. So I can see it being really useful for that* [Hattie]. One participant offered a different perspective, arguing that *if there is something that could help me avoid a mood episode then I would always go for that. I don't think a digital intervention would necessarily be enough when I'm in, say a really bad period of depression. And I probably wouldn't engage with it if I was in a period of high mood. So, you know you have to kind of pick the right delivery method for symptoms I guess* [Roy].

Regarding specific treatment elements, participants found SE to be a useful metric, saying that *if I notice my sleep slipping again, I'd start like tracking the sleep efficacy. Just to keep an eye on it… and then that way at least I could take it to my psychiatrist and be like okay this is, this is something* [Milan]. People also indicated an intention to reimplement sleep restriction *as I get other parts of my life rebuild, so getting back in to work… get more into routine* [Clara], and continue engaging generally *with the behavioural elements* [Milan].

6.4.4 Theme 4: Experience with the Sleepio App

Positives of the Sleepio app

Regarding the app, participants said that *on the whole I found it quite good* [Giovanni], that *this experience has been really positive* [Roy], and they *recommended it to other people* [Rufus; John].

Sleepio is just so easy to use [Hattie]. The most common positive element of the app were the *notifications about when sessions are ready* [Richard] and the *daily reminder for logging the sleep diary* [Elisha]. There was also a lot of positive feedback about the Sleepio interface, such as the *narrator* [David; John; Clara] and general *presentation* [Richard] of information. The most important element in this respect was the fact that *Sleepio was not too cheesy or patronizing which some [mental health apps] are sometime* [Richard]. *I mean despite being really cynical about it, I think it was pitched at the right level. So even though it was telling me stuff I already knew, I was like actually you know it was kind of treating me like an adult, and talking about kind of real life situations and stuff* [Clara].

Participants appreciated that Sleepio provided them access to their own data so they can track their progress: *there is a balance I guess to understand the data without getting obsessed by it, and generally, I'm pretty comfortable. I quite like knowing roughly how long I slept and seeing the confirmation of that… It just gives me a bit a reference* [Daniel]. *I've seen the benefit and it's really suited my bipolar and the condition that I've got. It's just been a real positive experience that I've actually been able to see the*

results myself because I've gone alone. So that's made a big difference as well [Isaac]. In this respect, participants were also grateful *that you could integrate [Sleepio] with Fitbit* [Roy], and were using their personal actiwatches in conjunction with the Sleepio diary to maximise the sleep information they were receiving: *I'll always charge up my watch, making sure it's charged before I go to bed so I can get that sleep data. It just give me a bit a reference, but having the Sleepio diary actually is an enhancement to that I think. You get a little bit more of a backup. It's a bit more consistent. And it makes me think about how long I've taken to get out of bed. Whereas that's not really a thing in, with the watch* [Daniel].

Some people also thought *it was also quite good that you could access this range of resources… there is a little bank of like worksheets and stuff you could access if you wanted to* [Milan] and liked the freedom and autonomy Sleepio provided them with, since *the app was giving you different things to do each day and you were having some choice in which of those things you would pick and that I think is the big plus point* [John].

People enjoyed the incremental nature of Sleepio and that *the structure builds upon the different things… step by step and doesn't try to bombard you with too many things at once. It gives you space to try and tailor [the recommendations]* [Clara]. *I think it's very clear. I think the, the way it's structured [where] you can see the kind of path it's following. It's quite logical. Everything follows on from the last thing quite well, so it does flow. It's got a bit of kind of a storyline to it which is nice* [Richard]. Generally, *it's very structured, which I think the many people would work very well* [Clara], *the more you get into the app, the more of these tools or techniques you learn, and the more of these suggestions you follow, the better it becomes* [John]. Participants appreciated *the length of it as well. You know it wasn't too long, but it felt like there was enough content each week* [Roy]. *I liked that they were weekly… [and that] at the end of each session [Sleepio indicates] what you will do next* [Tish].

Finally, although the intervention could also be accessed from a laptop or computer through a browser, most participants only used Sleepio through their phone app: *having the*

app on your phone than having to go and open up a laptop or start up a desktop and do a similar thing through a browser or whatever. The app is definitely the way to go. I've enjoyed doing it on the app [John].

Negatives of the Sleepio app

A few participants found it *annoying that I can't do the next session for a week, but I can get that at the same time because then somebody might just rush through them. But there's been a couple of times where I wanted to just do like another session and not have to wait a week* [Hattie]. Participants acknowledged that this might be due to poor *time management* [Sonny], and although *the staggering bit sort of makes sense, it's actually resulted in me taking ages to complete the course rather than week by week* [Clara]. There were also difficulties adhering to the Sleepio schedule, with people *putting it off for days* [Tish]. *It's just been difficult sometimes being as disciplined as I would have like because my kind of general mood at the moment hasn't been great so I do wonder if I had been in a, a maybe kind of more, kind of normal kind of period whether this would have benefited me more* [Sonny].

Some people had enquiries about the SE outcome that was used by Sleepio to monitor progress, and expressed frustration that *something is stopping me from reaching that 10 [100%]* [John]. Others found it difficult to *pinpoint the specific things that I'm struggling with* [Tish] on the app, and one participant disagreed with the notion in the app that *reading is an activating activity… I find that really relaxing and actually it sends me to sleep* [Roy]. Participants also found Sleepio to be more suited for insomnia as opposed to excessive daytime sleepiness, and even in insomnia they found the focus to be overly concentrated on improving onset latency rather than night-time awakenings.

– *I think it was more focused on people with insomnia rather than people who oversleep like myself. It can get one way or the other quite quickly. It can change from week to week, but I feel like the emphasis was more on insomnia* [Milan]

– *I went into the sleep restriction thinking, not sure it's really going help my particular problem, mainly because the app seemed to be geared towards people that struggled to get to sleep or that maybe woke up early* [Roy]

A few people experienced *irritating* [Milan] glitches with Sleepio, either when *logging in* [Rufus], *completing the daily questionnaire* [Elisha] or *finishing a session* [Hattie]. One participant also found the glitches disruptive for their sleep routine as *I listen to sessions before I went to sleep* [Elisha]. Apart from these glitches, no technical issues were mentioned by more than one participant. Some of them included too many notifications [Tish], not enough notifications [David], not being able to access Sleepio on airplane mode [David] and not being able to speed up the video sessions [Milan]. A participant mentioned that ideally, *I don't want to be more reliant on digital stuff really* [Clara] and another one said that by filling in the digital diary at night *I was probably breaking one of the rules by having the phone in the room* [Sonny].

Recommendations for improving the Sleepio app

The most common proposed improvement for Sleepio was *more personalisation* [Tish], with the ability to *ask questions* [Richard], *tailor it to what your sleep history is* [Gabriel], and *more flexibility [around] the action planning* [Roy]. Some participants suggested integrating more relaxation techniques within Sleepio, such as *mindfulness aspects* [Gabriel] and *yoga* [Clara]. Other proposed additions included components that *help people break bad habits… and follow through [with the treatment]* [David] and either *group sessions* [Tish] or *more of a community element to kind of engage with other people that are going through this and share experiences [*Roy].

Regarding technical elements of the app, participants would like to see an option to *fast forward* [Milan] and *choose the speed of videos* [Giovanni]. They also would like to *be reminded more than once [to complete the sleep diary]. The reminder comes up in the morning and often I would just think oh yeah, I need to do that, but I can easily just forget… I could do with being reminded again if I haven't done it* [Hattie]. Other participants also highlighted that have *another reminder during the*

day would have been helpful, you know like later on in the day [Leona]. Participants also suggested *access to a bit more data* [Giovanni], and better integration between the *digital interface and the actigraph* [Gabriel].

6.4.4 Theme 5: The Digital Element of the Study and Intervention

Past experiences with digital interventions

The majority of participants had never used a digital intervention before. The ones that did had all used meditation and mindfulness apps. People reported low adherence to these apps for a variety of reasons, including a *patronising* advice [Roy] and lack of *reminders* [David]. In the future, people said they *would be more than happy to take part in [another] digital intervention* [John] to *address another problem that I am having at the time* [Richard]. An important criterion for engaging with another digital intervention is the quality of the providers: *as long as the thing is credited, I'd be sensible about it. I wouldn't just be trying any old thing… because like on [social media] and stuff I'm constantly getting adverts for mindfulness apps and that kind of thing. See I wouldn't be averse to trying some of those, but again I would be very mindful to make sure it was only an app that had been produced and developed by people like yourselves rather than some random person… that has an online degree or something, you know what I mean* [Sonny].

Preference for digital or in-person

All but one participant said that they would prefer a digital version of the treatment, as opposed to in-person, if given the choice. *Accessibility* [David], *autonomy* [Tish] and *convenience* [John] were the most reported catalysts for making this decision. People mentioned that the *treatment was accessible anytime I wanted it* [Giovanni] which was important as some either did *not have the time to be able to physically go somewhere* [Richard] or *struggled to get out of the house… [when things were] really hard* [Isaac]. People also reported that in-person *appointments are lacking… the way that services are at the moment* [Elisha] and some *see my*

psychiatrist… digitally now too [Rufus]. People often referred to the concept of *being in the right headspace* [Isaac] for an intervention and how the app relieved *any pressure to do the sessions at a certain time and at a certain day. Must do it then. I've just done it when I had time or when I felt right to do it so* [DGB0022]. The *instant feedback* [Fonny] was also an element people of the app that people appreciated saying that *it was good to see your progress and the gaols you are working towards. It was good to look back and say okay I've improved from here to here* [Milan].

Some people also mentioned that this period they are particularly worried because *money has been awful* [John], and *I probably wouldn't have done [the treatment] if it wasn't free* [John]. More participants recognised that *the [lack of] money and resources… makes speaking to someone impossible for many people* [Clara]. Even though healthcare is free under the UK National Health Service, participants commented that *it still costs to go to somewhere to see a person obviously* [Elisha]. Others said that they would have *felt pressure* [Tish] meeting up with someone in-person, and *it would have been more difficult to turn up [to an in-person treatment]. I think I would have been like less engaged in the treatment plan just because it felt like quite like it would have felt really overwhelming* [Tish]. There was also a participant that was averse to in-person meetings, specifically due to concerns that *I'm going to get Covid* [David].

Additionally, *I think the thing with the digital is because you wake up fresh and first thing in the morning you can put the information in. Whereas [for in-person treatment] you'd had to write it down because you wouldn't really remember by the time you meet up with somebody. You'd forget the information* [Fonny]. The fact that Sleepio was digital also helped because *I could pause [the videos] and then I could come back later and carry on with where I was… cause my attention span isn't always great so I can kind of make sure that I am taking in all the information at a point that suits me* [Giovanni]. The digital element of Sleepio facilitated easier learning during the session as *if you've seen a particular sleep tool that you want to revisit, you can go into the app at any point and revisit that tool* [John], *which is good you know, cause you sort of need to refresh yourself every so often* [Fonny].

Only one participant showed a strong preference for in-person meetings, explaining *that's how I work… I like learning… through conversation… I realise for the last few years you can… use online stuff… but it's never quite the same… for me* [Clara]. Another mentioned that they would prefer a *50-50 split* [Gabriel] of in person and digital meetings. The rest of the participants showed a strong preference exclusively for a digital treatment, whether that is through an app, digital meetings with someone or a combination of both.

There was an even split between people who preferred using an app alone and those that preferred a combination of an app and digital meetings. None of these participants indicated a preference for digital meetings without the support of an app, arguing that *it would be great to have the app on a day-to-day basis* [Roy]. Among those that wanted an app exclusively, people said that *before taking part in the study maybe I would have opted for [virtual] face to face… but having done the app I'm really glad that it was available when I needed it to be available and I could kind of do it in my own time* [Giovanni]. The main reason was autonomy and the ability to choose the time they are in the *right headspace* [Isaac] to engage with an intervention, with people thinking that *I don't feel that there's really that much more that could be added by having a one-to-one person intervention that the app isn't already providing* [John].

- *No [I would not have preferred digital meetings], because then you'd be tied to a time and you might not be in a position to be receptive to learning. Like this is what I like. This way you can choose, set aside time when you can properly focus on it* [Hattie]
- *I wouldn't mind that [digital meetings]. But like I say, it's still, you're still tied to a time. You know things get in the way. For me, I work very varied hours. So, one time a week might suit me, and the next week maybe not suit me* [Leona]
- *No [I would not have preferred digital meetings] cause I can't commit to a certain time and day of the week. I don't know how I will be feeling… I think a regular meeting… would force me into a little section if you like, and this wouldn't work for me* [Isaac]

Among the people preferring a combination of an app with digital meetings, the main reason for opting for this type of blended intervention is so they can *ask questions, reassure you that you're doing it right or you know just to have that kind of additional support* [Roy].

- *If I've had low mood, then maybe I would have wanted that kind of reassurance. It's not necessarily to see someone physically or even have a videocall but It may be someone that you can send a message to within the app, or you know just outside to say oh can I just check on this, you know am I doing it right, should I do x, y, z, and that kind of thing. I think having that back up would be useful for a lot of people* [Richard]
- *At times when it's difficult or at times where you are perhaps not engaged and you might feel like. I am going to drop out, you know like the first week of sleep restriction, it would have be really good to kind have a check in at the end of the week and someone to say, keep going. It's working* [Roy]
- *And I have anxiety about outside the house as well. So it's depression in that situation but seeing somebody on a video and being able to talk through the progress and have a more organic conversation about the issue that you are having at the time may be more useful than the app. And use just the app to support the information and maybe ask questions about it* [Elisha]

6.5 Discussion

DIGIT-B is only the third study to examine the use of CBT-I in people with BD (Harvey et al., 2015; Jernelöv et al., 2022), and the first one to administer a digital adaptation of this intervention. It is also the first study to specifically recruit people with BD-II and deliver the treatment during a depressive episode. The aim of our research was to establish the safety, feasibility and acceptability of digital CBT-I for BD, and provide preliminary evidence regarding its clinical efficacy.

6.5.1 Feasibility, Acceptability and Safety

In line with previous publications (Harvey et al., 2015; Jernelöv et al., 2022), our research showed that CBT-I is safe, feasible and acceptable. Of the eligible participants, 83.33% completed 4/6 treatment sessions, which was our registered retention outcome. Participants provided a high overall acceptability rate (7.42 [sd=1.01]/10) on the modified theory informed acceptability measure, with particularly high scores on the items around acceptability (3.53 [sd=0.51]/4) and how much they liked the intervention (3.35 [sd=0.61]/4). The high scores on the importance of improving sleep (3.76 [sd=0.44]/4) render it possible that these effects are influenced by selection bias, a phenomenon that is highly prevalent in psychotherapy research (Kaźmierczak et al., 2023). Notwithstanding, sleep disruptions are among the most salient symptom domains for people living with BD (Chevance et al., 2020; Gordon-Smith et al., 2021), and clinical phenotyping of BD has highlighted that in 60-80% of depressive episodes in BD the underlying mechanism of action can be traced to a circadian dysregulation (Carpenter et al., 2021). As such, the high affinity for improving sleep could be a prevailing, yet arguably underappreciated, outcome in BD, instead of one that is prevalent in our sample due to selection bias.

No serious adverse events were reported, there was no indication of increased suicidality throughout the protocol, and the total unadjusted mean ASRMS scores remained below the cut-off point for possible hypomania. Although there was a steady increase in hypomania scores during treatment, our ASRMS scores at post-treatment were comparable to those obtained by larger trials on digital CBT-I in community samples, such as the OASIS trial (Freeman et al., 2017). The OASIS trial was a single blind RCT of digital CBT-I in university students, recruiting 3,755 participants split between arms. In this trial, the mean ASRMS scores increased in the treatment group between baseline and post-treatment, and at post-treatment participants in the active arm scored significantly higher in the ASRMS

compared to people in the control arm. At post-treatment, the unadjusted mean ASRMS score in the treatment arm of the OASIS trial was 3.77 (3.33), comparable to the one obtained by our study 3.94 (1.80). In both cases, higher ASRMS scores could indeed indicate an increase in hypomanic symptoms. However, it has been previously reported that ASRMS exhibits a poor correlation with self-reported measures of energy and elation (Tsanas et al., 2016), so an increase in mean scores could reflect a general increase in mental wellbeing (Freeman et al., 2017). Previous systematic reviews on symptom monitoring in BD have emphasised the difficulty of capturing elated mood, suggesting that mania self-reports might not necessarily represent the true nature of the clinical condition of (hypo)mania (Faurholt-Jepsen et al., 2016). Corroborating this line of evidence, psychometric evaluations of the ASRMS have shown that the measure has good sensitivity (93%) but low specificity (33%) (Altman et al., 2001). High sensitivity coupled with low specificity can lead to a high rate of false positives, i.e. people identified as exhibiting symptoms of (hypo)mania when they are not. Presently, ASRMS is the best measure available for pilot studies where the risks of a false negative outweigh the costs of a false positive in terms of switch to hypomania, yet a nuanced, granular re-examination of the available (hypo)mania measures and associated cut-off scores is needed.

6.5.2 Improvements in Sleep Outcomes

The digital intervention was associated with large improvements on our primary outcome of insomnia at post-treatment (d=-1.87; 95%CI: -2.77 to -0.98) and 3-month follow-up (d=-1.67; 95%CI: -2.72 to -0.62). There was also a notable reduction in the number of people screening positive for insomnia as post-treatment (27.78%) and follow-up (42.11%) compared to baseline (100%). These were corroborated by large improvements in sleep quality both at post-treatment (d=-1.18; 95%CI: -1.7 to -0.58) and at follow-up (d=-0.91; 95%CI: -1.48 to -0.33). Large improvements in insomnia scores are in line with

previously published studies on digital CBT-I in insomnia (Espie et al., 2019; Gao et al., 2022) and unipolar depression (van der Zweerde et al., 2019), as well as with the two aforementioned studies of in-person CBT-I in BD (Harvey et al., 2015; Jernelöv et al., 2022). Our findings reiterate the role of sleep as a modifiable target for intervention in BD, and emphasise the potentiality of digital CBT-I to improve insomnia symptoms in BD.

The improvements observed in global measures of insomnia were not as strong compared to those reported by sleep diaries. With the exception of a large improvement in SOL at post-treatment (d=-1.10; 95%CI: -1.95 to -0.24) and a moderate-to-large improvement in SE at post-treatment (d=0.76; 95%CI: 0.01 to 1.51), changes in in all outcomes across timepoints ranged between small and moderate. Although these results are not in line with the moderate-to-large improvements in sleep diary outcomes typically observed in digital CBT-I trials in insomnia disorder (van Straten et al., 2018), they are comparable with the results from Harvey et al (2015). In their trial of CBT-I in BD, Harvey et al reported a significant difference in insomnia remission at post-treatment (72.7% vs. 14.3%; χ^2=14.88, p<0.001) and 6-month follow-up (63.6% vs. 21.1%; χ2=7.51, p=0.006) between the active and control arm. However, no significant between groups difference was reported in sleep diary outcomes at post-treatment or follow-up, with effect sizes ranging from small to small-to-moderate (Cohen's d=0.01 to 0.41). Harvey et al (2015) argued that these findings indicate that the control arm of psychoeducation can, a least to some extent, yield sleep benefits, corroborating other sources of evidence that psychoeducation is an active treatment component that can have a therapeutic effect in BD (Colom & Vieta, 2006). However, comparable small effect sizes on sleep diary outcomes were also reported in our study as well as in the group CBT-I in BD study by Jernelöv et al (2022) (Hedge's g for SE=0.27; 95%CI: − 0.32 to –0.87), both of which were uncontrolled. As such, in addition to the possible therapeutic effects of psychoeducation, our study indicates that there might be other factors limiting the effect of CBT-I on diary outcomes in BD. In our thematic

analysis of the post-treatment semi-structured interviews, participants explained that although they experienced some benefits in behavioural sleep outcomes, the most profound and impactful improvements were in terms of their worry and rumination around sleep, and the effect that a night of bad sleep had in their life. Consequently, it is justifiable that purely behavioural measures of sleep such as SOL, WASO, TST and SE are not as good at reflecting the improvements experienced by participants compared to global measures of sleep that include items on worry, functioning and satisfaction related to sleep.

Actigraphy results for SOL, WASO and TST did not match the diary results for the respective outcomes. Across all timepoints, there was an overestimation of SOL and TST and an underestimation of WASO between diary and actigraphy measures. This phenomenon might be due to two factors. First, people with BD tend to report more disruptions with sleep maintenance rather than initiation, while the reverse effect is observed in unipolar depression (Slyepchenko et al., 2019). Approximately only 32% of people with BD report symptoms of sleep initiation insomnia, whereas 61% report symptoms of sleep maintenance insomnia (De la Fuente-Tomás et al., 2018). This phenomenon was replicated in our semi-structured interview, where most participants reported that their primary disruption is with maintaining rather than initiating sleep. Consequently, it is likely that participants overestimate their onset latency, if they typically tend to fall asleep fast. Second this discrepancy might also arise from methodological differences. In our protocol, a sleep window was defined by intention rather than opportunity, meaning that participants are asked to press the event marker when the lights are off and they intend to fall asleep. This choice might be most appropriate for populations with long time in bed, and previous research has highlighted that BD might be characterised by longer bedrest duration rather than long sleep duration (Kaplan et al., 2015).

With the exception of a small post-treatment reduction in SOL (d=-0.23; 95%CI: -0.75 to 0.28), all other actigraphy outcomes were of small magnitude and in the opposite direction than predicted and typically seen when actigraphy is used in CBT-I trials (Mitchell et al., 2019). More specifically, TST and SE were both reduced at post-treatment, and WASO was increased. However, reduction in TST only reflected an adjusted mean difference of 2.45 minutes, the increase in WASO 8.87 minutes, and the decrease in SE 1.07%. The DIGIT-B study was not powered to detect actigraphy effects, and these small effects coupled with profoundly large CIs, highlight why it would be inappropriate to draw conclusive interpretations based on these results. Actigraphy remains an invaluable measure in the sleep and circadian research toolkit and our study illustrates that its integration in digital CBT-I studies in BD is feasible.

6.5.3 Improvements in Mood, Cognition and Functioning

The treatment was also associated with large improvement in depression scores as measured using the QIDS. There was a large reduction in depression scores at post-treatment (d=-1.91; 95%CI: -2.95 to -0.88), that were reduced but remained large at the 3-month follow-up (d=-1.67; 95%CI: -2.57 to -0.77). There was also a reduction in the number of people screening positive for depression as post-treatment (55.56%) and follow-up (63.16%) compared to baseline (100%). These effects were corroborated by large increases in behavioural activation for depression both at post-treatment (d=1.02; 95%CI: 0.30 to 1.75) and at follow-up (d=0.84; 95%CI: 0.15 to 1.54). Our results indicate a stronger reduction in depression symptoms compared to previous research on in-person CBT-I in BD (Harvey et al., 2015), a discrepancy that is potentially due to our participants being recruited during a depressive episode, as opposed to participants in Harvey et al that were recruited during euthymia. Digital CBT-I has also been linked to reductions in depression scores in other populations, and in a meta-analysis, people with insomnia had a small-to-

moderate improvement in depression scores at post-treatment following digital CBT-I (standardised mean difference=−0.42; 95%CI: −0.56 to −0.28; $p < 0.001$) (Lee et al., 2023). In this meta-analysis, studies were included if they contained a depression measure, but not necessarily recruited people with depression. In fact, the authors reported that only one study recruited participants with clinically significant symptoms of depression (Lee et al., 2023). Consequently, the possibility remains that the stronger effects detect in our study stem from a larger room for improvement, considering our sample endorsed scores for a possible bipolar depressive episode at baseline.

A notable finding regarding changes in depression scores during our study was the strong reduction in depression scores before accessing treatment, between baseline (week 0) and pre-treatment (week 2). During this time, although the number of people meeting the criteria for a depression diagnosis only decreased from 100% to 85%, when considering the continuous QIDS scores, there was a large reduction in depression scores (d=-1.07; 95%CI: -1.59 to -0.56). There is not a large volume of research that includes a pre-treatment phenotyping period, but in a recent study exploring the effects of total sleep deprivation in unmedicated people with unipolar depression, the largest antidepressant effects were observed in the period between screening and baseline rather than from baseline to post-treatment (Goldschmied et al., 2023). In this study, participants completed a depression measure for screening, followed by a week of sleep diaries while encouraged to maintain their habitual sleep schedule. At the end of this period, participants spent two nights in a sleep lab completing polysomnographic assessments as part of a habituation protocol. At this point, a second record of depression scores was provided, and the next morning, participants were introduced to a 36-hour total sleep deprivation protocol, followed by a 12-hour recovery period. At the end of the total sleep deprivation treatment another depression measure was collected, and then another one after the recovery night. The authors observed a significant reduction in depression symptoms between screening and baseline, and between

post-treatment and recovery, but not between baseline and post-treatment (Goldschmied et al., 2023). The largest reduction was between screening and baseline. Goldschmied et al suggested that demand characteristics related to entering a study and contact with research staff might have yielded some antidepressant effects that are masking improvements typically seen in total sleep deprivation research. Our qualitative data corroborate the arguments made by Goldschmied et al, with some participants highlighting that the pre-treatment period was therapeutic. They explained that the routine of completing the diary, couple with the ability to see the data themselves and reflect on their sleep-related practices helped them improve their sleep and mood.

There was a moderate improvement in anxiety symptoms at post-treatment (d=-0.69; 95%CI: -1.13 to -0.25) that was reduced to small at follow-up (d=-0.35; 95%CI: -0.75 to 0.06). Despite anxiety disorders having a 45% lifetime prevalence in BD (Pavlova et al., 2015), anxiety is rarely assessed in sleep and circadian intervention research in BD. Our meta-analysis in Chapter 5 revealed that only one out of the 19 included studies on sleep and circadian psychotherapies in BD assessed anxiety symptoms (Sit et al., 2018). Presently, there is limited evidence regarding the direction of the relationship between sleep and anxiety in BD. Research in insomnia has identified a bidirectional relationship (Alvaro et al., 2013), in line with the central role that cognitive and physiological arousal plays in most aetiological models of insomnia (Morin et al., 2015). In insomnia research, digital CBT-I has been found to lead to small-to-moderate reductions in anxiety scores (standardised mean difference = −0.29; 95%CI: −0.40 to −0.19; $p < 0.001$) (Lee et al., 2023). Cross-sectional studies in BD have established an association between sleep quality and anxiety symptoms, showing that people with BD and a comorbid anxiety disorder report lower sleep quality even when controlling for age, gender, medication use, depressive (hypo)manic symptoms (Oakes et al., 2022). Although there is a lack of longitudinal data in this area, our study

provides preliminary evidence that digital CBT-I has the potential to improve general anxiety symptoms in BD.

In insomnia disorder, digital CBT-I can lead to robust reductions in self-reported cognitive complaints at post-treatment (d= −0.86; 95%CI: −1.02 to −0.70; p<0.0001) and at a 3-month follow-up (d=−0.96; 95%CI: −1.15 to −0.78; p<0.0001) (Kyle et al., 2020). Our study replicated these findings in people with BD, showing a large decrease in cognitive complaints at post-treatment (d=-0.97; 95%CI: -1.58 to -0.36) and at follow-up (d=-0.90; 95%CI: -1.42 to -0.38). In the semi-structure interview people also reported improvements in attention, memory and productivity following treatment. Significant cognitive impairments, defined as more than one SD below control scores in two independent cognitive domains, have been suggested as a potent stratification outcome in BD, presenting reliably in 30-40% of people with BD (Burgess et al., 2022; Douglas et al., 2018; Iverson et al., 2011). As such, identifying a mechanism of action for cognitive complaints in BD is a salient research target. In people with insomnia, reductions in cognitive complaints following digital CBT-I are partially mediated by improvements in insomnia (Kyle et al., 2020). Although our study is not powered to detect such effects, previous studies in BD have shown that impairments in cognitive abilities such as attention and processing speed are directly related to sleep (Bradley et al., 2020). In fact, cognitive impairments were only present in people with BD that also had disrupted sleep, defined as an actigraphy measured TST of less than 6 or more than 10 hours, whereas people with BD that had typical sleep did not differ in terms of cognitive abilities than healthy controls (Bradley et al., 2020). The BD group also performed worse on average in cognitive tests compared to controls, but this effect was driven by the fact that the group of BD participants with atypical TST represented 61% of the clinical sample (Bradley et al., 2020). Larger longitudinal trials including self-report measures and objective tasks are necessary to elucidate the relationship between cognition and sleep in BD.

Finally, our treatment was associated with large improvements in mental wellbeing (d=0.97; 95%CI: 0.18 to 1.77) and socio-occupational functioning (d=-0.94; 95%CI: -1.49 to -0.39) at post-treatment. These effects were maintained, albeit reduced in magnitude, at follow-up, with moderate improvements in mental wellbeing (d=0.50; 95%CI: -0.21 to 1.20) and socio-occupational functioning (d=-0.69; 95CI: -1.23 to -0.12). There are multiple sources of evidence showing that sleep is related to functioning and quality of life in BD (Jermann et al., 2022). Studies have shown that symptoms of insomnia and excessive daytime sleepiness are related to quality of life in BD (Jermann et al., 2022), and that people with BD and atypical sleep duration, defined as a self-reported TST of less than 6 or more than 10 hours, score worse on quality of life and all outcomes of functioning, including work, relationships, recreation and satisfaction (Gruber et al., 2009). Such associations are present both during acute and euthymic periods (De la Fuente-Tomás et al., 2018; Jermann et al., 2022). Despite considerable evidence identifying such links between sleep and functioning (Boland et al., 2015; De la Fuente-Tomás et al., 2018; Keskin et al., 2018), other studies have only found an indirect link between sleep and functioning, with residual depression symptoms and perceived cognitive performance being the strongest determinants of psychosocial functioning (Samalin et al., 2017).

6.5.4 Qualitative Data on Sleep Disruptions Prior to Accessing Sleepio

In the semi-structured interview, people talked about the sleep problems they experience, with many of these sleep patterns being manifestations of insomnia symptoms. However, most people also reported symptoms related to hypersomnia, such as excessive daytime sleepiness and prolonged sleep duration, while some participants described symptoms indicative of a delayed circadian phase disorder.

Hypersomnia is highly prevalent in BD, and, depending on the definition, the prevalence rates vary between 29-40% (Kaplan & Harvey, 2009; Steinan, Scott, et al., 2016;

Walz et al., 2013). However, notwithstanding its prevalence in BD, hypersomnia remains underexplored and undertreated (Grigolon et al., 2019). There is a lack of a consistent definition and assessment method of hypersomnia in BD research, reflecting a general lack of consensus in sleep and circadian science over the core components of hypersomnia (Kaplan et al., 2015). There are two common yet distinct characterisations of hypersomnia in diagnostic manuals. The DSM-5 defines hypersomnia, referred to in the manual as hypersomnolence disorder, on the basis of an increased need for sleep accompanied by longed sleep duration and significant sleep inertia (American Psychiatric Association, 2013). On the other hand, the ICD-11 and ICD-3 define hypersomnia on the basis of excessive daytime sleepiness indexed by a propensity to fall asleep in the daytime, that is not wholly accounted by an inadequate amount of sleep (American Academy of Sleep Medicine, 2014; World Health Organization, 2018). Large epidemiological research in the general population has suggested that the constructs of long sleep duration and excessive daytime sleepiness do not necessarily overlap (Ohayon et al., 2012). A study in BD has replicated this finding, showing that long sleep duration and excessive daytime sleepiness are two distinct and uncorrelated features in BD (Kaplan et al., 2015), contrasting other studies that have found the two constructs to at least correlate with each other (Ohayon et al., 2013). Although hypersomnia in BD most often presents comorbid with insomnia rather than independently (Soehner et al., 2014), participant reports from the semi-structured interviews provided conflicting information over whether treatment for insomnia could also improve symptoms of hypersomnia. Some participants felt that digital CBT-I decreased their daytime sleepiness and helped them feel more alert during the day, whereas others argued that the intervention was very specifically targeted at insomnia rather than hypersomnia. Our study never intended to explore the effects of an insomnia treatment on hypersomnia, however, hypersomnia measurements should be integrated in routine sleep assessments of BD, to represent the profile of this population more accurately.

There is great variability in reports around the prevalence of circadian rhythm disorders in BD, yet there is ample evidence that the most common one in BD is delayed sleep phase disorder (Cruz-Sanabria et al., 2023; Takaesu et al., 2016). Prevalence rates of delayed sleep phase disorder in BD vary between 10-35% (Cruz-Sanabria et al., 2023; Steinan et al., 2016; Takaesu et al., 2016), with 62% of people with BD at least having a late chronotype (Robillard et al., 2013). A delayed sleep phase in BD has been linked to poorer sleep quality and lower sleep efficiency (Cruz-Sanabria et al., 2023), a younger age at onset (Romo-Nava et al., 2020; Takaesu et al., 2016), greater cognitive impairments (Cruz-Sanabria et al., 2023), disruptions with energy and activity levels (Steinan, Morken, et al., 2016), and a higher frequency of mild to severe depression episodes during a 5-year longitudinal assessment (Vidafar et al., 2021). Recent investigations have proposed that delayed sleep phase could be a distinct clinical subphenotype in BD (Romo-Nava et al., 2020), but this has not been corroborated with further empirical evidence. Although we did not include any measures of phase, in our study, the digital CBT-I did not lead to any change in chronotype.

Regarding the clinical management of reported sleep disruptions, although participants acknowledged that clinicians often inquire about their sleep and activity, they reported a dissatisfaction with the treatment response, which was mostly limited to pharmacological options and did not address sleep problems in their own right. There is no public health evidence regarding the treatment of sleep problems in primary and secondary care for people with BD, but the most frequent response to sleep disruptions in general is the prescription of (hypnotic) medication (Crescenzo et al., 2022; Siriwardena et al., 2010). This trend was one of the primary reasons why participants were motivated to participate in our study.

6.5.5 Qualitative Data on Digital Interventions

Digital technologies are often cited as an area of strategic policy priority for healthcare, where investments have the strongest potential to improve the resilience and efficiency of the healthcare system (Colombo et al., 2020). However, in particular for mental health, the published evidence for sustained clinical impact in real-world settings is often limited (The Lancet Psychiatry, 2024). Although this is not the case for our digital CBT-I intervention, Sleepio, given that it is a recommended treatment for insomnia according to NICE (National Institute for Health and Care Excellence, 2022), this was the first time Sleepio was specifically administered to people with BD. In fact, in most Sleepio trials, BD together with psychosis remain common exclusion criteria, even if otherwise there are no restrictions on mental health comorbidities (Espie et al., 2019; Kyle et al., 2020). This choice is most likely due to concerns over the adverse effect of sleep loss as a result of sleep restriction therapy in (hypo)mania. In our study, despite initial fears by the participants over the effect of sleep restriction, most participants found the treatment to be useful with some even acknowledging that it was arguably the most potent element of the intervention. A caveat here is that in our study sleep restriction was limited to no less that 6 hours minimum, similar to past protocols by Harvey et al (2015) that found 6.5 hours of minimum restriction to safe and tolerable. Nevertheless, some participants reported finding the restriction element particularly difficult and only partially following the advice provided by the app.

In general, most participants enjoyed Sleepio and perceived the digital element of the intervention as an advantage. People liked the accessibility and autonomy that came with receiving the intervention through an app, and all but one person argued that after having participated in the DIGIT-B study they would choose a digital over a face-to-face intervention for their sleep. There was a divide in opinion over whether the app should be supplemented with digital face-to-face consultations with a member of the study team to ask

questions and check on their progress, or solely rely on an un-supported version of the app. Some participants also suggested more community engagement or a group-based treatment aspect, something that Jernelöv et al (2022) integrated in their group-version of face-to-face CBT-I for BD. Some participants argued that the benefit of autonomy would be severely limited if a face-to-face component is added, even a digital one. On the other hand, one participant explained that access to an attending member of staff is essential in BD to ensure safe use of the Sleepio advice, especially around the beginning of sleep restriction therapy.

For conditions characterised by frequent recurring episodes, like BD, longitudinal assessments are essential to capture disease trajectories, symptom change and long-term outcomes (Bauer et al., 2023), and people with BD are particularly interested in long-term self-monitoring (Michalak et al., 2016). In our study, participants emphasised the usability of digital symptom monitoring, and some of them mentioned that they were already trying to monitor their sleep and mood manually before entering our study. Notwithstanding, it is likely that our sample is influenced by selection bias, meaning that participants more likely to be in favour of digital interventions were more likely to indicate an interest to participate in our study. In an Australian survey of people with BD, 65% of responders endorsed a blended approach of digital and in-person face-to-face, with only 1% endorsing a fully digital approach (Gates et al., 2024).

Digital tools have been widely implemented in BD to aid in longitudinal symptom monitoring, and enable researchers to identify robust early marker of episodic relapse (Bauer et al., 2023; Bufano et al., 2023; Busk et al., 2020; Ebner-Priemer et al., 2020; Gordon-Smith et al., 2021; Tsanas et al., 2016). In studies were sleep and circadian parameters were integrated into the symptom monitoring conglomerate, they were shown to be among the most salient symptoms for participants (Gordon-Smith et al., 2021), and among the most robust predictors of an emerging bipolar episode (Bauer et al., 2023; Ebner-Priemer et al.,

2020; Tseng et al., 2022). In a recent review, authors recommended a triaging of digital tools to monitor and treat sleep disruptions in BD, including apps, ecological monetary assessments and actigraphy (Boccagno et al., 2023). Our study provides evidence over the use of all three elements: Sleepio as an app, sleep diaries for ecological monetary assessments, and 3-month continuous actigraphy, and through our semi-structured interviews highlights areas of improvement for future studies.

6.5.6 Strengths and Limitations

Our study provides preliminary evidence over the safety, feasibility, acceptability and effectiveness of a digital CBT-I for BD. We integrated a wide range of assessment methods over a 3-month period, ranging from questionnaires to sleep diaries and actigraphy. The DIGIT-B is the first study to integrate a digital format of CBT-I in BD, the first to deliver CBT-I to people with BD during depression, the first to include a 2-week pre-treatment period, the first to integrate actigraphy measures, and the first to combine quantitative and qualitative data in its treatment evaluation. However, our study also comes with a range of conceptual and methodological limitations.

First, we specifically recruited people with BD-II. This choice was primarily due to ethical concerns over conducting a digital CBT-I study for the first time and for doing so without regular meetings with participants, yet this choice confers limitations in the interpretation of our findings. Bipolar subtypes exhibit different responses to sleep loss, with BD-II not showing vulnerability to hypomania following sleep loss, whereas in BD-I sleep loss is a potential trigger for a manic episode (K. S. Lewis et al., 2017). As such, we cannot draw conclusions over the safety of digital CBT-I for BD-I. However, it is worth highlighting that Harvey et al (2015) and Jenrelov et al (2022) only recruited people with BD-I in their in-person CBT-I studies and both established favourable safety profiles for their interventions.

Second, although our study focused specifically on insomnia, it remains an omission that we did not systematically assess for possible comorbid diagnosis and symptom changes in hypersomnia and circadian phase. Future studies should benefit from hypersomnia questionnaires (Kaplan et al., 2019), and adapt sleep diaries for use in BD in order to reflect the complexities of the clinical presentation of this population (Harvey et al., 2015).

Third, although there is variability in the educational attainment and professional status of our participants, our sample is notably homogeneous in terms of gender and race. The lack of gender heterogeneity can be partially explained by the fact that BD-II is typically associated with female gender compared to BD-I (Grigolon et al., 2019). More specifically, over 67% of people with BD-II identify as female (Benazzi, 2006). The lack of race heterogeneity might have limited the generalisability of our findings, given that sleep disruptions are among the symptoms with the highest racial disparity in BD (Li et al., 2023). In a meta-analysis, black individuals were less likely to endorse a decreased need for sleep and symptoms of hypersomnia, but were more likely to report symptoms of insomnia (Li et al., 2023). Compared to their white counterparts, black people with BD were also less likely to be prescribed lithium treatment (Li et al., 2023). Poorer sleep outcomes have been previously found to be more common in black individuals regardless of a mental health comorbidities (Carnethon et al., 2016; Kim et al., 2022), potentially representing a manifestation of multifaceted psychological distress in underrepresented minority populations (Li et al., 2023).

Finally, the study is constrained by certain methodological limitations, with the lack of a control group being the most important one. In addition to known methodological caveats of within-group comparisons, this is a particularly important limitation in our study given that in our semi-structured interviews, people acknowledged that not all benefits can be attributed to the digital CBT-I treatment, since they were already approaching remission

of their depressive episode upon entering our study. A control group, with a greater number of participants and a randomised design would have ensured that such confounding effects, even when present, do not interfere significantly with the main outcomes of our study. Here, it is also important to note that due to the small sample size, there is great heterogeneity in the magnitude of our effects, a pattern that becomes noticeable when looking at the range of 95%CIs. Given that this study is only a pilot, we standardised the time of delivery of our intervention to occur during a depressive episode. However, in the semi-structured interview some participants challenged this choice, arguing that they could have potentially benefited more from our intervention if it was delivered during a hypomanic or euthymic episode.

7

General discussion

Contents

7.1 Summary of Findings

The aim of this thesis was to investigate the role of sleep and, to a lesser extent, circadian rhythms in BD. In doing so, we conducted a series of studies to elucidate this multifaceted role, reflecting our current understanding of sleep and circadian disruptions in BD as prodromal features, hallmark symptoms and therapeutic targets (Geoffroy, 2018; Kaplan, 2020; Morton & Murray, 2020).

First, we used a large national survey to characterise the sleep profile of BD, and compare it against HC and people with MDD that were identical to the BD group in age, gender, current occupation and educational attainment. In this study we showed that when compared to HC, the sleep profile of BD is characterised by increased insomnia symptoms, with 61% of the group meeting the criteria for a diagnosis of insomnia disorder. Additionally, people with BD showed a later chronotype, shorter sleep duration, increased need for sleep and medication use, longer and more frequent napping, higher use of hypnotics, and greater dissatisfaction with sleep. The BD group also reported higher symptoms of depression, more

frequent cognitive complaints and a lower quality of life. The BD and MDD groups had a comparable sleep and mental health profile, with the only significant difference being that the BD group had more frequent cognitive complaints than the MDD group.

Next, we capitalised on a long-standing cohort of BD high-risk offspring, and set out to comprehensively characterise the sleep and rest-activity rhythms of this cohort, while comparing it against a group of peers. The protocol also included comparisons in depression, anxiety, (hypo)mania, behavioural activation and inhibition, and cognitive abilities, such as sustained attention, inhibitory control and processing speed. Due to unforeseen circumstances around Covid-19 and changes in the executive leadership of the cohort, we were unable to achieve our pre-registered intended sample size. In the end, we recruited 33% of the intended sample of bipolar offspring (n=11/33), and we paused recruitment of the control group at 64% of the intended sample size (n=21/33). Although our primary and secondary targets were in the direction we predicted, with bipolar offspring reporting higher insomnia, lower sleep quality, increased depression and anxiety, and worse performance in most cognitive domains, unsurprisingly, none of these differences was statistically significant.

In order to understand the evidence base around the role of sleep and circadian rhythms as potent intervention targets in BD, we conducted a systematic review and meta-analysis of RCTs of behavioural and psychosocial interventions that target sleep and circadian rhythms in BD. The review included 19 RCTs investigating six treatment modalities: bright light therapy (n=6), interpersonal and social rhythm therapy (n=5), blue-light blocking glasses (n=2), cognitive behavioural therapy for insomnia (n=1), total sleep deprivation (n=1) and combination treatments (n=4; two of which delivered triple chronotherapy protocols). There was only enough data to meta-analyse the effect of BLT on reducing depression, revealing a medium-to-large post-treatment effect. The main finding of our review was that the evidence base for the effectiveness of these interventions is

currently limited, since 52% of the included trials (10/19) did not measure sleep or circadian rhythms in any capacity, despite this being the principal target of the intervention. Impeding on this phenomenon is the variability in the participant profiles, outcomes and treatment protocols, as well as the limited number of included trials and small sample sizes.

Despite CBT being the first line of treatment for insomnia, and insomnia being the most frequent complaint in BD, there is a notable lack of literature on CBT-I in BD. In an effort to address this gap, our final study was a mixed methods single-arm pilot trial of a digital CBT-I for people with BD-II. Our results indicated that the intervention was safe, acceptable and feasible. Over 83% of eligible participants completed at least 75% of the intervention (4/6 sessions), and 56% completed all available sessions. Large improvements in insomnia scores were observed at post-treatment and maintained at a 3-month follow-up. A similar pattern of improvements was observed for all outcomes, including depression, behavioural activation for depression, sleep quality, anxiety, cognitive complaints, mental wellbeing and work and social adjustment. There was also a small yet sustained increase in hypomania symptoms throughout the intervention that was maintained at follow-up. Results from the sleep diaries and actigraphy were less clear, with reductions in SOL at post-treatment as measured using both diaries and actiwatches. There was an increase in diary SE and TST and a decrease in WASO at post-treatment, whereas actigraphy detected a small decrease in SE and TST and an increase in WASO.

The qualitative part of the study also offered valuable insights. People reported various presentations of sleep problems, with disruptions in sleep maintenance appearing more frequently. Participants reported using sleep to monitor the onset of other symptoms of BD, and given the adverse effects of sleep problems in their mood and daily life, most participants already had ways to manage their sleep. Almost all participants recalled being asked about their sleep by a clinician, but their satisfaction with the clinical response varied,

with most people feeling like sleep disruptions were not addressed in their own right. Overall, people enjoyed the intervention, despite various views on which sessions were the most difficult or the most useful, with sleep restriction therapy being the focus of a lot of these conversations. Some people reported adjusting the treatment advice to fit their needs and schedules. In terms of improvements, the response was overwhelmingly positive. Participants mentioned that although some improvements in behaviour around sleep occurred, the most notable improvement was the reduction in stress and sleep preoccupation. Finally, although all but one participant supported a strong preference for digital interventions, although some argued that a hybrid digital model that includes an app intervention and virtual sessions with a therapist might be optimal.

7.2 Strengths and Limitations

Prior to drawing conclusions, in Table 7.1 we summarise the most important strengths and limitations for each study of this thesis. Some of the limitations we had little control over (e.g. UK Sleep Census not designed for mood disorders, not enough trials per treatment modality in the review), others we had control over but only considered retrospectively (e.g. lack of meaningful assessment of excessive sleepiness in the DIGIT-B study), and some were the result of Covid-19 emerging 6 months into the DPhil and lasting for the majority of this doctoral work (e.g. recruitment rate of the high-risk phenotyping study). In order to reflect on them critically, these strengths and limitations were integrated into a research agenda and presented as opportunities for future research.

Table 7.1 Strengths and limitations for each study in the thesis

	Strengths	Limitations
(CHAPTER 3). The Sleep Profile in Bipolar Disorder	• Large sample size (n=1,072 in each group) that far exceeds most observational studies • Balanced control groups that were identical in age, gender, occupational status and educational attainment • Comparisons against both a healthy control group as well as another clinical group with a mood disorder • Wide range of sleep assessments, giving a detailed perspective on the BD sleep profile • Integration of mental health, cognition and quality of life assessments	• All outcomes were self-report, including the diagnosis of BD and MDD • No assessment of excessive sleepiness which is highly prevalent in BD • The survey was not designed to assesses mood disorders, so some items were missing, such as (hypo)mania and episode polarity • Selection bias, meaning that the control group had high rates of insomnia, and it is likely that people with more severe sleep problems participated • Sample was predominantly older, white and highly educated
(CHAPTER 4). Sleep and Activity Phenotyping in High-Risk Individuals	• Focus on a well-characterised high-risk group, with data on parents and children • Familial risk for BD and no participant was diagnosed with BD at recruitment • Comprehensive assessment, including items for most common sleep and circadian disorders • Use of diaries and actigraphy to characterise sleep as well as rest-activity • Integration of items on mental health and tasks on cognitive abilities	• Did not achieve intended sample size, so our comparisons were not adequately powered • No difference was statistically significant • Cross-sectional comparisons, meaning that we cannot make inferences on whether sleep disruptions can predict the emergence of other mental health problems in the future
(CHAPTER 5). Sleep and circadian interventions in Bipolar Disorder	• Focus on RCTs as the study design with the highest evidentiary value • Review of all relevant treatment modalities • Appraisal of BD subtype, treatment protocols and all collected outcomes • Discussion about relevant RCT protocols on trial registration platforms that have not published any results yet	• RCTs or assessments of combinations with pharmacological treatments were out of scope • Limited trials per treatment modality, so only one meta-analytic model was possible • Small sample sizes and variation in treatment protocols • Data extraction was not possible for all trials, authors were not responsive to data requests • Majority of participants were experiencing a depressive episode at recruitment, limiting the inferences we can make about effectiveness in (hypo)mania and euthymia
(CHAPTER 6). Digital Sleep Intervention for Bipolar Disorder, the DIGIT-B Study	• Mixed methods trial, using quantitative and qualitative approaches to address our aims • Focus on first line treatment for insomnia, the most frequent sleep disruption in BD • Use of an established digital intervention for insomnia that can be potentially scalable • Range of outcomes, including questionnaires, sleep diaries, actigraphy and interviews • Investigation of a wide range of domains, including feasibility, acceptability and safety, insomnia, depression, hypomania, anxiety, sleep quality, chronotype, mental and socio-occupational functioning and rest-activity • 5 major assessment timepoints, including a 2-week pre-treatment assessment period and a 3-month follow-up • Detailed assessment of mood and sleep prior to entering treatment • Sleep diaries and actigraphy for 10 weeks • Qualitative interviews with all participants	• Single arm trial, so effects are pre-to-post rather than between active and control arms • Low number of participants, so results should be interpreted with caution • Participant drop-out rate was not sufficiently taken into account, and we sought to recruit simply the number of people we needed • Registration was submitted after participant enrolment, and although ethics application is provided and analysis plan was registered prior to end of recruitment, we cannot claim that this study was pre-registered • Focus was solely on BD-II, so no inferences can be made for BD-I • Lack of an assessment of excessive sleepiness • Assessment of hypomania possible reflecting increased activity and positive affect • Sample is all white and predominantly female • Time constraints meant that the 10-week data for diaries and actigraphy were out of scope

Abbreviations: BD, Bipolar Disorder; MDD, Major Depressive Disorder; RCTs, Randomised Controlled Trials

7.3 Future directions

Building upon these strengths and limitations, below we present a scientific agenda and directions for future research on sleep and circadian rhythms in BD. In contrast to the discussion section in each individual chapter, the directions in this chapter represent top-level recommendations for the entire field.

7.3.1 Concurrent Assessment of Sleep and Circadian Rhythms

In this thesis we set out to measure sleep and circadian rhythms in a variety of ways, including questionnaires, sleep diaries, actigraphy and qualitative interviews. Although our approach builds upon past efforts to combine different measurement tools to characterise sleep in BD (Kaplan et al., 2012), perhaps the most notable limitation of this thesis is the overwhelming focus on sleep outcomes, and the limited integration of circadian assessments.

Chronotype, an outcome presented in Chapters 3, 4 and 6, is only a proxy of the circadian system and does not measure circadian rhythms per se (Reid, 2019). In healthy people, preferred chronotype aligns well with circadian phase measures, such as cory body temperature and dim-light melatonin onset, but in clinical populations these relationships are less clear (Dijk & Duffy, 2020; Reid, 2019). Rest-activity is a prominent output of the circadian system, albeit it is not a rhythm that is purely a function of the circadian clock given masking effects caused by its significant influence by behaviour (Reid, 2019). Rest-activity was captured in Chapters 4 and 6, and we expressed our intention to extract circadian outcomes of actigraphy, such as L5, M10, intradaily stability, interdaily variability and relative amplitude. However, these outcomes were judged to be out of scope for this thesis. Due to time and word restrictions, this thesis included only our pre-registered primary and secondary outcomes on sleep and mental health, while rest-activity was decided a-priori to be a wholly exploratory outcome.

Nevertheless, circadian pathways have been implicated in multiple levels in BD from genetic and cellular to physiological and behavioural (Bellivier et al., 2015; McCarthy et al., 2022). Circadian genes have been implicated in the diathesis of BD with several nominally significant fundings (Gordovez & McMahon, 2020; McCarthy, 2019). Although no specific clock gene has been established as a risk factor for BD in GWAS studies, there is GWAS evidence of an increased genetic risk for a late chronotype and sleep disruptions (McCarthy et al., 2022; Mullins et al., 2021). Animal models and pupillometric investigations in humans have also proposed potential light hypersensitivity in BD (Madsen et al., 2021; Timothy et al., 2018). An investigation of light measurements captured by actigraphy from the UK Biobank found that greater nighttime light exposure was associated with an increased risk of lifetime BD, but found no relationship between daytime light exposure and lifetime diagnosis of BD (Burns et al., 2023). Other sources of evidence have identified markers of disrupted circadian phase in BD, with alterations in both melatonin and cortisol secretion showing a phase delay in depression and a phase advance in (hypo)mania (McCarthy et al., 2022; Moon et al., 2016; Takaesu, 2018). There are also differential patterns of melatonin release in BD, with reduced levels in depression and increased levels in (hypo)mania (Carpenter et al., 2021; Gold & Kinrys, 2019). In contrast, a review of actigraphy studies in BD noted the lack of rest-activity outcomes from the included studies (De Crescenzo et al., 2017). A study from the UK Biobank found that lower relative amplitude is associated with lifetime prevalence pf BD (Lyall et al., 2018), an effect that has also been observed during euthymic episodes of BD (Ng et al., 2015). In a more detailed investigation of rest-activity rhythms, authors compared people with BD and people with MDD and showed that people with BD exhibit a higher total rest per 24-hours, and lower L5 and M10 average values (Leseur et al., 2024).

Delineating causal effects and identifying a mechanism of action has been challenging given the case-series nature of these studies (McCarthy et al., 2022; Melo et al.,

2017). Notwithstanding, circadian rhythm disruptions are highly prevalent in BD, and there is ample evidence to at least suggest that they are involved in the aetiology of BD (Hickie & Crouse, 2024). Circadian disruptions are also likely to contribute to sleep disruptions, given the concomitant influence of the homeostatic sleep drive and circadian processes on the sleep-wake regulation.

The limited integration of sleep science and chronobiology is not unique to BD, but it is a common phenomenon across mental health research (Meyer et al., 2024). As a research agenda, future studies in BD should combine measures of sleep and circadian function, investigating outcomes over 24-hours. Such measurements should include items on sleep, light, social schedules, physical activity, eating, medication, and robust markers of circadian phase such as melatonin, cortisol or core body temperature. To achieve this, there is a need for a wider integration of novel approaches in circadian phase assessment, as well as remote sleep measuring technologies, such as wireless at-home EEG devices, wearable sleep trackers and apps on mobile devices, will be central to this endeavour (Meyer et al., 2024). In combination with improvements in automated scoring (Yuan et al., 2024), these approaches are likely to be the catalyst in this research endeavour. We firmly believe that there are great opportunities in BD research for more meaningful theoretical and practical integration of sleep science and chronobiology (Meyer et al., 2024), and that concurrent assessments of sleep and circadian rhythms are likely to afford more valuable insights regarding their role in the heterogenous presentation and complex aetiology of BD.

7.3.2 Transdiagnostic Sleep and Circadian Interventions

Growing evidence has shown that the sleep and circadian disruptions observed in BD are not disorder specific and might in fact represent transdiagnostic targets that manifest in a range of mental health disorders (Freeman et al., 2020; Hickie & Crouse, 2024; McCarthy et al., 2022; Meyer et al., 2020). In fact, sleep disruptions have been implicated in the

trajectory of most mental health disorders, including depression, anxiety, psychosis, BD, posttraumatic stress disorder, and attention deficit hyperactivity disorder (Freeman et al., 2020; Hertenstein et al., 2022, 2023). This is a compelling notion as it suggests that sleep and circadian rhythms not only have a shared mechanistic role across mental health disorders, but also that the same sleep and circadian interventions might be effective in treating sleep, circadian and mental health disruptions across different disorders.

In an RCT of people with serious mental health disorders, including BD, seeking treatment in a community mental health centre, over 85% of participants presented with indications of at least 2 sleep and circadian disorders (Sarfan et al., 2021). Around 32% of people with BD present with a circadian rhythm disorder, with 77% of these cases being delayed sleep phase disorder (Takaesu et al., 2016). Furthermore, around 30% of people with BD also meet the criteria for the diagnosis of hypersomnia (Grigolon et al., 2019), with other sources of evidence suggesting that 28% of people with BD actually present both insomnia and hypersomnia (Soehner et al., 2014). Similarly, although all participants in our digital CBT-I study in Chapter 6 met the diagnostic criteria for insomnia, in the qualitative interview many reported that excessive sleepiness is one of the most debilitating sleep disruptions that they experience.

Beyond co-occurrence, it has been suggested that sleep and circadian rhythms are *"mechanistically transdiagnostic"*, meaning that the observed co-occurrence arises from a shared causal mechanism between sleep and circadian disturbances and mental health disorders (Harvey et al., 2011). The proposed pathway by Harvey (2009) is that genetic factors, including circadian genes, influence neuromodulatory substrates such as dopaminergic and serotoninergic function. In return, these underlying deficits render individuals vulnerable to emotionally challenging conditions, such as sleep loss, and create a propensity towards emotion dysregulation. Through bidirectional feedback loops, these two factors lead to the

emergence of mental health disturbances and disorders (Harvey, 2009). More recent transdiagnostic frameworks further emphasise the interaction between sleep and circadian mechanisms in mental health (Meyer et al., 2024). Here, the onset and maintenance of mental health disorders is partly explained through the synergy of genetic associations, mistimed or insufficient light entrainment, circadian misalignment, and impairments in memory consolidation, neuroplasticity and emotion regulation driven by sleep disruptions (Meyer et al., 2024).

Consequently, transdiagnostic treatments for sleep and circadian disruptions have been developed and tested in a range of different populations (Harvey et al., 2021; Schneider et al., 2020; Sheaves et al., 2018; Yau et al., 2024). The most well-studied of these protocols is the Transdiagnostic Intervention for Sleep and Circadian Dysfunction (TranS-C) treatment (Harvey, 2009; Harvey et al., 2021). Trans-C includes 4 core modules aimed at every person with a sleep or circadian disorder, and 7 optional modules, designed to be delivered according to the needs of each individual (Harvey et al., 2021). No trial to date has compared these transdiagnostic treatment protocols against a standard treatment like, CBT-I, so there is no evidence that these modifications are necessary to observe improvement. Nevertheless, in Chapter 6, participants argued that our digital intervention did not sufficiently address all their sleep disruptions, particularly around excessive sleepiness, and others highlighted that some treatment components, such as stimulus control or sleep restriction therapy, might not be appropriate for their condition or living arrangement. One solution for future studies could be adapting CBT-I specifically for BD, in line with what other past studies have proposed. For example, there are adaptations for CBT-I that contain treatment components for nightmares aimed at people with posttraumatic stress disorder (Belleville et al., 2018), chronobiological treatment elements for people with attention deficit hyperactivity disorder (Jernelöv et al., 2019), and a novel technique to reduce sleep inertia aimed at people with BD (Kaplan et al., 2018). Although there are some clear benefits in

such approaches, a recent review highlighted that developing discrete sleep and circadian interventions for each mental health disorder might be counterintuitive given the heterogeneity of the sleep and circadian profile within each disorder (Hertenstein et al., 2022).

We believe that the contribution of sleep and circadian rhythms to the symptom profile of BD is complex and multifactorial, so much like our argument in the previous section, treatment development in this space is also likely to benefit from the integration of sleep science and chronobiology. Novel, multi-component interventions, such as TranS-C, further benefit from the integration of a sleep health approach, focusing on the treatment of a range of sleep and circadian dimensions that are relevant to BD as opposed to strict definitions of categorical disorders (Meyer et al., 2024). For example, individual adaptations of TranS-C for every person with BD could combine modules that address sleep regularity, bedtime routine and environment, rumination, circadian phase, excessive daytime sleepiness, light exposure, activity, daytime dysfunction, and even domains that we did not cover in this thesis, such as parasomnias and sleep-related movement and breathing disorders. In chapter 6, although our digital CBT-I intervention was found to be feasible, acceptable, safe and potentially effective, participants understandably reported that it did not focus sufficiently on symptoms other than insomnia. Building upon our work, future studies should aim to explore transdiagnostic treatments that reflect the heterogeneous sleep and circadian profile of BD.

7.3.3 Longitudinal Assessment of Sleep and Circadian Rhythms

BD is a chronic and dynamic condition, with a multitude of factors suggested to contribute to its aetiology. Discrete episodic periods are defined on the basis of a combination of clinical symptomatology described in diagnostic manuals. Notwithstanding, these categories are *"disjunctive"* and *"discordant"* (McInnis et al., 2022), meaning that certain

symptoms hold diagnostic value in more than one episodes, and people experience different symptoms of the same category in recurrent episodes (McInnis et al., 2022). There is also frequent overlap in depressive and (hypo)manic symptomatology during mixed state episodes (McIntyre et al., 2020), and symptoms that persist treatment and are highly prevalent outside acute episodes during euthymia. As such, the boundaries of these discrete episodic categories might not be as rigid as initially believed to be, necessitating a paradigm shift in how we approach research in BD (McInnis et al., 2022). McInnis et al (2022) suggested that in order for research to establish robust evidence about the development, progression and treatment of BD, longitudinal research is essential. This recommendation echoed previous calls over the necessity of longitudinal research in BD (Bauer et al., 2004), given that the key qualifier in BD is not simply the presence of a symptom, but its profile of variation over time (Harrison et al., 2018).

With the presentation of sleep and circadian disruptions across acute episodic and euthymic phases, and accumulating evidence of their role in the multifactorial causation of BD, sleep and circadian rhythms have a central role to play in this paradigm shift towards more longitudinal research in BD. In longitudinal research spanning a period of 20 years, sleep outcomes were shown to be the most salient predictors of the emergence of an acute episode, and the most useful parameter for understanding the course of the disorder (Bauer et al., 2004, 2023). Furthermore, longitudinal research from the Flourish cohort showed that sleep disruptions are the earliest identifiable markers of pathology in the developmental trajectory of BD (Duffy et al., 2019).

Although in this thesis we did not directly set out to conduct a longitudinal study, Chapter 4 is informed by research in a BD high-risk cohort, and the greater aim of this work was to inform future longitudinal investigations in this space. We believe that future research on sleep and circadian rhythms in BD should focus on longitudinal approaches that capture

changes in the developmental trajectory of BD and those at high-risk across the lifespan (Duffy & Grof, 2024). Longitudinal research on sleep and circadian rhythms in BD has a two-fold potential. First, it can provide critical evidence on the role of sleep and circadian rhythms in the causation and maintenance of the BD. Second, it could identify critical periods of vulnerability in BD, where early transdiagnostic interventions on sleep and circadian rhythms are likely to be most effective (Meyer et al., 2024). Consequently, we believe there is a need for the integration of sleep and circadian outcomes in routine longitudinal research in BD, and further studies with a more targeted focus on between- and within-participant changes in sleep and circadian rhythms in BD.

7.3.4 Improved Measurement of (Hypo)Mania

To make meaningful progress in our understanding of the role of sleep and circadian rhythms in BD, it is essential that we ensure good measurement of bipolar symptomatology. The onset of (hypo)mania has been historically and intrinsically linked to the study of sleep loss in BD (K. S. Lewis et al., 2017; Plante & Winkelman, 2008; Wehr et al., 1987). As such, although a call for better assessment of (hypo)mania is not specific to research of sleep and circadian rhythms in BD, it is one that is uniquely pertinent and important for our field.

In Chapter 6 we discussed specific limitations relevant to the use of ASRMS for measuring hypomania, yet the lack of a widely adopted measure of (hypo)mania has been a long-standing issue in BD research (Cerimele et al., 2022; Meyer et al., 2020; Phillips & Kupfer, 2013; Poolsup et al., 1999). The challenge in measuring (hypo)mania arises from difficulties in demarcating typical from clinically elated and irritable mood, and increased activity (Meyer et al., 2020). As such, common clinician-rated measurements, such as the Young Mania Rating Scale (Young et al., 1978), often rely on individual interpretations of symptoms rather than pre-determined clinical criteria (Meyer et al., 2020). However, evidence suggests that such interpretations are influenced by the clinician's personal views

on prototypical symptoms of (hypo)mania and the number reported symptoms (Meyer & Meyer, 2009; Meyer et al., 2011), with reports of a reduced need for sleep being an example of a prototypical symptom of (hypo)mania (Meyer et al., 2011). Additionally, it has been suggested that changes in areas like self-esteem and activity are not as easily noticeable by clinicians (Meyer et al., 2020). In return, the use of (hypo)mania self-rated scales in BD research is infrequent (Meyer et al., 2020), owing to findings that people with BD have limited symptom insight during acute (hypo)mania episodes and that they often underreport symptoms due to accompanying positive mood (Regeer et al., 2015; Silva et al., 2013). These finding are unique to (hypo)mania, with the same research studies showing that reduced symptom insight is not common in bipolar depression or euthymia (Silva et al., 2013).

Presently, the choice over which (hypo)mania measure to use in BD research depends on the intended aim of its administration. In our study, given the minimal clinical supervision in a digital intervention, our priority was to ensure that people experiencing hypomania were not admitted to our study. Consequently, we adopted the most conservative of measures, and followed guidelines on the use of (hypo)mania scales in clinical settings for measurement based care in BD (Cerimele et al., 2019). As mentioned in Chapter 6 ASRMS shows poor correlations with measures of energy and elated mood (Tsanas et al., 2016), and might not reflect accurately the clinical condition of (hypo)mania (Faurholt-Jepsen et al., 2016). Thus, even though the ASRMS is among the (hypo)mania tools with the most robust evidence base (Meyer et al., 2020), we believe that future studies would benefit from a more nuanced measurement of (hypo)mania symptom monitoring. A candidate area likely to have a valuable contribution to the measurement of (hypo)mania is the recent development of tools specifically focused on for measurement-based care, such as the Patient Mania Questionnaire-9 (Cerimele et al., 2022).

7.3.5 Digital Measurement and Treatment for Sleep and Circadian Rhythms

The digital transformation of healthcare is among the highest priority areas for policymakers globally (Colombo et al., 2020), and it is an area particularly salient for mental health, given that mental health disorders are common yet underdiagnosed and undertreated (Lattie et al., 2022; Patel & Prince, 2010). People with BD in particular have indicated an interest in using digital technologies to support their mental health (Brunette et al., 2019). As such, future research in this field should capitalise on advances in digital sleep therapeutics as well as technologies of remote sleep and circadian assessments to deliver on the digital transformation of research in BD.

Among mental health disorders, BD is an ideal candidate for digital phenotyping (Anmella et al., 2022; Harrison et al., 2018). The chronic and recurrent nature of depression, (hypo)mania and euthymia translates to altered mood, activity, speed and general behaviour (Saccaro et al., 2021). Furthermore, people with BD have highlighted being interested in using apps to support their mental health (Brunette et al., 2019). In two systematic reviews of digital phenotyping platforms, sleep and rest-activity emerged as one of the most frequent symptoms that developers chose to monitor in BD (Bufano et al., 2023; Saccaro et al., 2021). In one of the longest digital phenotyping study, over 20 years of digital phenotyping in BD showed that sleep was the most potent predictor of emerging acute episodes and the most important factor for understanding the trajectory of the disorder (Bauer et al., 2023). Beyond symptom self-report, the use of 24-hour actigraphy monitoring (Chinoy et al., 2021; McDevitt et al., 2021), at-home devices for the assessment of sleep architecture (Rusanen et al., 2024; Tal et al., 2017; Yazdi et al., 2024), and ambulatory circadian measurement tools (Kolodyazhniy et al., 2011; Martinez-Nicolas et al., 2019) also have the potential to play a central role in the digital transformation of sleep and circadian symptom monitoring in BD.

On the other hand, the landscape for digital interventions for BD is different to that for digital phenotyping. A recent systematic review of digital interventions in BD identified 13 studies in this area, and meta-analytic models showed no improvements in depression, (hypo)mania, functioning and quality of life (Anmella et al., 2022). This finding is not without precedent. In general, although some digital interventions in mental health have produced positive effects in very controlled research environments, adherence and effectiveness are both often low in real-world settings (Folker et al., 2018; Lattie et al., 2022). This is not to say that there are no examples of digital interventions that have showed positive results even in real world settings (Etzelmueller et al., 2020). A review identified that a major barrier in uptake of digital interventions is acceptability by the targeted end users in terms of the programme and how they want to use their personal technologies (Borghouts et al., 2021). From a public mental health perspective, this is a clear drawback, as effectiveness is meaningless if acceptability is low and people are not engaging with the digital interventions (Lattie et al., 2022). In our study in Chapter 6, the average completion rate was 96%, with 83% of the eligible participants completing at least 75% of the intervention and 56% completing every session. This is markedly higher than the typical completion rate of 65% for digital CBT protocols (Van Ballegooijen et al., 2014), and that of the same digital intervention delivered to people with insomnia where 58% completed at least 75% of the treatment sessions and 48% completed every session (Espie et al., 2019). Although selection bias might have influenced the interest of our participants in digital technologies and might have inflated their adherence to our study, the data from the semi-structured interviews still provide valuable insight into the benefits and barriers related to digital interventions.

We believe that future studies in sleep and circadian rhythms in BD are well placed to capitalise on digital tools. Assessment of sleep and circadian rhythms through remote technologies that are cheaper and less intensive have the potential for longitudinal symptom monitoring at-scale. Additionally, previous work on digital therapeutics for insomnia could

be used as the springboard for future research to explore setting up and testing multi-modality transdiagnostic interventions for sleep and circadian rhythms in BD.

7.3.6 Methodological and Analytical Rigour

An overarching theme in our research agenda is a call for methodologically and analytically robust studies that focus on pre-registered testable hypotheses that are relevant to people with BD.

First, this can be through improved engagement with open science principles. Open science denotes the theoretical framework and practical methods of making the content and process of science transparent and accessible to others (Munafò et al., 2017). Open science is not a strict collection of rules, and indeed in this thesis we engaged with open science principles to varying degrees. Although, making data openly available is a challenge given the nature of the research in this field, our studies in Chapters 3-5 are pre-registered, while the analytical decisions and source code of all studies are openly available online. Our research agenda for more meaningful and coordinated engagement with open science is in line with convergent calls from both BD researchers (Manchia et al., 2020; McInnis et al., 2022), and researchers in the field of sleep science and chronobiology (Spitschan et al., 2021). In light of well-documented unreplicable findings in biomedical research (Begley & Ellis, 2012; Camerer et al., 2018; Crook et al., 2013; Open Science Collaboration, 2015), a coordinated engagement with open science in our field has the potential to create a robust and credible evidence base around the role of sleep and circadian rhythms in BD. Furthermore, the use of open science can facilitate the integration of sleep science and chronobiology research in BD, by facilitating equitable and transparent exchange of data and information.

Another area of priority for future studies is the involvement of people with lived experience. Meaningful involvement of lived experience expertise necessitates that people with lived experience are stakeholders in relevant research and not only participants in it

(Robotham et al., 2016). In Chapter 6, people with lived experience of BD were consulted on the aims and methodology of the project, and contributed significantly to the establishment of the interview schedule for the qualitative part of the study. In turn, qualitative data from these interviews offered valuable insight into the gaps and opportunities for future research in this area that would not otherwise been captured by aggregate change scores from quantitative measures. For example, people emphasised that the most important improvement following digital CBT-I was on decreased worry and rumination around sleep, as opposed to a concrete change in sleep behaviour. Additionally, it became evident that future research in this area needs to investigate transdiagnostic treatment protocols that target the heterogeneous sleep and circadian profile of people with BD beyond just insomnia.

There is growing interest in the involvement of people with lived experience in mental health (Banfield et al., 2018) and BD research more specifically (Morton et al., 2022). The involvement of lived experience expertise varies depending on the study type, and it ranges from priority setting and commissioning, to conducting, communicating and using research. Systematic evaluations of the contribution of lived experience have shown that this type of expertise enhances the quality of research, ensuring its relevance and appropriateness (Brett et al., 2014). Active lived experience involvement in BD research also ensures that research addresses outcomes valued by people with lived experience (Morton et al., 2022). In fact, the growing interest in the study of sleep and circadian rhythms in BD can be partly attributed to an aliment between research and lived experiences priorities, owing to people with BD emphasising the importance of areas such as sleep, energy and physical productivity for symptom self-monitoring (Chevance et al., 2020; Gordon-Smith et al., 2021). Even in terms of treatment efficacy, in a survey exploring pharmacotherapy options in people with BD, participants reported that the improvements in sleep and functioning were the most important personal determinants of treatment efficacy (Rosenblat et al., 2019). The involvement of BD lived experience expertise was invaluable for this thesis, both in terms

of priority setting and methodological rigour, but also in terms of identifying opportunities for improvement, and we believe that future research should prioritise the involvement of people with lived experience of BD in their work.

7.4 Concluding remarks

The multifaceted involvement of sleep and circadian rhythms in BD constitutes both an opportunity and a challenge for the field. An opportunity for extensive and diverse research to explore sleep and circadian disruptions as phenotypes, prodromes and potent treatment targets in BD, but also a challenge to ensure that these research endeavours remain collaborative, focused and coherent.

Reflecting this notion, this thesis approached the question over the role of sleep and circadian rhythms in BD from multiple angles. Our findings in Chapter 3 add to accumulating efforts to elucidate the sleep profile of BD. We showed that people with BD have an adverse sleep profile compared to healthy controls, albeit a potentially similar one to MDD. In Chapter 4 we capitalised on a well-characterised BD high-risk cohort and set out to describe its sleep and rest-activity profile. Limitations regarding the final sample size did not allow for adequately powered comparisons, and no differences were statistically significant, although the direction of effects followed our predictions. In Chapters 5 and 6 we explored the role of sleep and circadian rhythms as intervention targets. After identifying and appraising gaps in the literature, we set out to address them in a mixed-methods pilot trial which provided preliminary evidence that a digital CBT-I is safe, feasible, acceptable and potentially effective treatment in BD-II.

The findings of this thesis are far from exhaustive, yet they provide evidence-informed and methodologically rigorous contributions to our understanding of the role of

sleep and circadian rhythms in BD, and highlight a potential research agenda. Future studies should focus on integrating sleep medicine and chronobiology research in BD, setting up and investigating transdiagnostic sleep and circadian interventions for BD, including longitudinal assessments of sleep and circadian rhythms in the BD developmental trajectory, improving measures of (hypo)mania, capitalising on digital innovations in assessment and treatment of sleep and circadian rhythms in BD, and prioritising research that is methodologically and analytically rigorous.

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Supplementary Materials

Appendix 1: UK Sleep Census Questions and Possible Answers

SECTION 1: DEMOGRAPHICS			
Questionnaire	**Question text**	**Response format**	**Input type**
Bespoke: Gender	Which of the following best describes your gender	01=Male 02=Female 03=Non-binary 04=Other 05=Prefer not to say	Radio button, single option
Bespoke: Age in years	What is your age (in years)	Number drop down 18 to 101+	Drop down
Bespoke: Pregnancy	Are you currently pregnant	01=Yes 02=No 03=Not applicable 04=Prefer not to say	Radio button, single option
Bespoke: BMI Height	What is your current height? In metres (feet). Please select the closest value.	Number drop down 1.40m (4 feet 7.1 inches) or below to 2.4m (7 feet 10.5 inches) or above	Drop down m (ft)
Bespoke: BMI Weight	What is your current weight? In kg (stone and pounds). Please select the closest value.	Number drop down from below 40KG (6 stone 4.2 pounds) to 140KG (22 stone and 0.6 pounds) or above	Drop down kg (st)
Bespoke: Employment status	What is your employment status?	01=Employed (full-time) 02= Employed (part-time) 03= Employed (furloughed) 04=Unemployed, but looking for work 05=Unemployed, but not looking for work 06=Student (full-time) 07= Student (part-time) 08=Carer (unpaid) 09=Other volunteer / unpaid role 09=Unable to work 10=Retired 11=Other 12=Prefer not to say	Radio button, single option
Bespoke: Marital status	What is your marital status	01=Single 02=In a relationship/married but not living with partner 03= In a relationship/married and living with partner 04=Divorced / Separated 05= Widowed 06=Prefer not to say	Radio button, single option
Bespoke: Household	How many people currently live in your household (including yourself)	Drop down from: I live by myself to 10 or more.	Drop down

Bespoke: Co-sleeping	Do you share a bed with another person?	01=Never / Not during the past month 02= Rarely: less than once a week 03= Sometimes: one to three times a week 04=Often: four to six times a week 05= Always: every night DA=Prefer not to answer	Radio button, single option
Bespoke: Household 3	Please indicate the number of children you have in each of the age brackets	Drop down entry on a scale of 0 to 8 or more for each of the following 0 to 2 years old 3 to 5 years old 6 to 11 years old 12 to 18 years old	Drop down
Bespoke: Ethnicity (format is set to the standard from the Office for National Statistics)	What is your ethnic group? Please choose one option that best describes your ethnic background	01=White: English/Welsh/Scottish/Northern Irish/British 02= White: Irish 03=White: Gypsy or Irish Traveller 04=White: Other 05=Mixed/Multiple ethnic group: White and Black Caribbean 06=Mixed/Multiple ethnic group: White and Black African 07=Mixed/Multiple ethnic group: White and Asian 08=Mixed/Multiple ethnic group: Other 09=Asian /Asian British: Indian 10= Asian /Asian British: Pakistani 11= Asian /Asian British: Bangladeshi 12= Asian /Asian British: Chinese 13= Asian /Asian British: Other 14= Black / African / Caribbean / Black British: African 15= Black / African / Caribbean / Black British: Caribbean 16= Black / African / Caribbean / Black British: Other 17=Arab 18=Other ethnic group not described here 19=Prefer not to say	Radio button, single option
Bespoke: Education	What is your highest level of formal education?	01=None 02=GCSE or equivalent 03= A-levels or equivalent 04=University Undergraduate 05= University Postgraduate 06=Prefer not to answer	Radio button, single option
Bespoke: Geographic location 1	To allow us to group responses by area of the UK, please enter the first half of your postcode (your postcode	Free text but locked at 4 characters in length so participants cannot give us their full postcode.	

	district). This will be 2 to 4 characters long and contain letters and numbers.		
Bespoke: Geographic location 2	How would you describe the area you live in?	01=Urban (densely populated city/town) 02=Suburban (on the edge of town/city or a village with >10,000 inhabitants) 03=Rural (sparsely populated area) 04=Prefer not to answer	Radio button, single option
SECTION 2: HEALTH AND QUALITY OF LIFE			
Questionnaire	**Question text**	**Response format**	**Input type**
Bespoke: Self-rated health (item taken from the Biobank)	In general, how would you rate your overall health?	01=Excellent 02=Good 03=Fair 04=Poor 05=Do not know DA=Prefer not to answer	Radio button, single option
Quality of life	Please drag the slider below to the position on the ruler which best represents your quality of life at the moment. The scale ranges from 0 (= worst possible quality of life) to 100 (= best possible quality of life).	Slider scale 0 to 100	Slider
Adapted: Mental and Physical Health	Have you been diagnosed with, or are currently receiving treatment for, any of the following. Please tick all that apply. If you are not entirely sure how to classify your illness, please select 'Other'.	A=Diabetes B=Arterial hypertension C=Cardiovascular disorder D= Cerebrovascular disorder E=Other neurological disorder F=Asthma G= Chronic obstructive pulmonary disease (COPD) H=Rheumatic disorder I=Cancer/Use of cytostatic medications J=Allergy (atopy, seasonal allergy, other) K=Autoimmune disease L=Depression M=Bipolar depression N=Anxiety /panic disorder O=Other Mental health problem P= Problems of attention or concentration / ADHD Q= ME/CFS, chronic fatigue R=Digestive disorder S=Hormonal Disorder T= Other U= No illness/disorder/disease DA = Prefer not to answer	Radio button, single option
Bespoke: Covid 1	Have you ever tested positive for COVID-19	01=No 02=Yes 03= Prefer not to answer	Radio button, single option

Bespoke: Covid 2	When did you last test positive for COVID-19	01= less than 1 month ago 02 = more than 1 month ago but less than 3 months ago 03= more than 3 months ago but less than 6 months ago 04= more than 6 months ago 05=prefer not to answer	Only presented if above is yes. Radio button, single option
Bespoke: Covid 3	Are you currently or did you experience any long COVID symptoms?	01= Yes and currently experiencing symptoms 02 = Yes but not currently experiencing any symptoms 03= No 04= Prefer not to answer	Only presented if above is yes. Radio button, single option
Bespoke: Menopause	Are you post-menopausal?	01=Yes 02=No but currently undergoing the menopause 03=No 04=Not applicable 05= Prefer not to answer	Radio button, single option
SECTION 3: SLEEP HISTORY/ENVIRONMENT			
Questionnaire	**Question text**	**Response format**	**Input type**
Bespoke: Sleep disorders 1	Have you ever been diagnosed with a sleep disorder by a medical professional	01=Yes 02=No DA=Prefer not to answer	Radio button only allowing one selection.
Bespoke: Sleep disorders 2	Please select all that apply	01=Insomnia 02=Sleep disordered breathing (e.g. sleep apnoea) 03=Sleep related movement disorder (e.g. restless leg syndrome, periodic limb movement disorder) 04=Parasomnia (e.g. sleep walking, REM behavior disorder, night terrors, nightmare disorder) 05=Circadian Rhythm Disorder (e.g. delayed sleep phase syndrome) 06=Hypersomnia (e.g. Narcolepsy) 07=Other DA=Prefer not to answer	Only presented if above is yes. Multi selection
SECTION 4: WORK AND SLEEP			
Questionnaire	**Question text**	**Response format**	**Input type**
Bespoke: Shift work	In the past month, did you typically work a non-standard shift schedule? Here we define non-standard shift schedule as working hours that typically take place outside the hours of 8am to 8pm. *We define work as either paid or unpaid work including volunteering or carer responsibilities. For these questions work is defined as a "fixed day" whereby you have to get up and work/volunteer*	01= No – I didn't work 02= No – I worked standard hours (e.g. 9:00am-5:00pm) 03=Yes – I worked evening shifts (work typically finished between 9:00pm and midnight) 04=Yes - I worked morning shifts (work typically started between 4:00am and 7:00am)	Radio button only allowing one selection.

		05=Yes – I worked night shifts (work typically took place between 9:00pm and 8:00am) 06=Yes – I worked rotating shifts (periodically changed or had irregular work hours) DA=Prefer not to answer	
Bespoke: Workday time into bed	Thinking about the last month, what time did you go to bed on a work/school/college/university day? This may be the same time you turned the lights off and tried to go to sleep or it could be slightly early if you get into bed and do activities like reading or using social media before trying to go to sleep.	Drop down from 20:00 in 15 minute increments for the whole 24hr period	Only if working (exc rotating shift) Whole 24hr period given as we want to also include night shift workers.
Bespoke: Workday bed time	Thinking about the last month, what time did you typically turn the lights off to try and go to sleep on a work/school/college/university day? This may be different to the time you went to bed	Drop down from 20:00 in 15 minute increments for the whole 24hr period	Only if working (exc rotating shift) Whole 24hr period given as we want to also include night shift workers.
Bespoke: Workday wake time	Thinking about the last month, what time did you usually wake up on work/school/college/university days? By 'wake up' we mean your final awakening time before getting up for the day	Drop down from 04:00 in 15 minute increments for the whole 24hr period	Only if working (exc rotating shift) Whole 24hr period given as we want to also include night shift workers.
Bespoke: Alarm clock work day	Do you use an alarm clock to wake up on work/school/college/university days? This refers to any type of alarm for example a clock or a mobile phone.	01= Yes, always 02= Yes, sometimes 03=No, never DA Prefer not to answer	Radio button only allowing one selection
Bespoke: Workday get out of bed	Thinking about the last month, what time did you usually get out of bed on work/school/college/university days? By 'get out of bed' we mean the time you decided to get up for the day. This may be the same time as you wake up or slightly later if you read in	Drop down from 04:00 in 15 minute increments for the whole 24hr period	Only if working (exc rotating shift) Whole 24hr period given as we want to also

	bed or watch TV before getting up to start your day.		include night shift workers.
Bespoke: Free day time into bed	Thinking about the last month, what time did you go to bed on a non-workday? For example a day off or the weekend. This may be the same time you turned the lights off and tried to go to sleep or it could be slightly early if you get into bed and do activities like reading or using social media before trying to go to sleep.	Drop down from 20:00 in 15 minute increments for the whole 24hr period	All participants
Bespoke: Free day bed time	Thinking about the last month, what time did you typically turn the lights off to try and go to sleep on a non-workday? For example a day off or the weekend. This may be different to the time you went to bed	Drop down from 20:00 in 15 minute increments for the whole 24hr period	All participants
Bespoke: Free day wake time	Thinking about the last month, what time did you usually wake up on non-work days? By 'wake up' we mean your final awakening time before getting up for the day	Drop down from 04:00 in 15 minute increments for the whole 24hr period	All participants
Bespoke: Alarm clock free day	Do you use an alarm clock to wake up on non-work days? This refers to any type of alarm for example a clock or a mobile phone.	01= Yes, always 02= Yes, sometimes 03=No, never DA Prefer not to answer	Radio button only allowing one selection
Bespoke: Free day get out of bed	Thinking about the last month, what time did you usually get out of bed on non-work days? By 'get out of bed' we mean the time you decided to get up for the day. This may be the same time as you wake up or slightly later if you read in bed or watch TV before getting up to start your day.	Drop down from 04:00 in 15 minute increments for the whole 24hr period	All participants
SECTION 5: SLEEP DURATION			
Questionnaire	**Question text**	**Response format**	**Input type**
Sleep duration	Thinking about the past month, on average how many hours of sleep per night did you have? This excludes naps. For night shift workers, this refers to your main sleep block for the day. Times given in hours to the nearest half an hour where 0.5 = 30 minutes	Drop down 0.5 to 24 in 0.5 increments.	
Bespoke: perceived sleep need	How many hours of sleep per night do you think you need to feel and perform at your best? Times given in	Drop down 0.5 to 24 in 0.5 increments.	

	hours to the nearest half an hour where 0.5 = 30 minutes		
Bespoke: sleep relative to others	Do you consider your sleep to be better, worse or average in comparison to other people of your age?	01=Much Better 02=Somewhat better 03=About the same 04=Somewhat worse 05=Much Worse DA=Prefer not to answer	Radio button only allowing one selection
SECTION 6: SLEEP QUALITY			
Questionnaire	**Question text**	**Response format**	**Input type**
Sleep Condition Indicator (SCI; Espie et al., 2014) = 8 items. Modified to include a "Prefer not to answer" option.			
Bespoke: Early morning awakening	Thinking about the past month, how long before you *intend* to wake up do you actually wake up? (e.g. if you intend to wake up at 7am but wake-up at 6:15am most mornings this would be a difference of 45 minutes.)	01=0-15 mins early 02=16-30 mins early 03=31-45 mins early 04=46-60 mins early 05= more than 60 mins early DA = Prefer not to answer	Radio button only allowing one selection.
SECTION 7: SLEEP INTERRUPTERS. ***DURING THE PAST MONTH, HOW OFTEN HAVE YOU HAD TROUBLE SLEEPING BECAUSE YOU…***			
Questionnaire	**Question text**	**Response format**	**Input type**
Items from the Pittsburgh sleep quality Index (PSQI; Buysse et al., 1988)	Have to get up to use the bathroom	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Matrix table with all except children and bed partner items
Items from the Pittsburgh sleep quality Index (PSQI; Buysse et al., 1988)	Cannot breathe comfortably	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Matrix table with all except children and bed partner items
Items from the Pittsburgh sleep quality Index (PSQI; Buysse et al., 1988)	Cough or snore loudly	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Matrix table with all except children and bed partner items
Items from the Pittsburgh sleep quality Index (PSQI; Buysse et al., 1988)	Feel too cold	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Matrix table with all except children and bed partner items
Items from the Pittsburgh sleep quality Index (PSQI; Buysse et al., 1988)	Feel too hot	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week	Matrix table with all except children and

		DA=Prefer not to answer	bed partner items
Items from the Pittsburgh sleep quality Index (PSQI; Buysse et al., 1988)	Have bad dreams	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Matrix table with all except children and bed partner items
Items from the Pittsburgh sleep quality Index (PSQI; Buysse et al., 1988)	Have pain	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Matrix table with all except children and bed partner items
Bespoke (based on PSQI)	Find it noisy	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Matrix table with all except children and bed partner items
Bespoke (based on PSQI)	Find the bed uncomfortable	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Matrix table with all except children and bed partner items
Bespoke (based on PSQI)	Are disturbed by the light levels	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Matrix table with all except children and bed partner items
Bespoke (based on PSQI)	Are worried about something	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Matrix table with all except children and bed partner items
Bespoke (based on PSQI)	Are disturbed by children	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Single item matrix table. Only if answer to " Do you share your household with any children" is yes
Bespoke (based on PSQI)	Are disturbed by your bed partner	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Single item matrix table. Only if answer to " Do you share your with another

			person" is NOT "never/not during the past month" OR "prefer not to answer"
SECTION 8: SLEEP HYGIENE AND HABITS. ***DURING THE PAST MONTH HOW OFTEN HAVE YOU ….***			
Questionnaire	**Question text**	**Response format**	**Input type**
Bespoke: sleep tracker devices	…used a sleep-tracking device to monitor your sleep pattern? For example, using a wristband (e.g. Fitbit) or smartphone app?	01= Daily 02=More than once a week 03= 3-4 times per month 04= 1-2 times per month 05= I own a sleep-tracking device but have not used it in last month 06= I do not own a sleep-tracking device DA Prefer not to answer	Radio button only allowing one selection
Bespoke: alcohol use	…consumed alcohol to help you fall asleep?	01= Daily 02=More than once a week 03= 3-4 times per month 04= 1-2 times per month 05= Not at all DA Prefer not to answer	Radio button only allowing one selection
Bespoke: sleep aids 1	.. taken prescription medicine to help you sleep?	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Radio button only allowing one selection
Bespoke: sleep aids 2	Thinking about the prescription sleep aids that you use, how effective do you think these are at improving your sleep?	01=Not at all 02=Some 03=Quite a bit 04=Very much DA=Prefer not to answer	Only shown if answer to "taken a prescription medication to help you sleep" is NOT "not during the past month" OR "prefer not to answer"
Bespoke: sleep aids 3	… taken something to help you sleep that wasn't a prescription medication? For example supplements, herbal teas, or non-prescription sleeping tablets.	01=Not during the past month 02=Less than once a week 03=Once or twice a week 04=Three or more times a week DA=Prefer not to answer	Radio button only allowing one selection
Bespoke: sleep aids 4	What non-prescription sleep aid do you use? *Please select all that apply*	a. Melatonin or tryptophan containing products (Gummies, tablets/capsules etc.) b. Over the counter sleeping tablets (products like	Only shown if answer to "taken something to help you sleep that

		Nytol, Kalms, Sleepeaze, Sominex or other own brand products.) c. Cannabidiol (CBD) containing products (oils, tablets/capsules etc.) d. "Sleepy" Teas (Chamomile, passionflower, Green tea, tea products marketed to help you sleep etc.) e. Supplement tablets or drops (Magnesium, Valerian Root, Gingko Biloba, black cherry etc.) f. Homeopathic Tinctures and Tonics (Rescue Remedy, Coffea cruda, Hyoscamus niger, Sulphur etc. or items purchased from a homeopath) g. Pro or prebiotic supplements. h. Other	wasn't a prescription medication" is NOT "not during the past month" OR "prefer not to answer" Multiple selection
Bespoke: sleep aids 5	Thinking about the non-prescription sleep aids that you use, how effective do you think these are at improving your sleep?	01=Not at all 02=Some 03=Quite a bit 04=Very much DA=Prefer not to answer	Only shown if answer to "taken something to help you sleep that wasn't a prescription medication" is NOT "not during the past month" OR "prefer not to answer"
Bespoke: sleep aids 6	Are you currently receiving, or have ever received, psychological treatment for your sleep? For example, Cognitive Behavioural Therapy or any talking based therapy in person, over the phone, or digital.	01=No / Never 02=Yes, but not in the past month 03=Yes, currently receiving treatment DA=Prefer not to answer	Radio button only allowing one selection
Bespoke: sleep aids 7	Thinking about the psychological treatment for your sleep, how effective do you think it is at improving your sleep?	01=Not at all 02=Some 03=Quite a bit 04=Very much DA=Prefer not to answer	Only shown if answer to "Are you currently receiving, or have ever received, psychological treatment for your sleep?"

			is NOT "no / never" OR "prefer not to answer"
Bespoke: nap 1	…napped or dozed during the day?	01= Daily 02=More than once a week 03= 3-4 times per month 04= 1-2 times per month 05= Not at all DA Prefer not to answer	Radio button only allowing one selection
Bespoke: nap 2	When you do nap during the day, how long do you typically nap for?	01=0-20 minutes 02=21-40 minutes 03=41=60 minutes 04=1-2 hours 05=More than 2 hours DK= I don't know DA= Prefer not to answer	Only shown if answer to "napped or dozed during the day" is NOT "not during the past month" OR "prefer not to answer"
Bespoke: exercise 1	…exercised? This refers to exercise that requires a moderate amount of effort and noticeably accelerates your heart rate	01= Daily 02= More than once a week 03= 3-4 times per month 04= 1-2 times per month 05= Not at all NA=Unable to exercise DA Prefer not to answer	Radio button only allowing one selection
Bespoke: exercise 2	What time of the day do you usually exercise?	01=Early morning 02=Late morning 03=Early afternoon 04=Late afternoon 05 =Evening before meal 06=Between evening meal and bedtime V=Varies significantly DA=Prefer not to answer	Only shown if answer to "exercised?" is NOT "not at all" OR "unable to exercise" OR "prefer not to answer" Radio button only allowing one selection
Caffeine 1	How many cups/glasses of coffee, tea or cola-drinks (caffeine-containing drinks) do you consume per day? (1 cup of coffee = standard 6 ounce restaurant cup)	Drop down 0.5 to more than 20 for each of the following: Cups of Coffee Cups of tea Cans of cola drinks (or similar) Cans of energy drinks	
Bespoke: Caffeine 2	What time of day do you usually drink your last caffeinated drink?	01=Early morning 02=Late morning 03=Early afternoon 04=Late afternoon 05=Between evening meal and bedtime V=Varies significantly N/A=I don't drink caffeinated drinks DA=Prefer not to answer	Radio button only allowing one selection

Bespoke: Devices 1	How long before bedtime do you last use a computer, tablet, mobile phone or television?	01=I use them in bed 02=Less than 1 hour 03=1-2 hours 04=2-3 hours 05=3 hours or longer NA= Not applicable DA=Prefer not to answer	Radio button only allowing one selection
Bespoke: Bedtime routines 1	Do you do anything in bed to help you get to sleep (tick all that apply)	Relaxation/mindfulness exercises Counting Lying still Watching TV/Films/YouTube Listening to radio, music, podcasts, audiobooks Reading Use aromatherapy (e.g lavender scents or pillow sprays) Other Not applicable / Do not have a bedtime routine Prefer not to answer	Multiple selection
SECTION 9: THOUGHTS BEFORE SLEEP			
Questionnaire	**Question text**	**Response format**	**Input type**
Modified Glasgow Content of Thought Inventory (GCTI; Harvey & Espie, 2004)	Please select up to three key thoughts that have kept you awake over the past month. *Click not applicable if you don't experience any of these thoughts or did not have difficulties with sleep in the past month*	Thinking about things in the future Thinking about how tired/sleepy you feel Thinking about things that happened during the day Thinking about how nervous/anxious you feel Thinking about how mentally awake you feel Thinking about checking the time Thinking about trivial things Thinking about how you can't stop your mind from racing Thinking about how long you've been awake Thinking about your health Thinking about ways you can get to sleep Thinking about things you have to do tomorrow Thinking about how hot/cold you feel Thinking about your work/responsibilities Thinking about how frustrated/annoyed you feel Thinking about how light/dark the room is Thinking about the noises you can hear Thinking about being awake all night	Multiple option, column

		Thinking about pictures of things in your mind Thinking about the effects of not sleeping well Thinking about your personal life Thinking about how thinking too much is the problem Thinking about things in your past Thinking about how bad you are at sleeping Thinking about things to do to help you sleep	
SECTION 10: CHRONOTYPE			
Questionnaire	**Question text**	**Response format**	**Input type**
Reduced Morningness-Eveningness Questionnaire (rMEQ; Adan & Almirall 1991, Horne & Ostberg, 1976). 5 items. Modified to include a "prefer not to answer" option			
SECTION 11: MOOD			
Questionnaire	**Question text**	**Response format**	**Input type**
Patient Health Questionnaire 4 (PHQ-4; Kroenke et al., 2009). 4 items. Modified to include a "prefer not to answer" option			
SECTION 12: COGNITION			
Questionnaire	**Question text**	**Response format**	**Input type**
British Columbia Cognitive Complaints Inventory (BC-CCI; Iverson & Lam, 2013). 6 items. Modified to include a "prefer not to answer" option			
SECTION 13: SLEEP SATISFACTION			
Questionnaire	**Question text**	**Response format**	**Input type**
Sleep satisfaction	How satisfied / dissatisfied are you with your current sleep pattern	01=Very Satisfied 02=Satisfied 03=Neutral 04=Dissatisfied 05=Very Dissatisfied DA=Prefer not to answer	Radio button only allowing one selection

Bespoke: Monetary cost of a good night of sleep	Imagine you were given £100 to spend on improvements to your health, how much of that money would you spend on improving your sleep?	Slider 0 to 100		
Bespoke: Sleep adjective 1	What one word describes how you feel after a good night of sleep?		Text	Set max length at 15 characters
Bespoke: Sleep adjective 2	What one word describes how you feel after a poor night of sleep?		Text	Set max length at 15 characters

Appendix 2: Pre-registration of the Sleep Profile in Bipolar Disorder Study

The proposed investigation is based on a national survey conducted in the UK in 2021, called *"The UK Sleep Census"*. As part of the survey, participants had to report whether they *"have ... been diagnosed with, or are currently receiving treatment for"* a range of physical and mental disorders, one of which was BD. Our study will focus on this group of responders. In addition to the large sample size, the UK Census includes variables covering several attitudes, behaviours, and disruptions around sleep and circadian rhythms, many of them never been explored in the context of BD. The survey will also allow us to investigate differences in the sleep profile between BD and major depression disorder, as well as any potential subtypes within the BD group.

Participants

Participants will be retrieved from the national survey dataset and will be divided into three groups of equal size. The first group will consist of people who reported that they have received a diagnosis of BD. The second group will be matched on age, gender, education, and employment to the BD group and will consist of people who have indicated that they have not received any mental health diagnosis, excluding sleep disorders (HC group). The third group will also be 1for1 matched on age, gender, education, and employment to the BD group and will consist of people who have indicated that they have received a diagnosis of major depression disorder (MDD group).

Matching will be implemented using the matching imputation method with subset selection performed by stratification. Distance matching via nearest neighbour will be applied to match one-to-one the HC and MDD groups to the BD sample.

Outcomes

Outcomes will consist of answers to questionnaires and bespoke items included in the survey. The primary outcome will be the Sleep Condition Indicator. Secondary outcomes will include the Patient Health Questionnaire-4, the British Columbia Cognitive Complaints Inventory, and quality of life. All other variables will be analysed in an exploratory manner. Below is a list of all variables that will be retrieved and summarised:

<u>Demographic information:</u> Gender, Age, BMI, Ethnicity, Education, Employment, Marital status, Household, Geographic location, Shift-work

<u>General Health:</u> Self-rated health, Quality of life, Co-morbid disorders (physical and mental including sleep), Alcohol Use, Caffeine, Exercise

<u>Mood and Cognition:</u> Patient Health Questionnaire-4, British Columbia Cognitive Complaints Inventory

<u>General Sleep:</u> Time into Bed (workday and non-workday), Bedtime (workday and non-workday), Wake Time (workday and non-workday), Get out of bed (workday and non-workday), Sleep tracker devices, Sleep aids (prescribed, over the counter, and psychological), Nap, Bedtime routines, Co-sleeping, Chronotype

Sleep Disturbances and Satisfaction: SCI, Sleep duration, Sleep need, Sleep relative to others, Early morning awakenings, Pittsburgh Sleep Quality Index items, Glasgow Content of Thoughts Inventory, Sleep satisfaction, Cost of a good night of sleep, Sleep adjective (for good and for poor sleep)

Hypotheses

We predict that the BD group will show greater insomnia scores compared to the healthy control group, measured by the Sleep Condition Indicator. We also predict that the BD group will show worse outcomes on depression, cognitive skills, and quality of life compared to the healthy control group, measured by the Patient Health Questionnaire-4, the British Columbia Cognitive Complaints Inventory, and a self-rated question on quality of life, respectively.

Exploratory analyses will focus on the association between sleep, depression, quality of life, and cognitive impairments in BD, differences between the BD and MDD on the above outcomes, as well as potential sleep profile subtypes within the BD group.

Analysis

Analyses of the collected data will be conducted in the statistical software R. Initially, scatter and density plots of every outcome will be constructed to evaluate the distribution pattern and the extent to which the collected data meet the assumptions for parametric tests. Means and standard deviations will be presented for all continuous data, and total amount of instances and proportions for the categorical data.

Confirmatory: the confirmatory analyses will rely on a series of independent samples t-test between the BD and HC group based on their scores in the Sleep Condition Indicator, the Patient Health Questionnaire-4, the British Columbia Cognitive Complaints Inventory, and a self-rated question on quality of life. The presented results will include degrees of freedom, t- and p-values, confidence intervals as well as Cohen's d effect sizes.

Exploratory: exploratory analyses will have three aspects:

A. Differences in sleep behaviour between BD and HC

To explore this question, independent sample t-tests and chi-square tests will be employed for scales with continuous and categorical data, respectively. For the t-tests, results will include degrees of freedom, t- and p-values, confidence intervals as well as Cohen's d effect sizes. For the chi-square tests, degrees of freedom, Chi-square and p-values, as well as odd ratios will be calculated and presented.

B. Differences in sleep, mood and cognition between BD and MDD

This comparison will be based on a series of independent samples t-test between the BD and MDD group based on their scores in the Sleep Condition Indicator, the Patient Health Questionnaire-4, the British Columbia Cognitive Complaints Inventory, and a self-rated question on quality of life. The presented results will include degrees of freedom, t- and p-values, confidence intervals as well as Cohen's d effect sizes. We make no predictions for the direction of these results.

C. Predictive role of insomnia score for mood, cognition, and quality of life in BD

We will explore the potential of insomnia scores as a predictor of depression, cognitive problems, and quality of life in BD. The predictive validity of insomnia scores will be explored through regression analyses.

D. Sleep profile subtype in the BD group

Appendix 3: Pre-registration for the Sleep and Activity Phenotyping in Individuals at High-Risk of Bipolar Disorder study

Study Information

Study Hypothesis: Bipolar offspring will score lower on sleep quality (assessed through the PSQI) and higher on insomnia severity (assessed through the ISI) compared to controls

Study design

The study design will be case-control and cross-sectional. Group will be the only independent variable with 2 levels: bipolar offspring and control

Sampling Plan

Data collection procedures

Participants will be volunteers between the ages of 16 and 25 years. Bipolar offspring will be recruited in Canada through the Flourish cohort, and controls will be recruited in Oxfordshire, UK through standard advertising. Data collection will commence in May 2021 and will end after the necessary numbers of participants is recruited. To achieve balanced age and gender groups, the recruitment in Oxfordshire might be altered to target a specific age and gender group, in line with data collected in Canada. Participants will be compensated with a £30 Amazon voucher. The inclusion criteria for the bipolar offspring will be: 1. participant in the Flourish cohort with a parent that has received a diagnosis of BD 2. willing and able to give informed consent for participation in the study 3. aged 16-25 years 4. able to read and understand English 5. reliable internet access 6. not allergic to rubber bands (due to the strap of the actiwatch) 7. no occupation that requires shift work 8. no current pregnancy 9. not planning to move between time zones during the two weeks of data collection or travelled between more than 2 time-zones in the previous 3 months The inclusion/exclusion criteria for controls are: 1. participant is willing and able to give informed consent for participation in the study 2. aged 16-25 years 3. able to read and understand English 4. reliable internet access 5. live in Oxfordshire, United Kingdom 6. no first degree relative (blood parent or blood sibling) with any mental health diagnosis, including sleep disorders 7. no diagnosis of a psychiatric disorder 8. not allergic to rubber bands (due to the strap of the actiwatch) 9. no occupation that requires shift work 10. no current pregnancy 11. not planning to move between time zones during the two weeks of data collection or travelled between more than 2 time-zones in the previous 3 months

Sample size

Sample size was calculated using a power analysis in the package "pwr" in the software R, version 3.6.2. The expected effect size was that of the difference between high- and low-risk individuals in sleep quality indexed by the Pittsburgh Sleep Quality Index in Zanini and colleagues (2015). As such, to observe an effect size of 0.7 with 0.80 power and an alpha level of 0.05, 66 participants are needed in each group: 33 high and 33 low risk participants.

Stopping rule

Adjustments to recruitment plans might be made dynamically during the study to ensure that the Canadian and British groups are under similar lockdown rules. This might mean pausing recruitment at a study site for a given amount of time to ensure the two groups are comparable. This study is part of a larger DPhil (PhD) project, so recruitment might have to stop at a sensible time for analysis and write-up even if the satisfactory number of participants has not been reached.

Variables

Measured variables

The questionnaires and tasks we will administer include: 1. Demographics questionnaire 2. Pittsburgh Sleep Quality Index (PSQI) 3. Insomnia Severity Index (ISI) 4. Reduced Eveningness-Morningness Questionnaire (MEQ) 5. Sleep Disturbance Questionnaire (SDQ) 6. Epworth Sleepiness Scale-Children and Adolescent version (ESS-CHAD) 7. British Association of Psychopharmacology: Circadian Rhythm Disorders module 8. Alliance Sleep Questionnaire: Parasomnias module 9. Sleep Hygiene Index (SHI) 10. Patient Health Questionnaire-9 (PHQ-9) 11. Generalised Anxiety Disorder-7 (GAD-7) 12. Mood Disorders Questionnaire (MDQ) 13. Behavioural Inhibition and Avoidance Scale (BIS/BAS) 14. Stroop Colour Word Test 15. Continuous Performance Task (CPT) – Identical Pairs version Actigraphy and sleep diary data will also be collected for 2 weeks

Indices

Both speed and accuracy will be recorded and used as dependent variables in the Stroop Colour Word Task. A measure of the ability to discriminate between targets are distractors (index d) will be the dependent variable in the Continuous Performance Task Identical Pairs.

Analysis Plan

Statistical models

Analyses of the collected data will be conducted in the statistical software R. Initially, scatter and density plots of every outcome will be constructed to evaluate the distribution pattern and the extent to which the collected data meet the assumptions for parametric tests. Means and standard deviations will be presented for all continuous data, and total amount of instances and proportions for the categorical data. Exploratory analyses will investigate the mediating effects of sleep problems in mood and cognition.

Questionnaires: Independent sample t-tests will be used for the analysis for the following sleep and mental health questionnaires: PSQI, ISI, MEQ, SDQ, ESS-CHAD, SHI, PHQ-9, GAD-7, MDQ, and the BIS/BAS. The presented results will include degrees of freedom, t- and p-values, confidence intervals as well as Cohen's d effect sizes. Chi-square tests will be used for the British Association of Psychopharmacology: Circadian Rhythm Disorders module, and the Alliance Sleep Questionnaire: Parasomnias module. Degrees of freedom, Chi-square and p-values, as well as odd ratios will be calculated and presented.

Sleep diaries and actigraphy: Actigraphy data will be processed via a modified algorithm mirroring the scripts in the statistical package "GGIR" in the software R, developed for the analysis of accelerometer data derived from the actigraphy watches. SOL, WASO and TST will be presented in minutes, and SE in percentage scores, with means and standard deviations describing each group. L5, M10, intra- and inter-daily variability, and relative

amplitude will also be extracted. As with the questionnaires, paired sample t-tests will be used. The presented results will include degrees of freedom, t- and p-values, confidence intervals as well as Cohen's d effect sizes.
Cognitive tasks: measures of speed and accuracy will be the dependent variables derived from the Stroop task, estimated as reaction time in milliseconds and total number of correct responses. ANOVA will be used to analyse the data. The presented results will include degrees of freedom, F- and p-values, confidence intervals as well as eta squared effect sizes. The measure d will be used as the dependent variable of the CPT. Independent sample t-tests will be used for the analysis. The presented results will include degrees of freedom, t- and p-values, confidence intervals as well as Cohen's d effect sizes.

Exploratory analysis
The effect of demographic characteristics on the outcomes as well as the mediating effect of sleep on mood and cognitive functioning will be investigated in an exploratory way

Appendix 4: Registration of the Digital Sleep Intervention for Bipolar Disorder, DIGIT-B Study

Our study examines the implementation of digital version of CBT-I for bipolar disorder type II, given that a major barrier in the wider implementation of CBT-I is access to treatment and the scarcity of qualified providers. As such, the aim of the DIGIT-B study is to assess the safety, feasibility and acceptability of a digital CBT-I for BD-II, and explore its effects on sleep, mood and functioning, with a view of performing a larger trial in the future.

2. Study information *(List specific, concise, and testable hypotheses. Please state if the hypotheses are directional or non-directional. If directional, state the direction. A predicted effect is also appropriate here. If a specific interaction or moderation is important to your research, you can list that as a separate hypothesis)*

The DIGIT-B study is a pilot trial of a digital sleep intervention for BD-II. Our primary aim is to examine safety, feasibility and acceptability, and we hypothesise that our intervention will be safe, feasible and acceptable for BD. Operational definitions of safety, feasibility and acceptability are provided in a subsequent section (Measured Variables in section Variables, and Statistical Models in Analysis Plan).

Our secondary aim is to investigate, in an exploratory manner, the effects of our intervention on symptom improvement, primarily insomnia. Measures of sleep quality, rest-activity, depression, hypomania, anxiety and functioning are also included. More information on these outcomes is provided in subsequent sections (Measured Variables in section Variables, and Statistical Models in Analysis Plan). Qualitative data from the post-treatment semi-structured interviews will also be investigated.

3. Design Plan

We involved two people with BD from the Patient and Public Involvement group of the NIHR Oxford Biomedical Research Centre who provided comments on the study methodology, the language used, and the questions of the semi-structured interview. These individuals were given access to participant facing documents, interview guides and other forms containing details of the study methods and design.

The study is conducted fully remotely, employs both qualitative and quantitative methods, and contains a single treatment arm. All comparisons are within subjects.

Following positive screening, participants are invited for an online meetings via Microsoft Teams where their diagnosis is confirmed using the Structured Clinical Interview for the DSM-5. If eligibility is established then they progress to the baseline meeting (week 0). Following the baseline meeting, participants enter a 2-week pre-treatment monitoring period where they are offered the chance to meet with a member of the study team twice. At the end of this period, participants are invited to another Teams meeting, where eligibility is re-assessed, and if re-established, they are given access to treatment. The treatment phase lasts 10 weeks and is delivered through Sleepio. The treatment contains 6 sessions that become available to participants weekly. Participants are contacted again for 'mid-treatment'

assessment on week 7, and a post-treatment assessment on week 12. Both these assessments are done on Microsoft Teams. During all assessments participants complete a series of questionnaires, and during the post-treatment assessment the participants are also invited to a semi-structured interview. From baseline to post-treatment, participants also wear an actiwatch and complete daily sleep diaries. All questionnaires are hosted on Qualtrics.

Three months post-treatment (week 24) participants are sent a link to complete a final series of online questionnaires on Qualtrics.

4. Sampling Plan

4.1 Data collection procedures

Our intended sample size was 25, and at the time of registration recruitment is completed with 24 people recruited in the study. Participants are all adults between the ages of 18 and 65. Inclusion and exclusion criteria were pre-defined and approved by the appropriate ethics board.

More specifically, the inclusion criteria included: (1) self-reported diagnosis of BD-II that will later be confirmed by the researcher using the Structured Clinical Interview for the DSM-5; (2) A positive screen for depressive phase as indexed by a score of 6 and above in the Quick Inventory for Depressive Symptomatology (QIDS≥6), and a score of 5 and lower in the Altman Self Rating Mania Scale (ASRM≤5); (3) endorsement of symptoms of insomnia disorder as indexed by a score above 10 in the Insomnia Severity Index (ISI>10); (4) for assessment of mania, symptoms to remain stable at week 2 prior to the participant accessing the treatment; (5) access to a laptop or desktop computer and a phone and reliable internet access either at home or work; (6) being able to read and understand English; and (g) currently living in the UK.

The exclusion criteria included: (1) currently engaged in psychotherapy for insomnia; (2) previous or current participation in online sleep treatments; (3) psychiatric comorbidity with psychosis; (4) diagnosis of epilepsy or other neurological disorder, (5) diagnoses of mild cognitive impairment or dementia; (6) meeting the threshold of a probable sleep related movement disorder or sleep related breathing disorder in the Brief Sleep Disorders Screen; (7) reported diagnosis of a sleep related movement disorder or sleep related breathing disorder, hypersomnia or parasomnia; (8) serious physical health concerns necessitating surgery or with a survival prognosis of < 6 months; (9) habitual night shift, evening, or rotating shift-workers; (10) suicidal thoughts (Score >1 "yes" on the last CSSRS suicide item) or history of recent suicide attempt in the past 12 months; (11) psychiatric hospital admission in the past year, or crisis team support within the past year; (12) clinically concerning alcohol misuse and dependence, operationalised a score of 20 or above in the Alcohol Use Disorders Identification Test (AUDIT≥20); (13) illicit drug use.

4.2 Sample size

The intended sample size was pre-defined at 25 people. The number was decided based on the work of Whitehead et al (2016) on the use of pilot studies. For main trials designed with

90% power, two-sided 5% significance and expecting to yield small effect sizes ($0.1 \leq d < 0.3$), the recommended size of the pilot study was 25 participants. This number was also deemed appropriate to get a level of engagement with intervention and study procedures and gives enough participants for semi-structured interviews

5. Variables

5.1 Manipulated variables

The digital CBT-I is delivered through the Sleepio programme from Big Health Ltd. It can be accessed via a laptop or computer on the associated website (www.sleepio.com) or via a phone or tablet device using the Sleepio app. The program is fully automated, and its underlying algorithms feed the delivery of information, support, and advice in a personally tailored manner.

The intervention is delivered in 6 sessions lasting approximately 20 minutes each. The content of the intervention is based on CBT manuals for insomnia and includes behavioural (i.e. sleep restriction, stimulus control, and relaxation), cognitive (i.e. paradoxical intention, cognitive restructuring, mindfulness, positive imagery, and putting the day to rest), and educational (i.e. psychoeducation and sleep hygiene) components. The programme is interactive, and content is presented by an animated virtual therapist. Prior to the start of the treatment, participants are asked complete a questionnaire regarding their sleep and mental health. We asked participants in our study to declare their BD diagnosis at this stage. The programme and treatment goals are tailored based on the answers to this questionnaire.

During the intervention participants complete a daily sleep diary, which is used by the programme to provide tailored, personalised advice. Participants are also able to set daily phone notifications on the Sleepio app to prompt them to fill their sleep diary. An option is also provided for the reminders to be sent via email or text message. Additionally, participants gain access to an online community forum, and a library of information on sleep and sleep disorders. They can also access their case file, containing a progress review, a reminder of strategies to try out between sessions, an agreed sleep schedule, and a list of further readings. Sleepio also provides online analytics which can be used to monitor adherence by assessing how many sessions were completed and the number of weeks to complete the course.

5.2 Measured variables

Safety: Adverse events will be recorded at pre-treatment (i.e. for the two weeks prior to the start of treatment), mid-treatment and post-treatment. Safety will also be assessed through symptom monitoring of suicide and mania at mid-treatment and post-treatment. Suicidality will be measured using item 12, thoughts on death and suicide, on the Quick Inventory of Depressive Symptomatology. Any new reports of daily suicidal thoughts with potential plan (i.e. a score of 3) will be reported as an adverse event. Hypomania will be measured using

the Altman Self-Rating Mania Scale. An adverse event here is defined as any score higher than 5, interpreted as high probability of a hypomanic episode.

There is no evidence that digital CBT-I causes serious harm, so the likelihood of a serious adverse event occurring in our study is low. Following established guidelines, all serious adverse events will be assessed on their seriousness, expectedness and relatedness. Planned hospital visits and changes unrelated to participants' clinical state will not be reported. Serious adverse events are defined as (a) any medical occurrence that results in death, (b) any suicide attempts, and (c) any admission to secure units.

Feasibility: Although we sought out to explore if we can reach our recruitment target, given we have already achieved this, feasibility is registered here as retention and adherence rates. More specifically, retention is defined as the percentage of participants completing the providing post-treatment data for the insomnia outcome. The reason for all drop-outs will be reported, when applicable. Adherence is defined as the percentage of participants completing at least 4 out of 6 treatment sessions.

Acceptability: Acceptability was assessed using a modified theory informed acceptability measure by Sekhon et al (2022) developed for use in healthcare interventions. The questionnaire utilises a 5-point Likert scale to measures eight domains of acceptability, namely: affective attitude, burden, ethicality, perceived effectiveness, intervention coherence, self-efficacy, opportunity costs and general acceptability. Our modified version does not include a question on ethicality and the questions on perceived effectiveness and self-efficacy have been modified. Following scaling, scores on the questionnaire range from 1 to 10, with higher scores reflecting higher acceptability.

Questionnaires: We will also measure several other domains related to sleep, mental health and functioning using a range of questionnaires. The following list includes the questionnaires used, the domains assessed and the time points of administration. For reference, week 0 is baseline, week 2 is pre-treatment, week 7 is mid-treatment, week 12 is post-treatment, and week 24 is follow-up. For more information see Design Plan section.

- Insomnia Severity Index (insomnia; weeks 0, 2, 7, 12 and 24)
- Pittsburgh Sleep Quality Index (sleep quality; weeks 0, 7, 12 and 24)
- Morningness-Eveningness Questionnaire (chronotype; weeks 0, 12 and 24)
- Quick Inventory for Depressive Symptomatology (depression; weeks 0, 2, 7, 12 and 24)
- Behavioural activation for depression (depression; weeks 0, 12 and 24)
- Altman Self-Rating Mania Scale (hypomania; weeks 0, 2, 7, 12 and 24)
- Generalised Anxiety Disorder-7 (anxiety; weeks 0, 7, 12 and 24)
- British Columbia Cognitive Complaints Inventory (cognitive functioning; weeks 0, 12 and 24)
- Warwick-Edinburgh Mental Wellbeing Scale (mental wellbeing; weeks 0, 12 and 24)
- Work and Social Adjustment Scale (social and occupational functioning; weeks 0, 12 and 24)

Sleep diaries and Actigraphy: In addition to safety, feasibility and acceptability, as well as the aforementioned questionnaire measures, we will also measure sleep related thoughts and behaviours using daily sleep diaries, and rest-activity using wrist worn actigraphy devices.

6. Analysis plan

6.1 Statistical models

All quantitative analyses will be conducted in the statistical software R. Although a full dataset will be sought, missing data are expected. Single missing items from otherwise complete questionnaires will be replaced using mean imputation. Descriptive results will be presented (means and standard deviations for continuous variables; frequencies and percentages for binary and categorical variables) together with 95% confidence intervals.

A mixed-level linear model will be fitted on our post-treatment (week 12) insomnia measure, the Insomnia Severity Index. Timepoint will be the fixed covariate, and a participant-specific random covariate will be added to account for repeated measures. Effect sizes will be defined as the standardised mean change, and estimated as the pre-to-post change scores over the standard deviation of the baseline scores. Other questionnaire outcomes and effects for follow-up will be modelled following the same principles. The analysis will focus on descriptive statistics, effect sizes and 95% confidence intervals, following published recommendations that this should be the focus of pilot trials (Lancaster et al 2004).

Actigraphy data will be processed via a modified algorithm mirroring the scripts in the statistical package "GGIR" in the software R, developed for the analysis of accelerometer data derived from the actigraphy watches. The scoring of actigraphy will be based on a bespoke standardised operating procedure.Sleep onset latency, wake after sleep onset, and total sleep time will be presented in minutes, while sleep efficiency in percentage scores, with means and standard deviations describing each outcome. L5, M10, intra- and inter-daily variability, and relative amplitude will also be extracted. Two-week periods will be used to define the baseline, mid and post-treatment points, and outcome data will be analysed following similar principles as described above.

Similar to the actigraphy data, sleep onset latency, wake after sleep onset, total sleep time, and sleep efficiency will be extracted from the sleep diaries. Sleep diary outcomes on mood will be described using root mean square successive differences, to capture their change over time. Two-week periods will be used to define the baseline, mid and post-treatment points, and outcome data will be analysed following similar principles as described above.

Additional analyses might be performed to further explore the data.

Qualitative data acquired through the semi-structured will be analysed using thematic analysis as outlined by Braun and Clarke (2006). The analysis will follow six phases: familiarisation, generation of initial codes, searching for relevant themes, review of themes, definition and naming of such themes, production of report.

Appendix 5: Interview Schedule of the Post-treatment Semi-structured Interview in the DIGIT-B study

First, we want to hear about your experiences. I want to assure you that there are no "right" or "wrong" answers – we are simply interested in your thoughts and opinions. You are the expert here, and we are seeking your input, so we know what works and what does not. You do not have to answer any question if you do not feel comfortable doing so.

Topic I: Experience with sleep problems and their impact
Now, I would like to discuss your sleep problems and their impact in your life.

1. Would you mind telling me a little bit about your sleep problems before participating in this study?
Probe: What were your most troubling sleep problems?

2. How did these problems affect your mood and your life more generally?
Probe: What was the most profound effect? personally and professionally

3. When do your sleep problems start relative to other symptoms of bipolar disorder?
Probe: Would you say problems with your sleep start earlier, later or about the same time as other symptoms like changes in mood and appetite?

Topic II. Prior engagement with sleep treatment(s)
Now I would like us to talk about the treatment of these sleep problems prior to participating in our study

4. Have you previously discussed your sleep problems with a health professional? If so, what was your experience of how these issues were handled?
Probe: Did you receive any treatment or referred to a specialist team? Were you satisfied with the response?

Topic III: Overall experience in the study
Now about our study and your experience with this particular treatment

5. I was wondering if you could share with me what led you to participate in this study
Probe: What ideas or expectations did you have before attending your treatment? What did you hope to gain? What did you feel were the possible benefits?

6. What was your overall experience with the intervention? Both positive and negative
Probe: What did you find most helpful about this treatment? Is there any element you disliked or found particularly difficult?

7. Okay now thinking back to what you told me about your sleep problems before participating in this study. How would you describe these problems now?
Probe: Have these problems changed at all?

8. What impact do you think the treatment has had on your mood and life more generally?
Probe: Has the treatment led to any changes? Both positive and negative

Topic IV: Digital aspect of the intervention

For the last part of our discussion, I would like to focus on the delivery method, i.e. the digital aspect of the intervention

9. What was your experience participating in a digital intervention?
Probe: What were the advantages and disadvantages? What did you like the most and least about this delivery method?

10. If you were offered the same intervention but delivered face-to-face, do you think you would have opted for that option over a digital format?
Probe: Why/why not? What are some of the benefits and difficulties of both methods of delivery?

11. Have you engaged with a digital intervention programme before? If not, do you think you will now in the future?
Probe: Why or why not?

Topic V: General recommendations

12. Finally how do you think we could improve the treatment for future participants?
Probe: What is the most important issue you would like us and others to know about your experience with this treatment?

Wrap-up
We are so grateful for your willingness to share your knowledge and experiences with us today. Please feel free to contact us if you have any questions about the discussion we had today or any comments you would like to add. Otherwise, we will contact you again in 3 months for the follow-up meeting
Thank you again for all your help