

An Investigation of the Association Between Sleep Disturbance and Mood Instability

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Abstract

Mood instability (MI) and sleep disturbance (SD) are common in the general population, especially among persons with mental illness. Independently, MI and SD are associated with a range of poor health outcomes; however, there exists little evidence about their relationship. Using a series of six studies, this thesis investigated the relationship between MI and SD as transdiagnostic features on a shared pathway to ill health.

A systematic review of the prevalence of MI in the general population showed few and highly heterogeneous reports available within the literature. The results of the review highlight pervasive challenges underlying the study of MI, particularly the absence of consistent definitions and thoroughly validated measurement tools.

To investigate the epidemiological association between MI and SD, studies two and three examined data from a nationally representative survey of English adult household residents. Study three revealed that both MI and SD are common and closely linked within the population and associated with increased occurrence of suicidal ideation and behaviour. Study four showed that MI and SD are strongly and significantly associated with a wide range of poor mental and physical health and social outcomes such as difficulties with activities of daily living, socioeconomic indicators, and diagnosed health conditions.

In study four, prospective data on MI and SD from electronic health records from secondary mental health care showed that MI and SD are associated with significantly higher rates of mental health services use, hospitalisation, and prescribed medication.

Finally, an attempt to disentangle the directionality between MI and SD found strong cross-sectional evidence, but weak evidence of temporal trends between mood and sleep changes.

Taken together, the results of this thesis highlight existing and ongoing challenges to the study of highly temporal data on a large scale. However, the findings of this thesis provide essential knowledge for linking future epidemiological studies with high resolution examination of dynamic processes such as MI. Clinically, there is a critical need for increased recognition of MI and SD as modifiable risk factors of illness and related complications, rather than secondary symptoms. Earlier and effective intervention may help to reduce the burden associated with MI and SD, and mental illness.

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Summary of Contributions

I devised the thesis aim and all research objectives within the data chapters. I was responsible for planning the methods used in all studies. Chapter 2 consisted of a systematic review. I was responsible for the literature search and extraction of data. The responsibility of reviewing titles and abstracts for inclusion was shared between me and Dr. Kiyomi Shinohara, and we both reviewed all full-text documents. The data for chapters 3 and 4 were collected as part of the Adult Psychiatric Morbidity Survey 2007. I obtained these data from an online archive. Chapter 5 used electronic health records from the Oxford Health Foundation Trust. With guidance from the UK-CRIS team in Oxford, I identified the variables required for the study and a member of the team (Adam Pill) extracted the data from the database. Members of a team at the South London and Maudsley (SLaM) Biomedical Research Centre applied the natural language processing application to the extracted data to identify the presence of mood instability, sleep disturbance, insomnia, and prescribed medications from the free text. Chapter 6 involved a retrospective analysis of data from the OXTEXT-6 study, which I obtained from the data holder. For all data chapters, I was responsible for planning and carrying out the data analyses and interpreting the results. I composed this thesis document and prepared associated manuscripts for publication. My supervisors, Dr. Kate Saunders and Dr. John Geddes, provided guidance and feedback on the plan, methods, and interpretation of the studies, and reviewed all written documents.

List of Publications

The results of Chapter 3 have been published in the Australian and New Zealand Journal of Psychiatry. The systematic review in Chapter 2, and results of Chapter 4 have each been submitted for publication. A manuscript is also in preparation to disseminate the results of Chapter 5.

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List of Abbreviations

Acronym	Definition
APA	American Psychiatric Association
ASRM	Altman Self-rating Mania Scale
BD	Bipolar disorder
BPD	Borderline personality disorder
CBT	Cognitive-behavioural therapy
CI	Confidence interval
CIS-R	Clinical Interview Schedule-Revised
CRIS	Clinical Research Interactive Search
dCBT	Digitally-delivered cognitive behavioural therapy
DSM	Diagnostic and Statistical Manual
EEG	Electroencephalography
EHR	Electronic health record
FIMM	Facilitator-supported Integrated Mood Management
HPA	hypothalamic-pituitary-adrenal
HoNOS	Health of the Nation Outcome Scale
ICD	International Classification of Disease
IDR	Incidence density rate
MI	Mood instability
MIMM	Manualised Integrated Mood Management
MZ	Mood Zoom
NHS	National Health Service
NIHR	National Institute of Health Research
NLP	Natural language processing
NPV	Negative predictive value
OCD	Obsessive compulsive disorder
OHFT	Oxford Health NHS Foundation Trust
OR	Odds ratio
PPV	Positive predictive value
PSG	Polysomnography
PTSD	Post traumatic stress disorder
QIDS	Quick Inventory of Depressive Symptomatology
REM	Rapid-eye movement
RMSSD	Root mean-squared successive difference
SCID-II	Structured Clinical Interview for DSM-IV Axis II Personality Disorders
SCRD	Sleep and circadian rhythm disturbance
SD	Sleep disturbance
sd	Standard deviation
Se	Sensitivity
se	Standard error
SLaM	South London and Maudsley NHS Foundation Trust

Acronym	Definition
SOL	Sleep onset latency
Sp	Specificity
TC	True Colours
TKEO	Teager-Kaiser Energy Operator

Chapter One: Introduction

1.1 Introduction

Mental illness contributes substantially to the burden of disease worldwide. The Global Burden of Disease study summarised the incidence, prevalence, and years lived with disability associated with chronic disease and injury in 188 countries between 1990 and 2013. Major depressive disorder, anxiety disorders, bipolar disorder (BD), and schizophrenia were among the leading causes of disability in nearly all countries in 2013. Mental and substance use disorders were the second leading cause worldwide, accounting for approximately 21% of the total years lived with disability (Global Burden of Disease Study 2013 Collaborators, 2015), and this in likely to be an underestimate (Vigo, Thornicroft, & Atun, 2016).

Mood instability (MI) and sleep disturbance (SD) are two symptoms that are common within a range of mental disorders. Independently, MI and SD are associated with considerably dysfunction (Eidelman, Gershon, McGlinchey, & Harvey, 2012; Marwaha, Parsons, Flanagan, & Broome, 2013b; Patel et al., 2015), and likely contribute to the substantial burden attributable to mental illness. Critically, MI and SD appear to not only represent symptoms of disorder, but they may also be involved in their origins and affect prognosis (Wulff, Gatti, Wettstein, & Foster, 2010). MI and SD have each been described as possible transdiagnostic features (Aldao, 2016; A. G. Harvey, Murray, Chandler, & Soehner, 2011a), and may be components on a shared physiological pathway to psychiatric and neurodegenerative disease (Wulff et al., 2010). The

remainder of this chapter will introduce key background information about MI, SD, and their relationship with each other and with poor health.

The following is a targeted review of the literature, intended to provide essential background information and context for the aims of the current thesis. References related to MI were identified through searches of PubMed and Medline for articles published in English between 1 January 1970 and 15 October 2016. Search terms included "mood swings" OR "mood instability" OR "mood lability" OR "mood variation" OR "affective instability" OR "affective lability" OR "emotional instability" OR "emotional lability". References related to SD were identified through searches of PubMed and Medline for articles published in English between 1 January 1970 and 15 17 November 2016. Search terms included ["mood"] AND ["insomnia" OR "hypersomnia" OR "sleep-wake" OR "circadian" OR "diurnal" OR “excessive sleepiness” OR “irregular sleep” OR "polysomnog*"]. Articles identified from these database searches, and relevant articles identified from their reference lists were selectively reviewed.

1.2 Mood Instability

1.2.1 Defining Mood Instability

Mood instability (MI) is inconsistently defined in existing literature, and often used interchangeably with a variety of different terms. A recent systematic review was conducted to examine definitions and measures of MI available in the literature (Marwaha, He, et al., 2014). The review included any studies with participants over 18

years of age, which had any definition and measurement of affective instability. In total, the review identified 37 reports that had a definition and measure related to MI. Among the reports, there were eight distinct terms in addition to MI, including affective instability, affective lability, affective dysregulation, emotional dysregulation, emotional lability, mood instability, mood lability and mood swings. Definitions were highly variable, even within the same terms. However, there was considerable overlap in their definitions, which typically included problems with one or more of four main features: (a) rapid changes in affect; (b) affect intensity (c) a deficiency in the capacity to regulate emotions; and (d) whether the changes in affect are precipitated by environmental stimuli.

In attempt to summarise the construct and unify the research area, Marwaha and colleagues suggested a definition of affective instability: “rapid oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioural consequences” (Marwaha, He, et al., 2014). This definition is somewhat useful and practical because it implies that affective instability is a multidimensional construct and allows for a flexible theoretical framework. However, it does not specify a time frame for experiencing symptoms, which is important because MI is a temporal construct. Research also suggests that the temporal information within MI may aid differential diagnosis. For example, temporal information about MI may contribute important information that distinguishes BD from borderline personality disorder (BPD).

It is notable that, in reference to MI, the terms *affect*, *emotion* and *mood* are not always distinguished. Marwaha and colleagues found that few definitions specified symptom durations (Marwaha, He, et al., 2014). However, in the wider psychiatric literature, emotion and affect, and mood are often distinguished by their durations, such that emotion and affect refer to immediate and short-lived experiences, whereas mood describes experiences over longer durations like days or weeks (Beedie, Terry, & Lane, 2005). In keeping with the wider literature, this thesis uses the term MI (unless otherwise specified) because the operationalisations throughout the chapters reflect experiences overs extended periods of time.

1.2.2 Measuring Mood Instability

The variety of definitions found in the literature has resulted in a broad range of methods to quantify MI. In their systematic review, Marwaha and colleagues identified 24 unique measures of MI—most often questionnaires, completed either by self-report or clinical interviews. Table 1.1 provides a summary of the measures identified in the review (Marwaha, He, et al., 2014) The instruments assessed a range of different aspects of MI. Most tools assessed rapid oscillations and intensity of affect, while fewer tools assessed general emotional functioning, the capacity to control affect or its behavioural consequences, and whether the changes are viewed as endogenous or in response to environmental stimuli. No single assessment tool appeared to assess all aspects of MI. Two of the measures were rated by a clinician informants (Wender-Reimherr Adult Attention Deficit Disorder Scale,WRAADDS; Wender, 1995); Affective Regulation and

Experience Q-Sort Questionnaire Version, AREQ-QV; Westen et al., 1997) and the remaining were based on participants' responses. Psychometric properties had not been assessed for some of the instruments. Instruments that had not been validated tended to include select items from larger scales or modified instruments with only a few questions, such as the Mood Lability Scale (MLS; Akiskal et al., 1995) and Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; First et al., 1997).

Table 1.1 Summary of tools to assess MI-related constructs identified in a systematic review of definitions and measurement of MI by Marwaha *et al.* (2015).

Tool	Type	Assessment	Items	Aspects of MI	Clinical Groups	Validated
Affective Control Scale (ACS; Williams et al., 1997)	Self-report questionnaire	Anxiety about loss of control over one's emotions and reactions to those emotions, including anger, elation, depression, and anxiety.	42	capacity to control affect or behavioural sequalae	BPD; dysthymia; MDD	Yes
Affective Lability Scale (ALS; Harvey et al., 1989)	Self-report questionnaire	Degree of sudden mood changes along six dimensions; euthymia-depression, euthymia-elation, euthymia-anxiety, euthymia-anger, anxiety-depression, depression-elation.	54	rapid oscillation	BD; BPD; MDD; PD; PTSD	Yes
Affective Lability Scale-Short Form (ALS-S; Oliver and Simons, 2004)	Self-report questionnaire	Degree of sudden mood changes between anxiety-depression, depression-elation., and shifts in anger	18	rapid oscillation	ADHD; MDD; PD	Yes
Affective Intensity Measure (AIM; Larsen et al., 1986)	Self-report questionnaire	Degree of intensity of emotional experience in response to daily life events, including negative and positive affect intensity and reactivity.	40	affect intensity; endogenous change or reaction to environmental trigger	BD; BPD; PTSD	Yes
Affective Regulation and Experience Q-Sort Questionnaire Version (AREQ-QV; Westen et al., 1997)	Clinician-rated questionnaire	Multiple components of affective experience and affect regulation, including experience of positive and negative emotions, and responses or coping styles.	98	general emotional functioning	BPD	Yes
Auxiliary Subscale of The Centre for Neurologic Study-Lability Scale (CNS-LS; Moore et al., 1997)	Self-report questionnaire	Degree of emotional lability, particularly for negative emotions including frustration, anger, impatience, and nervousness.	8	rapid oscillation	ADHD	Yes

Tool	Type	Assessment	Items	Aspects of MI	Clinical Groups	Validated
Difficulties in Emotion Regulation Scale (DERS; Gratz and Roemer, 2008)	Self-report questionnaire	Assesses levels of emotion dysregulation from six subscales: difficulties with accepting negative emotions, engaging in goal-directed behaviour when upset, and controlling impulses, and lack of emotional awareness, emotional regulation strategies, and emotional clarity.	36	capacity to control affect or behavioural sequalae	BPD; undefined clinical diagnostic group	Yes
Diagnostic and Statistical Manual, 3rd Ed., Revised (DSM-III-R; American Psychiatric Association, 1987)	Structured clinical interview	Four items assessed emotional reactivity and intensity including high emotional reactivity, rapid changes in emotion, instability of affect, and inappropriately intense anger or the inability to control anger. Items were derived from examination of DSM-III-R criteria with explicit reference to affective instability.	4	rapid oscillation; affect intensity	Mixed mental disorders	Yes
Emotion Dysregulation Measure (EDM; Newhill et al., 2004)	Interviewer administered questionnaire	Assesses general emotional arousal and intensity of positive and negative emotions.	18	capacity to control affect or behavioural sequalae	PD	Yes
Ecological Momentary Assessment (EMA; Stone and Shiffman, 1994; Stone et al., 2003)	Self-report questionnaire	Questions may vary.		rapid oscillation; affect intensity	BD; BPD; MDD; dysthymia	No
Emotion Dysregulation Scale (EDS; Kröger et al., 2010)	Self-report questionnaire	Assesses rapid shifts in emotions, affect intensity and clarity, and control over emotions and behavioural sequalae.	10	rapid oscillation; capacity to control affect or behavioural sequalae	Mixed mental disorders	Yes

Tool	Type	Assessment	Items	Aspects of MI	Clinical Groups	Validated
Emotion Regulation Interview (ERI; Gross, 1998)	Structured clinical interview	Assesses how one regulates their emotions in three anxiety-evoking situations. Five emotion regulation strategies assessed include situational avoidance, modification of the situation distraction, cognitive change, hiding visible signs of emotion	5	capacity to control affect or behavioural sequalae	Social anxiety disorders	Yes
Emotion Regulation Questionnaire; ERQ; Gross, 1998)	Self-report questionnaire	Assesses cognitive reappraisal, emotional suppression, and emotion regulation strategy.	10	emotion regulation strategy; capacity to control affect or behavioural sequalae	Social anxiety disorders; schizophrenia	Yes
Emotion Regulation Scale (ERS; Liverant et al., 2008)	Self-report questionnaire	Assesses awareness of emotions, cognitive reappraisal, emotion suppression and acceptance.	10	general emotional functioning	Dysthymia; MDD	No
General Emotion Dysregulation Measure (GEDM; Newhill et al., 2004)	Interviewer-administered	Assesses emotional dysregulation, intensity, and reactivity. Derived from factor analysis of the EDM.	13	general emotional functioning	PD	Yes
Impulsivity/ Emotional Lability Scale from the Conners' Adults ADHD Rating Scale (I/ELS; Conners et al., 1999)	Self-report questionnaire	The subscale is comprised of 6 items on emotion lability and 6 items pertaining to impulsivity. Questions about emotion lability include emotional reactivity and frequent mood changes.	12	rapid oscillation	ADHD	Yes
Mood Lability Scale (MLS; Akiskal et al., 1995)	Interviewer-administered	Two items assess frequent mood changes without clear cause.	2	rapid oscillation	BD; MDD	No
Personality Assessment Inventory–Borderline Features Scale (PAI-BOR; Morey, 1991)	Self-report questionnaire	A 6-item affective lability subscale assesses sudden mood shifts, affect intensity, control over affect.	24	rapid oscillation; affect intensity	BPD; MDD	Yes[a]

Tool	Type	Assessment	Items	Aspects of MI	Clinical Groups	Validated
Personality Disorder Interview-IV (PDI-IV; Widiger et al., 1995)	Semi-structured interview	Assesses frequent and intense mood shifts.	9	rapid oscillation; affect intensity	MDD	Yes
Responses to Emotions Questionnaire (REQ; Campbell-Sills et al., 2006)	Self-report questionnaire	Assesses different ways of changing emotions including suppression, distraction, reappraisal, and redirecting attention.	4	capacity to control affect or behavioural sequalae		No
Temperament Evaluation of the Memphis, Pisa, Paris, And San Diego Auto Questionnaire-a short version) (TEMPS-A; Akiskal et al., 2005)	Self-report questionnaire	Assesses 5 different temperaments including cyclothymic, depressive, irritable, hyperthymic, and anxious.	39	general emotional functioning	Anxiety disorders; BD	Yes
Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; First et al., 1997)	Structured clinical interview	A single item assesses the tendency for sudden mood changes over the past several years.	1	rapid oscillation; endogenous change or reaction to environmental trigger	BD	Yes[a]
Visual Analogue Scale (VAS; Bernstein and Garfinkel, 1992; Hotopf et al., 1999)	Self-report questionnaire	Assesses 26 discrete mood states such as dysphoria, hostility, anger and shame, and an overall mood state.	26	affect intensity; endogenous change or reaction to environmental trigger	Anxiety disorders; BPD; depression	No
Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS; Wender, 1995)	Clinician-rated	Three items assess emotional dysregulation including affective lability, reactivity, and temper control.	28	rapid oscillation; capacity to control affect or behavioural sequalae	ADHD	Yes[a]

[a] Validity for subscale and/or items directly pertaining to MI is unclear.
BD=bipolar disorder; BPD=borderline personality disorder; ADHD=attention deficit hyperactivity disorder; PTSD=post-traumatic stress disorder [Adapted from Marwaha, He, et al., 2014)].

Self-report questionnaires administered in laboratories or clinical research settings have traditionally been the chosen methods for measuring MI because they are cost effective, and easy to administer and score. However, they usually require a retrospective assessment of experiences, which is known to have limitations. Recall bias (systematic error in measurement arising from inaccurate or inconsistent reporting of events across participants) is a particularly salient problem in self-report measures, especially if the time period over which the participant must recall their experiences is long. For instance, individuals asked to retrospectively judge their symptoms over a period of time, typically base their reports on their most recent or intense experiences, rather than a true average over time (Stone, Broderick, Kaell, DelesPaul, & Porter, 2000). Additionally, MI involves features of both variability and temporal dependency, which traditional 'one-off' questionnaires cannot usually represent accurately. Given the pitfalls of retrospective questionnaires, more recent efforts have focused on methods for prospective assessment of MI.

Ecological momentary assessment, EMA (Stone & Shiffman, 1994), is a method of high frequency prospective data collection from individuals in their natural environment. EMA may include responses to self-report measures and/or passive collection of biological data through wearable devices, thereby reducing or eliminating the risk of recall bias. EMA also offers enhanced external validity because the measures are taken while participants are interacting with their natural environment.

In the case of MI, EMA permits direct assessment of the frequency and magnitude of fluctuations of mood over time, and typically involves the real-time collection of responses to questionnaires remotely using computers or smartphones. The patterns of mood alternations are then summarised to quantify MI. There have four main algorithms previously used to quantify MI using mood time series data: (a) Standard deviation (*sd*); (b) Root mean-squared successive difference (RMSSD); (c) Teager-Keiser energy operator (TKEO); and (d) Entropy. Specifically, these parameters can be estimated as

$$\mathrm{SD} = \sqrt{\frac{1}{\mathrm{N}}\sum_{\mathrm{i=1}}^{\mathrm{N}}(\mathrm{x_i} - \mathrm{u_x})^2}$$

$$\mathrm{RMSSD} = \sqrt{\frac{1}{\mathrm{N}}\sum_{\mathrm{i=1}}^{\mathrm{N-1}}(\mathrm{x_{i+1}} - \mathrm{x_i})^2}$$

$$\mathrm{TKEO} = \sqrt{\frac{1}{N}\sum_{i=2}^{N-1}({x_i}^2 * (x_{i-1} - x_{i+1}))}$$

$$\mathrm{Entropy} = \sqrt{\sum_{i=1}^{N} p(x_i) * log(p(x_i))}$$

where N is the length of the time series (number of mood responses), x_i is the i^{th} response in the time series (i^{th} mood response), and u_x is the mean of the time series (mean mood response).

These methods for quantifying MI differ by the sets of features that they describe. For example, *sd* may be considered the simplest measure, and the most readily interpretable given its widespread use in many research fields. However, it contains the least amount of information because it does not account for any temporal dependencies. RMSSD represents the average amount that mood differs between response times, and has been used recently in variety of mood variability applications (Gershon & Eidelman, 2015; O'Donnell et al., 2018; Tsanas et al., 2016). TKEO is the most comprehensive equation as it quantifies both amplitude and frequency of mood changes, but it is less frequently used measure and less readily interpretable. Finally, entropy is a measure of uncertainty or 'chaos' within the mood series. There is currently little evidence in terms of each parameter's suitability under different conditions. However, preliminary evidence shows similar trends across the different measures among patients with BD, BPD, and healthy controls (Tsanas et al., 2016).

1.2.3 Epidemiology of Mood Instability

Although interest in the importance of MI has increased substantially over the past decade, its epidemiology remains under-investigated. Given growing interest in MI as a clinically important feature in psychiatric disease, existing research has primarily been conducted in small samples with specific psychiatric illnesses. Epidemiological evidence of MI has been derived primarily from a small set of studies.

1.2.3.1 Prevalence of Mood Instability

Chapter 2 reports a systematic review of the prevalence of MI in the general population and provides detailed discussion of the state of evidence for prevalence of MI more generally. This section provides a brief overview of key evidence for the prevalence of MI.

MI appears to be common in the general population. Data from the Adult Psychiatric Morbidity Survey (APMS) 2007 (*n*=7403) measured MI using a single item from the Structure Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II): 'Do you have a lot of sudden mood changes' (First, Gibbon, Spitzer, Williams, & Benjamin, 1997). It was estimated that approximately 14% of the adult household population in England experienced MI over the past several years or longer (Marwaha, Parsons, et al., 2013b). This prevalence estimate is consistent with two other epidemiological studies, which each reported 13% prevalence of MI. Data from an 18-month follow-up study of participants from the APMS 2000 who previously reported symptoms of psychiatric disorders (*n*=2344) also measured MI using the SCID-II. MI was present in approximately 13% of participants who reported no history of non-suicidal self-injury. A study of Gulf War Veterans (*n*=576) from the United States (Iowa and surrounding states) with previously identified depression, chronic widespread pain, and cognitive dysfunction and healthy controls measured MI using the Schedule for Non-Adaptive an Adaptive Personality (SNAP; Clark, 1993). Approximately 13% of participants reported symptoms of MI (Black et al., 2006).

1.2.3.2 Determinants of Mood Instability

Knowledge about the determinants of MI is limited. According to the APMS 2007, age, gender, marital status, and several indicators of socioeconomic status are important determinants of MI. Prevalence decreased with age; approximately 26% of individuals aged 16 to 24 years reported MI, and this decreased across subsequent age groups, to only 4% of persons aged 75 and older. MI was also more frequently reported by females (18%) than males (12%). Nearly twice as many people who were single (23%) reported MI than people who were married (11%) or widowed (8%). Lastly, the prevalence of MI was highest among individuals of low socioeconomic status. MI was nearly twice as common in persons who were unemployed (25%) than those who were employed (14%) or economically inactive[a] (14%), and among individuals with lowest annual household income quintile (<£10,575; 22%) than those in the highest quintile (≥£40,384; 11%; Marwaha, Parsons, et al., 2013b).

1.2.3.3 Mood Instability and Poor Mental Health

While common in the general population, MI occurs even more frequently in people with mental illness. Importantly, MI appears to be a feature of many disorders, not just those for which it is traditionally recognised as a symptom, such as BD and BPD. According to the APMS 2007, the prevalence of MI was approximately 49.2% in generalised anxiety disorder (GAD), 56.1% in panic disorder, 60.9% in depressive

[a] In APMS 2007, persons aged 70 and older presumed to be retired, and classified as 'economically inactive'.

episode, 63.6% in post-traumatic stress disorder (PTSD), and 67.1% in obsessive-compulsive disorder (OCD) (Marwaha et al., 2013). The contribution of MI to the presence of mental illness may be independent of other predictors. Using the same data, the presence of MI was shown to increase the odds of depression and PTSD by nearly 9 and 11-fold, respectively, after adjusting for other factors sociodemographic, substance/alcohol use, and common mental disorders (Marwaha, Parsons, & Broome, 2013). Difficulties with emotional regulation have also been recognised in ADHD and severe mood dysregulation disorder, and schizophrenia (Broome, He, Iftikhar, Eyden, & Marwaha, 2015).

MI contributes to worse outcomes in persons with mental illness. Data from the British Health and Lifestyle Study suggest that MI may be a component of neuroticism—a personality trait with a central role in several psychiatric disorders such as mood, anxiety, and personality disorders—along with anxiety and depressive mood (Bowen, Balbuena, Leuschen, & Baetz, 2012). MI has also been found to predict impairment in romantic relationships in a 12-month follow-up study of patients with mixed mental illness (Miller & Pilkonis, 2006). In a large clinical sample of patients with psychotic, affective or personality disorders who presented to South London and Maudsley NHS Foundation Trust, MI was associated with significantly more frequent and longer hospitalisation and increased likelihood of being prescribed mood-stabilising medications (Patel et al., 2015). MI is strongly associated with suicidal behaviour. In an 18-month follow-up of the APMS 2000, MI was associated with significantly increased non-suicidal self-injury both cross-sectionally and at 18-months follow-up among (E. M.

Peters, Baetz, Marwaha, Balbuena, & Bowen, 2016). Another prospective study of patients with BPD showed that MI is the strongest factor in the diagnostic criteria for BPD that predicts suicidal behaviour (Yen et al., 2004).

Some evidence suggests that MI may not only play a role in maintaining and exacerbating mental illness, but also in their origins. According to Linehan (1993), emotional dysregulation is not only a symptom of BPD, but also a cause of the illness (Crowell, Beauchaine, & Linehan, 2009; Linehan, 1993). Prospective studies have found MI to significantly predict the onset of depression (Marwaha, Balbuena, Winsper, & Bowen, 2015; Thompson, Berenbaum, & Bredemeier, 2011), and paranoid ideations and auditory hallucinations (Marwaha, Broome, Bebbington, Kuipers, & Freeman, 2014). Furthermore, data from the Zurich Cohort Study suggest that 'ups and downs' of mood may be a stronger risk factor for BD than a positive family history of mania (Angst, Gamma, & Endrass, 2003).

1.2.3.4 Mood Instability and Bipolar Disorder

MI is a core feature of BD (Bopp et al., 2010; Trull et al., 2008). BD is classically characterised by recurrent shifts between elation and depression, and more recent evidence suggests that subsyndromal MI persists into interepisode periods (Bopp et al., 2010; Henry et al., 2008).

MI is associated with the onset and maintenance of BD. Two systematic reviews identified symptoms of MI as among the most common prodromal features of BD; Jackson and colleagues found that mood changes were the most common early symptom

of bipolar depression (Jackson, Cavanagh, & Scott, 2003), while Howes *et al.* found that mood lability/swings were the most common early sign of BD (Howes et al., 2011). In a study large cohort study by Angst *et al.* (2003), 'ups and downs' of mood was identified as the strongest predictor of BD and unipolar depression (Angst et al., 2003).

Furthermore, MI in BD is associated with substantially poorer outcomes. MI during inter-episode periods is associated with higher risk of relapse, hospitalisation, and poorer return to baseline functioning (Strejilevich et al., 2013). Prospective research shows that MI is associated with worse long-term functional outcomes, including work and home functioning and cognition (Gershon & Eidelman, 2015). Given the importance of MI in the onset and maintenance of BD, it is increasingly viewed as an entity requiring treatment rather than secondary symptom that will resolve upon treatment of another underlying illness.

The nature of MI appears to differ across disorders, and some evidence suggests that MI may be useful for differentiating BD subtypes and BD from other disorders. Patients with BDII tend to show more instability of depressive mood, whereas BDI show more instability of hypomanic/manic mood (Faurholt-Jepsen et al., 2015; O'Donnell et al., 2018). BPD is another disorder characterised by pervasive difficulties with MI. Like BD, individuals with BPD have much greater MI than healthy controls (Ebner-Priemer et al., 2007; Ebner-Priemer and Sawitzki, 2007). Close similarities in presentation between BD and BPD can make differential diagnosis difficult. It has been previously suggested that BD and BPD lie on the same spectrum of illness (Smith et al., 2004), and that MI

develops through the same mechanism in BD and BPD (Mackinnon and Pies, 2006; Paris, 2004). Some measures have been shown to differentiate BD and BPD in terms of patterns of MI. BD often shows high variance between depression, elation and euthymia. However, elation is less of a feature in BPD, which shows more shifts between depression, euthymia, other types of emotions such as anger and anxiety (Reich et al., 2012). Furthermore, the presence of precipitating factors, such as psychosocial stressors appears to be prominent in BPD (Henry et al., 2001; Koenigsberg et al., 2002), whereas in BD their role is less clear.

1.3 Sleep Disturbance

1.3.1 Basics of Normal Sleep and Circadian Rhythms

Sleep is a complex series of physiological and behavioural states, with highly organised patterns of neuronal activity (Foster & Wulff, 2005). Regulation of sleep involves the interaction between the circadian and homeostatic systems. Sleep-wake homeostasis involves an increased propensity to sleep that intensifies as the wake period is extended, and that dissipates during sleep. The circadian system involves cyclical rhythms of behavioural and physiological processes (Borbely, 1982). Therefore, in a general sense, the homeostatic system is responsible for the duration and intensity of sleep, while the circadian system controls sleep timing (Wulff, Porcheret, Cussans, & Foster, 2009).

1.3.1.1 Sleep Physiology

The circadian system and sleep-wake cycle work together to regulate sleep through multiple brain structures, and neurotransmitter and endocrine pathways. The homeostatic drive to sleep is controlled by two reciprocally inhibitory networks of arousal-promoting neurons and sleep-promoting neurons. These two opposing networks are often referred to as the 'flip-flop switch' (Figure 1.1; Brown, Basheer, McKenna, Strecker, & McCarley, 2012; Saper, Chou, & Scammell, 2001). The circadian system is coordinated by the suprachiasmatic nucleus (SCN), located within the hypothalamus. The SCN is the primary circadian pacemaker as it regulates the diurnal timing of endogenous oscillators and physiological processes such as those involving body temperature, and melatonin and cortisol release (Winkelman & Plante, 2010). Under normal conditions, external cues called *Zeitgebers*, such as light-dark cycles, ambient temperature, social interactions and medications, entrain (align) biological rhythms to an approximately 24-hour pattern.

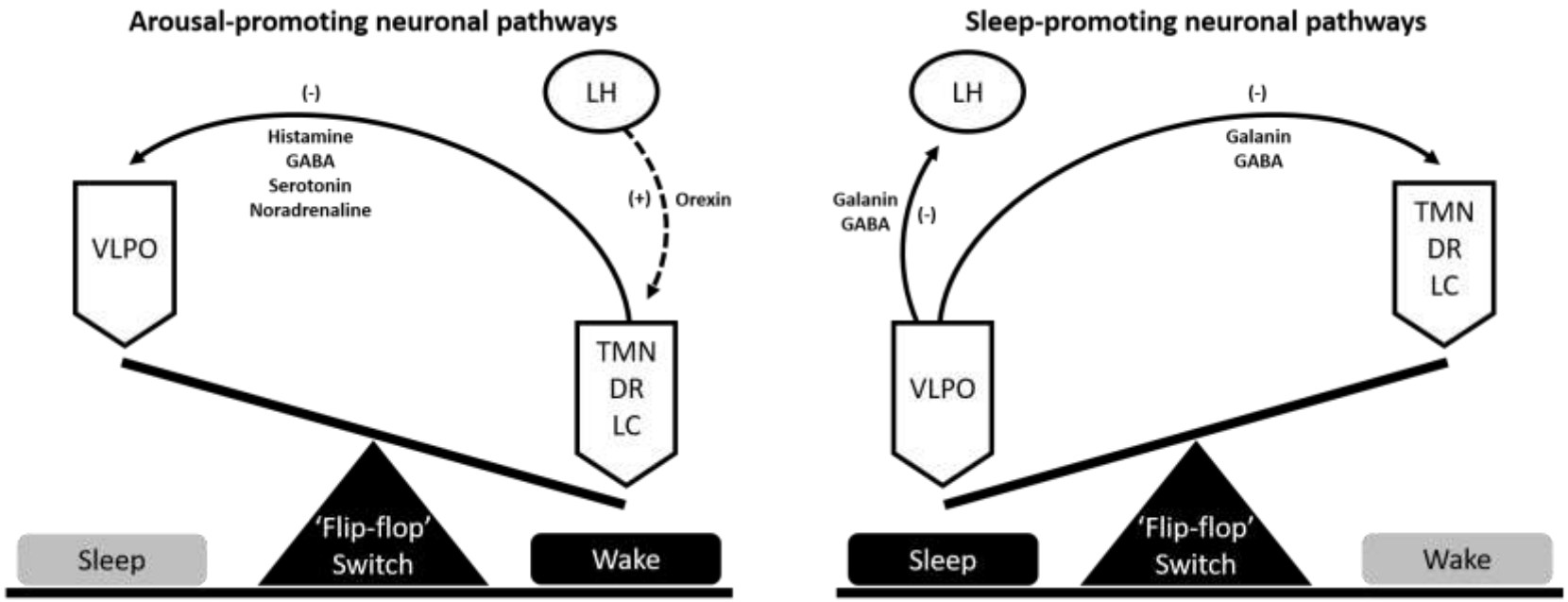


Figure 1.1 An illustration of the 'flip-flop' model of sleep-wake cycle [Adapted from Brown et al. (2012)]. Transitions between sleep and wakefulness are due to reciprocally inhibitory arousal-promoting and sleep-promoting neuronal pathways. During wakefulness (*left*), excitatory orexinergic neurons from the LH stimulate (+) wake related nuclei, and histaminergic neurons of the tuberomammillary nucleus (TMN), serotonergic neurons of the dorsal raphe nucleus (DR), and noradrenergic neurons of the locus coeruleus (LC) inhibit (-) sleep-related nuclei, including the VLPO. During sleep (*right*), galanergic and GABAergic neurons of the ventrolateral preoptic (VLPO) nucleus inhibit (-) wake promoting neuclei, including the lateral hypothalamus (LH).

1.3.1.2 Sleep Architecture

Sleep is characterised by a specific pattern of gradual changes in brain and muscle activity. The American Academy of Sleep Medicine (AASM) classifies sleep into four distinct stages, differentiated by their predominant, observable waveforms: Sleep stages N1, N2, and N3, and stage R sleep[b]. Sleep stages occur in order of increasingly deep sleep. N3 is characterised by slow wave sleep (SWS) or delta sleep, distinguished by the presence of slow, high amplitude waves of neural activity (Winkelman & Plante, 2010). R sleep is still widely known as rapid eye movement (REM) sleep. Typical sleep architecture consists of several cycles through stages N1, N2, N3 and R, with each full cycle lasting approximately 70 to 90 minutes (Foster & Wulff, 2005; Malhotra & Avidan, 2017). The duration of REM sleep typically grows with each cycle and predominates during the latter half of the night (Brown et al., 2012).

1.3.1.3 Purpose of Sleep

While the purpose of sleep is not fully understood, it is posited that a core function of sleep is to maintain synaptic homeostasis, replenish neuronal resources, and rid the brain of neurotoxins that accumulate during wakefulness (Cirelli & Tononi, 2008). Beyond the neural domain, sleep likely also plays important roles in a range of other physiological functions such as immunology, metabolism, tissue repair, and energy conservation

[b] Formerly, the Rechtschaffen & Kales (1968) sleep scoring manual dominated the literature and clinical practice. This manual classified sleep into 5 stages: Non-rapid eye movement (NREM) sleep stages 1, 2, 3, and 4, and rapid-eye movement (REM) sleep. The AASM scoring manual, released in 2007, largely replaced the R and K rules.

(Siegel, 2005). Given its roles in a wide variety of functions, good sleep is vital for mental and physical well-being.

1.3.2 Defining Sleep Disturbance

Sleep health can be characterised along several dimensions, such as duration, continuity, timing, alertness, and subjective satisfaction with the quality of sleep (D. J. Buysse, 2014). This thesis primarily examines dysfunction within the dimensions of duration and continuity, particularly problems with initiating and maintaining sleep, early morning awakening, and sleeping more than usual, in addition to sleep duration. For the purpose of this thesis, sleep disturbance (SD) is broadly used to refer to problems in any of these domains, regardless of a sleep disorder diagnosis.

A clinical sleep disorder warranting diagnosis may be differentiated from general SD in that they require specific thresholds for the severity and duration of symptoms and are accompanied by significant daytime distress and/or impairment (World Health Organization, 1992). In both clinical and research settings, terms related to sleep disorders such as insomnia and hypersomnia are often used to refer specifically to their associated diagnoses or more broadly to represent one or more symptoms characteristic of the related disorder. For example, insomnia is often associated with problems with initiating or maintaining sleep, or early morning awakening. Likewise, hypersomnia and excessive daytime sleepiness are often used interchangeably, and hypersomnia is also closely associated with problems with sleeping too much or non-refreshing sleep. Unless otherwise specified, the term insomnia will henceforth be used to denote sleep-specific

symptoms, whereas in reference to a clinical disorder the term diagnosis will be added (for example, insomnia diagnosis or diagnosis of hypersomnia).

It should be noted that symptoms of insomnia and short sleep duration and hypersomnia and long sleep duration are each related, but not necessarily equivalent. For example, one may have problems maintaining sleep or early morning awakenings, but still get a normal duration (6-8 hours) of sleep each night. Likewise, sleeping more than usual does not necessitate abnormal sleep duration in relation to the *population* (typically, 9 or more hours per night), it only indicates that it deviates from the *individual's* typical sleep duration.

1.3.3 Measuring Sleep Disturbance

Sleep can be characterised using subjective or objective measurement tools. Table 1.2 summarises several well-established sleep assessment tools.

Table 1.2 Common subjective and objective sleep assessment tools.

Method	Description
Subjective	
Sleep diaries	A record of an individual's sleeping pattern, usually collected over a period of several days or weeks, whereby individuals provide their best estimates of sleep indicators (such as bed/rise times, sleep onset/offset times, and duration and timings of daytime nap) upon rising.
Self-report questionnaires	Retrospective subjective assessments of satisfaction with sleep, often in terms of quality, timing, or amount of sleep.
Objective	
PSG	An overnight procedure that involves continuous recording of several physiological variables such as blood oxygen levels, heart rate, body movements, and breathing.
Actigraphy	Continuous monitoring of gross motor activity and rest and activity cycles using a device typically worn on the wrist.
EEG	A device that records electrical activity in the brain using electrodes placed on specific locations attached to the head.
Melatonin level	Melatonin levels rise sharply during the evening and peak during the middle of the night, followed by a gradual decline. Irregular patterns of melatonin release, identified from regular monitoring of melatonin concentration in saliva or urine, may indicate SD, particularly those related to problems with diurnal rhythms.
Core body temperature	Body temperatures usually peak in the evening and nadir in the morning. Continuous or intermittent measurements throughout the day/night may act as indicators of biological rhythms.

PSG=polysomnography; EEG=electroencephalography.

Self-report questionnaires are one of the most frequent methods of sleep assessment, particularly in epidemiological research settings because of their ease of administration and cost effectiveness. There is an abundance of different questionnaires that assess a wide range of sleep-related features. Examples of frequently used questionnaires include, Morningness-Eveningness Questionnaire (MEQ) to assess diurnal preference (Horne & Ostberg, 1976), Insomnia-Severity Index to assess the severity of difficulties with initiating sleep, maintaining sleep, and waking up too early (Morin, 1993), and the Pittsburgh Sleep Quality Index (PSQI) to assess global sleep problems (D.J. Buysse,

Reynolds, Monk, Berman, & Kupfer, 1989). However, self-report questionnaires often rely on retrospective recall, which may increase the likelihood of measurement bias. Sleep diaries provide more detailed information and may be less burdened by issues of recall bias, but still rely on subjective perceptions of sleep.

Objective measurement tools may have less problems with measurement bias. Polysomnography (PSG) is often considered the gold standard of sleep assessment, and is required for definitive diagnosis of many sleep disorders. However, it is both costly and time intensive, and therefore, not usually suitable to be carried out on a large-scale. Actigraphy is advantageous because it is passive, therefore contributing minimal participant burden, and permits collection of diurnal rhythms including daytime activity in addition to sleep data. Electroencephalography (EEG) is particularly useful in characterising sleep stages. While traditionally carried out within a laboratory, the introduction of portable EEG devices now permits remote measurements, which enables its use in large-scale studies.

Each of the above tools may be used to describe a person's sleep with different sets of parameters. Objective measurement tools typically measure standardised sets of parameters such as total sleep time (time from sleep onset until final awakening,), sleep onset latency (time from first attempt to sleep until first occurrence of sleep), sleep efficiency (percentage of time in bed spent asleep), or REM density (frequency of rapid eye movements during REM sleep). Parameters measured by subjective sleep tools are often much more variable.

A tool's utility depends on its intended function and the research question under assessment. For example, while PSG may be optimal for establishing a diagnosis, sleep diaries may be useful for establishing symptom severity in order to compare study groups or treatment outcomes and capturing a more representative sample of an individual's night-to-night sleep variability. Additionally, the research question (and associated study design and time period) may also influence the adequacy of a particular measure. For example, self-report questionnaires may allow adequate assessment of epidemiological parameters such as incidence or prevalence, but clinical trials may require tools that permit more accurate prospective sleep assessments (D. J. Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006).

Agreement between comparable sleep parameters derived from subjective and objective measurement tools have been assessed in a variety of different populations. Good correlations have been observed between objective and subjective sleep assessments for overall measures such as sleep quality and total sleep time. However, more specific measures, particularly those involving transition states, such as sleep onset latency and number of nighttime awakenings typically show much poorer correlations (Argyropoulos et al., 2003; Croy, Smith, Gidlof-Gunnarsson, & Persson-Waye, 2017; Gonzalez, Tamminga, Tohen, & Suppes, 2013; Lockley, Skene, & Arendt, 2002). Symptoms, such as depression, may contribute to the discrepancy between objective and subjective sleep assessments, as observed in persons with BD (Gonzalez et al., 2013; Krishnamurthy et al., 2018)

Given the relative advantages and disadvantages, use of complementary assessments (those offering different perspectives on the same construct) is often advisable. In insomnia research, recommendations for standard research assessment include the combination of tools (D. J. Buysse et al., 2006). For example, in sleep disorders, use of actigraphy as an adjunct to self-report has been found to produce more accurate estimates of total sleep time and sleep efficiency in relation to PSG (Kushida et al., 2001).

1.3.4 Epidemiology of Sleep Disturbance

1.3.4.1 Prevalence of Sleep Disturbance

SD–comprised of problems initiating or maintaining sleep, early morning wakening, or sleeping more than usual–is estimated to affect approximately one-third of the adult population (Roth et al., 2006; Stein, Belik, Jacobi, & Sareen, 2008). Individually, symptoms of insomnia are substantially more common than symptoms of hypersomnia. Data from two prospective cohorts of persons aged 36–76 years from Scotland observed prevalence estimates between 13% and 36% for problems initiating sleep and 15%–25% for problems maintaining sleep (Green, Espie, Hunt, & Benzeval, 2012). Similarly, data from a representative sample of the American adult population reported the 12-month prevalence of early morning awakening (25%), difficulty maintaining (20%) and initiating sleep (16%; Roth et al., 2006). Relatively few epidemiological studies have examined the prevalence of hypersomnia symptoms, but evidence suggests that the

prevalence of ‘problems with sleeping too much’ ranges between 3% and 10% (see for review; Ohayon, 2008).

Epidemiological studies of short and long sleep duration suggest that long sleep is more common than short sleep. One study summarised change in the prevalence of short (≤6 hours per night) and long (>9 hours per night) sleep over time based on data from repeated nationally representative cross-sectional surveys from 10 industrialised countries between 1971 and 2007. After adjusting for age, gender, number of weekdays and month of data collection, the prevalence of short sleep ranged from 0.5% (Netherlands) to 14.8% (United Kingdom), while the prevalence of long sleep ranged from 16.1% (United Kingdom) to 38.1% (United States). Long sleep duration was consistently and substantially more frequent than short sleep duration in all surveys. Comparability of specific ratios were limited by a number of factors, including differences in the time of survey completion, sample compositions such as age ranges of the participants, and heterogeneity in data collection methods (Bin, Marshall, & Glozier, 2013).

1.3.4.2 Determinants of Sleep Disturbance

There are several sociodemographic determinants of SD, including age, gender and some socioeconomic indicators. Age is a strong determinant of SD. Sleep patterns change substantially throughout the lifespan. A meta-analysis of sleep parameters in healthy individuals across all ages observed that total sleep time, sleep efficiency and the quantity of slow-wave sleep decrease with age, while sleep onset latency and wake after

sleep onset increase with age (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Additionally, age-related changes in sleep appear to interact with gender. For example, a meta-analysis of cross-sectional data on the prevalence of insomnia by sex found that females are more likely than males to report insomnia symptoms, and that the gender difference grows large with age (Zhang & Wing, 2006). Another determinant of SD is low socioeconomic status. For example, data from the APMS 2000 show that SD is most frequent among individuals who have low income, low educational qualifications and those who are unemployed or economically inactive (Arber, Bote, & Meadows, 2009).

1.3.4.3 Sleep Disturbance and Poor Health

It is widely recognised that SD is associated with poor health. Given the functions of sleep in a range of biological processes–such as metabolic, endocrine, immunity, and cognitive–dysfunctions in sleep manifest in a variety of health problems. This section provides a brief overview of the relation between sleep and health, with a particular focus on mental health.

SD is very common in persons with psychiatric disorders. SD is included in the diagnostic criteria for a number of psychiatric disorders. For example, according to the International Classification of Disease 10th Edition (ICD-10), insomnia and hypersomnia are possible symptoms of a depressive episode, while decreased need for sleep is a possible symptom of a manic episode (World Health Organization, 1992). SD is also present to a significant degree in illnesses for which sleep problems are not listed as symptoms within diagnostic systems. According to data from the National Comorbidity

Survey–Replication, approximately 50% of persons with psychiatric disorders have comorbid sleep problems during any one year. After controlling for several sociodemographic variables, sleep complaints were present in approximately 37% of persons with anxiety disorders, 25% with mood disorders, 18% with impulse control disorders, and 16% with substance and alcohol misuse (Roth et al., 2006).

The high prevalence of SD in psychiatric disorders is important because SD is often associated with complications of mental illness. In BD, compared with normal sleep duration, short sleep has been associated with greater mood elevation, earlier age at onset, and longer illness duration, while both short and long sleep is associated with more depressive symptoms, and diminished quality of life and functioning (Gruber et al., 2009b). Poor sleep quality is also inversely associated with psychosis symptoms severity in patients with schizophrenia (Waters et al., 2010).

While often considered a symptom of mental illness, SD may also be an early sign or symptom of a number of disorders. For instance, a systematic review of prodromal features of mania and bipolar depression, identified SD as the most robust predictor of mania (median prevalence 77%) and 6th most common early symptom of bipolar depression (median prevalence 24%; Jackson et al., 2003). SD also appears to occur in the early stages of psychosis (Reeve et al., 2018; Zanini et al., 2015).

Beyond psychiatric disorders, SD is associated with substantial morbidity and mortality. Sleep duration consistently shows a U-shaped association with health such that short and long sleep duration are associated with increased occurrence of a wide range of health

problems, particularly chronic diseases (Ferrie et al., 2007; Knutson, Van Cauter, Rathouz, DeLeire, & Lauderdale, 2010). Moreover, in the general population, SD has been associated with suicidal ideation and behaviour (Pigeon, Pinquart, & Conner, 2012), impaired cognition (Kyle et al., 2017), loss of productivity (Rosekind et al., 2010), cardiovascular disease (Michal et al., 2014), cancer risk (Schernhammer et al., 2001), diabetes risk (Leng et al., 2016), and all-cause mortality (Cappuccio, D'Elia, Strazzullo, & Miller, 2010).

1.4 The Relationship Between Mood Instability and Sleep Disturbance

The association between sleep and mood disturbances has long been recognised, and is supported by several lines of evidence. First, both sleep and mood are light sensitive. Light is the principal environmental zeitgeber. Light contributes substantially to entrainment of the circadian clock, and has a strong influence on mood. For example, mood changes correlate with diurnal rhythms (Boivin et al., 1997). Additionally, mood can vary with seasonal changes in sunlight exposure. Reduced exposure to sunlight during the winter and autumn months may predispose some individuals to seasonal affective disorder, and light may be used therapeutically to alleviate seasonal and non-seasonal depressive symptoms (Al-Karawi & Jubair, 2016; Glod, 2017).

Second, there is evidence that genes and physiological pathways involved in circadian rhythms overlap and interact with those involved in mood regulation. Animal studies have found at least six gene families involved in circadian rhythms that also implicated in mood regulation, of which, three (*Per3*, *CLOCK*, and *GSK3*) have also been observed

in humans (Landgraf, McCarthy, & Welsh, 2014b). Furthermore, there is extensive overlap of brain regions involved in the circadian rhythm and a number of systems that regulate affect, and the implicated neural circuits are known to interact in bidirectional pathways (Saper, Cano, & Scammell, 2005). For example, the hypothalamic-pituitary-adrenal (HPA) axis (Landgraf et al., 2014b), is a major neuroendocrine system that regulates many biological processes including stress, mood, and the sleep/wake cycle, among many other functions. Abnormalities in the HPA axis are known to precipitate mood disorders such as depression and BD. Specific neuroendocrine pathways within the HPA axis are activated in response to stress, and SD may produce atypical activation these pathways leading to an abnormal stress response. At the same time, activation of the stress response and heightened arousal may disrupt sleep. Together, these create a bidirectional association that may be mutually maintaining in the development and occurrence of mood disturbances (Eidelman et al., 2012; Landgraf, McCarthy, & Welsh, 2014a).

Third, alterations in sleep and/or circadian rhythms have effects on mood. In animal studies, manipulating light and dark cycles or mutating clock genes has been shown to alter affect (Landgraf et al., 2014b). Likewise, manipulations of sleep duration and timing in humans are shown to produce changes in valence and intensity of affect. For example, in a sample of healthy young adults, sleep restriction to 33% of normal nightly duration over seven consecutive nights resulted in significant mood disturbances, particularly increased confusion, anxiety, and fatigue (Dinges et al., 1997). In patients with BD, experimental sleep deprivation can precipitate mania (Wehr, Goodwin, Wirz-

Justice, Breitmaier, & Craig, 1982), while prolonged darkness may alleviate mood elevation (Barbini et al., 2005). Therapies designed to treat sleep symptoms often produce improvements in a range of other domains, including mood. For instance, sleep restriction therapy for treatment of insomnia improves both negative and positive mood (Miller, Kyle, Marshall, & Espie, 2013). In patients with BD, treating insomnia has been shown to yield sustainable improvements in mood, including significantly reduced relapse rate for manic episodes and marginally lower relapse rates for depressive episodes (A. G. Harvey et al., 2015).

Lastly, there is some preliminary evidence to suggest that mood may affect subsequent sleep. For example, a clinical study of BD patients versus healthy controls examined the effects of happy and sad mood inductions on subsequent sleep onset latency (SOL) and REM density measured by PSG and self-report. Participants slept in laboratory for two baseline nights, followed by a happy mood induction night and a sad mood induction night. While there was no difference in SOL between BD and healthy controls on baseline nights, SOL was significantly reduced following happy mood induction in the control group (but not the BD group). Following sad mood induction, both groups showed shorter SOL in relation to baseline nights. REM density was higher among BD patients than healthy controls for all nights, and both the BD and healthy control groups showed increased REM density following sad mood induction (Talbot, Hairston, Eidelman, Gruber, & Harvey, 2009). This suggests that affect immediately prior to bedtime may have an impact on subsequent night time sleep.

While extensive evidence is available for the association between sleep and acute changes in mood valence or intensity, considerably less research has been conducted on the relationship between sleep and MI. However, available evidence does suggest an important relationship. For example, a recent prospective study of participants with BD, BPD, and healthy controls across one-week follow-up examined the relationship between MI and several indicators of diurnal rhythms, including heart rate, activity levels, and sleep, MI across one week of follow-up, Mood was assessed approximately 10 time per day, and MI was calculated as the standard deviation of mood scores for each day. Participants with BPD showed the greatest variations in diurnal rhythms, followed by BD, and healthy controls (except for sleep for which BD participants showed the greatest variation). Furthermore, the BPD group showed the most robust correlations, followed by BD, then HC. Significant positive correlations were observed between MI and activity, heart rate and sleep within the BPD group, while the BD group showed only a significant positive correlation between MI and sleep (Carr et al., 2018). These findings are consistent with other evidence to suggest that some individuals may be particularly vulnerable to changes in circadian rhythms, which may predispose them to certain psychiatric illnesses (Landgraf et al., 2014a).

1.5 Significance and Rationale

Clarifying the relationship between MI and SD is important for a number of reasons. Foremost, SD and MI are independently associated with poor health, commonly occur in general population, and both may be risk and maintaining factors in psychiatric disease.

MI and SD may involve shared physiological mechanisms that underlie many, if not all, psychiatric and neurodegenerative diseases. According to Wulff and colleagues, all psychiatric disorders and neurodegenerative diseases involve, at their core, an abnormality in neurotransmitter signalling. Disruption of sleep and circadian timings can lead to mood disturbances, possibly by way of atypical behavioural patterns such as abnormal light exposure or social rhythms. Together with other potential factors such as the use of alcohol and substances or medications, these may exacerbate disruptions in sleep physiology including neural and neuroendocrine pathways (Wulff et al., 2010).

This suggests that MI and SD may be transdiagnostic processes in the development and maintenance of a wide range of brain diseases. Sleep and circadian timings require multiple brain structures and neurotransmitter systems. The considerable variability in the manifestations of abnormal sleep and circadian rhythms in the population may be explained by the interaction of different sets of factors to produce distinctive symptoms (Wulff et al., 2010). Their involvement in the development of poor health indicates that they should be treated promptly and not just dismissed as symptoms of another illness. Both MI and SD are modifiable, and may be good targets for treatment of a wide range of illnesses. Effective treatment of transdiagnostic processes may have extensive public health implications. For example, prevention or treatment strategies aimed at these processes may be effective for a wide range of illnesses, and for treating symptoms of comorbid illnesses simultaneously. Furthermore, advances in knowledge of these processes may propagate knowledge of many illnesses.

While the relationship between SD and MI appears to have both clinical and public health importance, scientific evidence is insufficient. Much of the existing literature focuses on SD in relations to unidimensional mood states and acute changes in mood, rather than MI. Furthermore, the majority of existing literature has been conducted in small clinical samples with specific psychiatric diagnoses. These limitations may be a consequence of methodological challenges of studying the two features concurrently. For example, in order to investigate MI and SD in detail, participants would need to provide high frequency information over several days or longer, which may require extensive resources. However, the emergence of digital health provides new opportunities to conduct research on a large scale.

Digital health is an emerging discipline that links digital technologies with healthcare planning, delivery, and research, providing opportunities to produce very large repositories of health-related information. In particular, the implementation of these technologies, such as mobile phone applications or actigraphy, may permit deep phenotyping of mood and sleep in large epidemiological samples.

1.6 Thesis Overview

This thesis investigates the relationship between MI and SD as transdiagnostic features on a shared pathway to ill health. Chapter 1 introduces essential background literature, and provides an overview of the current thesis. The thesis objectives are addressed using a series of five primary data chapters. Chapter 2 is a systematic review of available literature for the prevalence of MI in the general population. Chapters 3 and 4 are a set

of studies using data from the Adult Psychiatric Morbidity Survey (APMS) 2007 to investigate the epidemiology of MI and SD and their relationship in a nationally representative sample of the adult household population in England. Chapter 5 examines electronic health records of patients presenting to the Oxford Health Foundation Trust to assess comparable aims in a clinical population. Chapter 6 aims to further clarify the mechanisms of the association between MI and SD in finer detail using prospective data from a randomised controlled trial of two mood management interventions in patients with BD. Chapter 7 concludes this thesis with a summary of key findings, discussed in the context of the broader literature, and offers avenues for future research.

Chapter Two: Prevalence of Mood Instability in the General Population: A Systematic Review

2.1 Introduction

MI is an important transdiagnostic feature of psychiatric disorders because it is both common and associated with considerable dysfunction and impairment, irrespective of clinical diagnosis. MI is among the most commonly reported symptoms reported by patients referred to community mental health teams (Gilbert, Allan, Nicholls, & Olsen, 2005). It represents a core feature of BD (Henry et al., 2008), and it is part of the diagnostic criteria for BPD (American Psychiatric Association, 2013)[c]. Furthermore, MI is related to poor health and social functioning. A longitudinal study of outpatients with BD (*n*=55) found that persons with MI had significantly increased impairment in the domains of autonomy, work, cognition, finances, interpersonal relationships, and leisure time, after controlling for other psychopathological variables (Strejilevich et al., 2013). MI is also associated with longer and more frequent hospital stays, increased likelihood of compulsory admission and prescription of antipsychotic and mood stabilising medications (Patel et al., 2015).

Importantly, MI appears to be not only a symptom, but also a possible prodromal feature of several psychiatric disorders. Using data from the Adult Psychiatric Morbidity Survey 2000 at baseline (*n*=8580) and 18-month follow-up (*n*=2413), Marwaha and colleagues

[c] Five out of nine symptoms must be present, including: 'affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)'

found that, after controlling for other factors, MI significantly predicted the onset of depressive episode (OR=2.43, 95% CI: 1.03–5.76)(Marwaha et al., 2015). Additionally, a comprehensive literature review found that MI and depressed mood were the most frequently reported prodromal features of BD (Howes et al., 2011).

Together, this evidence suggests that MI is associated with increased risk of psychiatric disease and poorer clinical outcomes, and may present a large burden to the population. Given that MI might occur at the earliest stages of disease, it is important to examine it not only in persons with disease, but also in those who are still at risk for developing mental illness. General population sample can capture a wide range of individuals, including those who are undiagnosed or disengaged from health services–a portion of the population often missed from clinical research samples.

The burden associated with MI in the general population is still unclear. For example, two studies based on the UK adult population found widely different prevalence estimates. Data from a nationally representative sample of adults in England (*n*=7403) suggest that MI is present in approximately 14% of the population (Marwaha, Parsons, Flanagan, & Broome, 2013a), while a study using the UK Biobank, a large UK-based sample (*n*=113,968), found an estimated 35% prevalence of MI (Ward et al., 2017). Differences in the study designs, sample compositions, and measurement of MI might account for these differences. Although the two samples had similar gender distributions, the UK Biobank was comprised of a slightly older sample, and the tools to assess of MI varied–both may have contributed to discrepancies observed in the

prevalence estimates. The many possible sources of heterogeneity in the literature makes it difficult to know the true prevalence of MI.

2.1.1 Aim

The aim of this study was to systematically review prevalence data on MI in general population samples.

2.2 Methods

The protocol for this systematic review was registered with Prospero, number CRD42018085472.

2.2.1 Eligibility Criteria

Primary quantitative studies that assessed the frequency or proportion of MI in non-clinical samples were eligible for inclusion. In a previous systematic review of the definition and measurement of MI (Marwaha, He, et al., 2014), it was observed that labels are inconsistent in the literature, therefore we included any definition of MI that involved the presence of sudden, frequent, and/or intense mood changes, excessive reactivity of mood or difficulty regulating emotions, regardless of the label used.

Inclusion criteria:

(a) full-text article available in English

(b) the sample consisted of adults aged 16 years or older

(c) a report of proportion of MI or frequencies to permit calculation of prevalence and standard error

Exclusion criteria:

(a) Sample selection was based on the presence or absence of MI

(b) Samples of primary physical or mental illness without a healthy control group

(c) Case report or case study designs

Case-control studies were eligible for inclusion if they reported a frequency estimate for MI within a healthy control group–only the estimate from the healthy control group was included in the review. Studies of convenience samples were included, provided they met the inclusion and exclusion criteria.

2.2.2 Search Strategy

EMBASE, PsycINFO, PubMed, and Medline(R)[d] were searched for articles published up to 17 December 2017. Search terms for each database are listed in Table 2.1. Relevant journals were identified from a previous systematic review of MI definitions and measurement (Marwaha, He, et al., 2014), and hand-searched. These included the *Journal of Affective Disorders*, *Journal of Abnormal Psychology*, *The American Journal of Psychiatry,* and *Psychological Medicine.*

[d] Medline(R) including Epub ahead of print, in-process and other non-indexed citations.

Table 2.1 Search terms for each database.

Database	Terms
EMBASE	exp mental instability/
PsycINFO	exp emotional regulation/ OR exp emotional instability/
MEDLINE(R)	mood-swings OR mood-instability OR mood-dysregulation OR mood-lability OR affective-instability or affective-dysregulation OR affective-lability OR emotional-instability OR emotional-dysregulation OR emotional-lability
PubMed	"mood swings" OR "mood instability" OR "mood dysregulation" OR "mood lability" OR "affective instability" OR "affective dysregulation" OR "affective lability" OR "emotional instability" OR "emotional dysregulation" OR "emotional lability"

2.2.2.1 Study Selection and Data Extraction

Study selection and data extraction were carried out by two independent reviewers (K.M.[e] and K.S.[f]). The initial search identified a very large number of studies (>18,000). In order to review the studies more efficiently, titles and abstracts of the studies were divided between the two reviewers. Both reviewers assessed 17% (*n*=2468) of the titles and abstracts, K.M. assessed 55% (*n*=8000), and K.S. assessed the remaining 28% (*n*=4000) of the titles and abstracts. Percent agreement between the reviewers was calculated based on the inclusion/exclusion of reports during screening of titles and abstracts.

Data was extracted according to predetermined fields (Appendix B), including sample characteristics, study design features, details of the MI assessment tool, and MI prevalence estimate with standard error. Three studies did not report prevalence

[e] Keltie McDonald
[f] Kiyomi Shinohara, Department of Psychiatry, University of Oxford

estimates for MI but provided sufficient information to calculate prevalence and standard error. For these data, the following equations were used:

Prevalence: $p = \frac{n}{N}$

Standard error: $se = \sqrt{p\left[\frac{1-p}{n}\right]}$

where *n* is the number of subjects with MI, and *N* is the total number of subjects with and without MI.

In some instances, key data to be extracted were not provided in the original reports. To obtain the missing information, authors were contacted for additional details (or datasets were examined where available). This included clarification of study procedures, sample characteristics, and relevant estimates, such as details of the measurement of MI, the response rate, and distribution of age of the sample.

2.2.3 Risk of Bias Assessment

An adapted form of a risk of bias tool developed by Hoy et al. was used to assess the quality of studies included in the review (Hoy et al., 2012). This is an 11-item tool developed specifically to assess quality of prevalence studies. A single item from the original tool, whether the study sample was a close representation of the national population, was removed. This item was deemed unsuitable in the assessment the types of studies identified in the review because not all were intended to be nationally representative. For each of the remaining 10 items, studies were rated as high or low risk

of bias. If an answer to an item was unclear due to insufficient information, the item was rated as high risk. A summary of overall risk of bias was produced for each study based on a predetermined algorithm produced in consultation with K.S. (Appendix B).

2.2.4 Synthesis of Data

Studies and data were evaluated individually prior to a decision about the appropriateness of quantitative synthesis. Quantitative synthesis was not carried out due the large heterogeneity observed in the eligible studies.

2.3 Results

Database searches and hand searches of journals identified 14,468 potential papers after excluding duplicates. The review of titles and abstracts identified 39 papers that were identified for full-text assessment. Of these, seven studies met the inclusion criteria. Two reports were based on the same data (Marwaha, Parsons, et al., 2013a; Evyn M. Peters, Balbuena, Baetz, Marwaha, & Bowen, 2015). One study provided greater detail about the prevalence of MI and was, therefore, included in this review. Reasons for exclusion of reports during full-text screening were inclusion of children or adolescents in the sample or the absence of a prevalence estimate or frequencies. For example, some measures were an aggregate of MI with other symptoms or the symptom was measured dimensionally. The final sample included six studies.

Figure 2.1 shows a PRISMA flow diagram of study selection. Percent agreement between reviewers for the screening of abstracts and titles was 82%. Key information for each of the six studies is presented in Table 2.2.

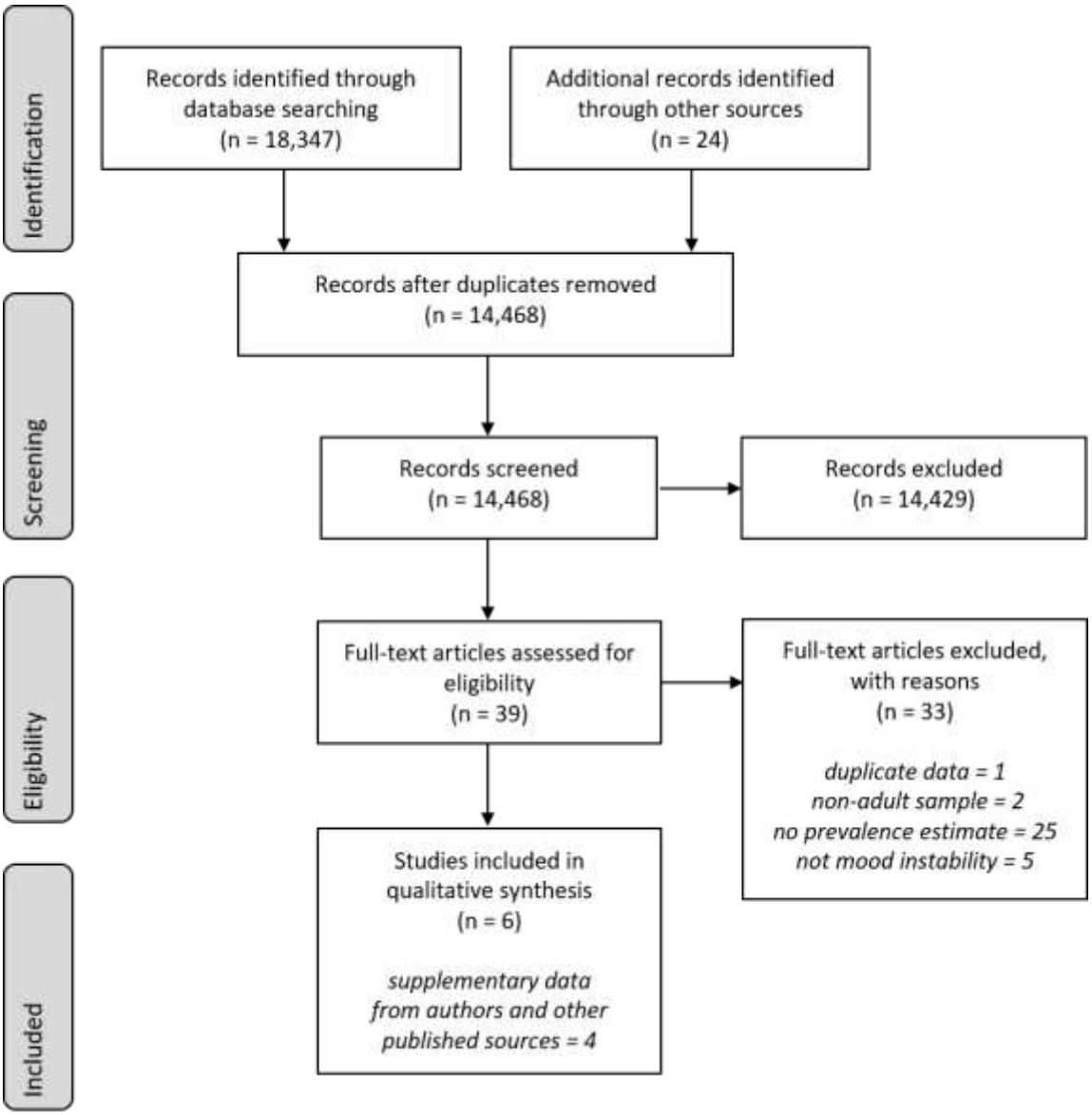


Figure 2.1 Prisma diagram: Flow of study selection.

Table 2.2 Summary of extracted data.

Authors (Year) Location	Location	Design	Source Population	Sampling Procedure	Sample Size	Time of Data Collection	Response rate (%)
Angst, J., *et al* (2003)[a]	Zurich, Switzerland	Age Cohort	Total population	Stratified random sample	A: 591 (261 controls) B: 499 (173 controls)	A: 1978-1993 B: 1986-2008	
Berenson, A. B., *et al.* (2008)		Cohort	Women of reproductive age eligible for use of contraception	Stratified random sample	608	2001-2004	75.5
Marwaha, S., *et al.* (2013)[b,c]	England	Cross-sectional	Household population aged 16 years and older	Multistage stratified probability sample	403	2006-2007	57.0
Milutinovic, D., *et al.* (2012)	Serbia	Cross-sectional	ICU nurses from 22 health centres	Random sample	1000		86.9
Peters, E. M., *et al.* (2016)[b]	England, Scotland and Wales	Cross-sectional	Household population aged 16-74 years	Multistage stratified probability sample	2344	2000	79.0
Ward, J., *et al*. (2017)	UK	Cross-sectional	Population aged 40-69 years	Population sample	113,968	2006-2010	5.5

Authors (Year)	% Female	Age range (*mean, sd*)	Prevalence %(*SE*)	Prevalence duration	Tool	Mood Instability Item
Angst, J., *et al* (2003)[a]	A: 50.6 B: 50.1	A: 19/20–34/35 (M/F) B: 26/27–49/50 (M/F)	A: 5.8 (1.4) B: 6.1 (0.8)	Lifetime	Professional interviews at home	'Would you say you are one of those people who have frequent ups and downs?'
Berenson, A. B., *et al.* (2008)	100.0	16-33	67.6 (3.6)	3 months	n/a	'mood swings'
Marwaha, S., *et al.* (2013)[b,c]	51.4	16+ (46.4, 0.3)	14.7 (0.5)	Several years	SCID-II	'Do you have a lot of sudden mood changes?'
Milutinovic, D., *et al.* (2012)	95.1	20+ (33.2, 4.3)	28.0 (0.0)	6 months	n/a	'frequent mood swings'
Peters, E. M., *et al.* (2016)[b]	57.5	16-74 (43.4, 0.5)	13.9 (0.9)	Several years	SCID-II	'Do you have a lot of sudden mood changes?'
Ward, J., *et al*. (2017)	52.3	40-69 (56.8, 8.0)	35.3 (0.03)	Lifetime	EPQ-R-S	'Does your mood often go up and down?'

[a] Prevalence estimates are specific to controls, A=original data, B=supplemental data, prevalence estimate B is weighted; [b] Prevalence estimates are weighted with corresponding linearised standard error; [c] Overall prevalence estimate in published report was unweighted, Weighted estimate obtained for review; SCID-II: Structured Clinical Interview for DSM Disorders–Borderline personality disorder module; EPQ-R-S: Eysenck Personality Questionnaire-Revised Short Form; SCL-90-R: Symptom checklist-90-R; CIS-R: Revised clinical interview schedule; M=male, F=female; Mood Instability Item=Question about mood instability or label used by authors if no question was reported.

2.3.1 Overall Prevalence Estimates

Estimates of prevalence ranged between 5.8% and 67.6%. Prevalence durations included lifetime (*n*=2), 3-months (*n*=1), 6-months (*n*=1), and 'several years or longer' (*n*=2). Tools used to measure MI included a single item from the Structured Clinical Interview for DSM IV Disorders-Borderline Personality Disorder Module (SCID-II)(First et al., 1997), a single item from the Eysenck Personality Questionnaire-Revised Short Form (EPQ-R-S)(Eysenck, Eysenck, & Barrett, 1985), and a professional interview conducted at home. Two studies did not provide information about the specific tool or item used to measure MI, but labelled the parameter 'mood swings'. All studies were conducted between 2000 and 2010, except a cohort study carried out between 1978 and 1993.

2.3.2 Age and Gender Specific Prevalence Estimates

Only one study provided prevalence estimates stratified by gender and age. The estimated prevalence of MI in females (17.6%) was higher than in males (11.5%). Prevalence estimates decreased across age groups: 16-24 (26.0%), 25-34 (19.5%), 35-44 (15.4%), 45-54 (14.7%), 55-64 (9.5%), 65-74 (6.7%) 75 and older (3.6%; Marwaha, Parsons, et al., 2013a). One study reported prevalence of MI in a female only sample (67.6%; Berenson, Odom, Breitkopf, & Rahman, 2008), and one study reported prevalence of MI in a sample comprised of 95% females (28%; Milutinovic, Golubovic, Brkic, & Prokes, 2012).

2.3.3 Risk of Bias Assessment

All of the studies included in this review were rated as having a high risk of bias in the prevalence estimate. Most of the studies showed low risk of bias on items related to selection of participants, however, measurement bias appeared to be inadequately controlled in all of the studies. While the SCID-II and EPQ-R-S have been assessed for overall reliability and validity according to their stated aim, the embedded items used in the studies to measure MI have not been assessed for their accuracy. The measurement tools used in other studies were also not assessed for their accuracy. The length of prevalence estimate might also have introduced some bias. Two studies included a prevalence duration of *several years or longer* and two reported lifetime prevalence, while other reported durations of less than one year. Due to the absence of information about validity and reliability of the measurement tools, potential presence of recall bias, and non-specificity of the measurement, risk of bias was classified as high for all studies.

2.4 Discussion

This systematic review identified six reports of prevalence data on MI, which ranged approximately 6% to 68%. The studies included in the review were highly heterogeneous in terms of study design, sample coverage, type of prevalence, and measurement of MI. Gender and age-specific prevalence data were highly limited, with only one study reporting stratified estimates. Marwaha and colleagues showed that prevalence of MI was higher in females than males, and the frequency of MI decreased

with age (Marwaha, Parsons, et al., 2013a). Consistent with these gender-specific estimates, the two studies of predominantly female samples reported some of the highest prevalence estimates (68% and 28%; Berenson et al., 2008; Milutinovic et al., 2012). Although, it is notable that these were the only two studies that examined mood swings, and provided the least information about MI was operationalised. The observed trend of decreased prevalence with age was not supported by Ward *et al.*, who studied a somewhat older sample, and observed one of the highest prevalence estimates (35%; Ward et al., 2017).

Heterogeneity in the prevalence estimates may be, in part, related to differences in the source populations across the studies. Among the reports included in this review, source populations differed substantially. For example, while some studies were intended to be nationally representative, one only included women of reproductive age with strict exclusion criteria, while another studied only nurses. These different source populations are highly likely to have different distributions of characteristics within them, and in turn, different prevalence estimates of MI. In fact, sample compositions varied between reports in terms of age and gender distributions, and both characteristics appear to be important determinants of MI.

Importantly, all studies included in the review showed a high risk of bias in the prevalence estimate. The two primary sources of bias include selection bias and measurement bias. Selection bias occurs if distributions of characteristics differ between the sample and the source population–specifically if those characteristics are related to

the probability of having the feature of interest (MI, in this case). Measurement bias refers to systematic error in the instrument used to measure the feature of interest.

Selection bias, in the form of non-response, may have also contributed some heterogeneity. For most reports, response rates were adequate (>75%), except for data from APMS 2007 (57%) and UK Biobank (5%). Psychopathology has been associated with a failure to locate participants (de Graaf, Bijl, Smit, Ravelli, & Vollebergh, 2000). Therefore, low response rates could lead to an underestimate of the prevalence of MI because persons with MI are underrepresented in the sample. Results can still be valid and generalizable if the sample has a large population base and adequately captures the distribution of exposures and backgrounds that exist in the population (Manolio & Collins, 2010). In the analysis phase, data from APMS 2007 were weighted to account for non-response. However, the volunteer-based sampling method, coupled with only 5% response rate, may have led to substantial systematic error in the estimate.

While issues related to sample selection and response rates may explain some heterogeneity in the prevalence estimates, a great deal of the variability is likely attributable to the measurement of MI. Disparate estimates might be the result of differences in underlying concepts being measured. Studies that examined *frequent ups and downs* had both lower and higher estimates than studies that assessed *sudden mood changes.* Although it is notable that the report with the lowest prevalence estimate, which examined frequent up and downs, was carried out two to three decades prior to

the other studies. This might be explained, to some degree, by cohort effects[g] that resulted in an increased prevalence of MI over time. The reports that used the questions labelled *mood swings* had minimal information provided about the measures, but both produced high prevalence estimates relative to the other studies. Since none of the studies in the current review used validated measures of MI, it is difficult to determine which estimate, if any, accurately reflects the true prevalence of MI.

This exemplifies a key issue in nearly all research of MI; there is a lack of consensus on the definition of MI, and in turn, how to operationalise the construct. A systematic review of the definition and measurement of MI identified nine different terms and 24 measures (Marwaha, He, et al., 2014), and many were associated with distinct (but related) constructs. For example, the Affect Lability Scale (P. D. Harvey, Greenberg, & Serper, 1989), Affect Intensity Measure (Larsen, Diener, & Emmons, 1986), and Difficulties in Emotion Regulation Scale (Gratz & Roemer, 2008), are intended to measure rapid changes in affect, affect intensity, and the capacity to control affect, respectively. Although all of these are often considered features of MI, they are not necessarily equivalent, and they do not, individually, represent the complete MI construct. Likewise, the presence of *sudden mood changes* or *frequent ups and downs* is unlikely to adequately capture MI in its entirety.

[g] Cohort effects are variations in the risk of health outcomes as a function of age, which usually correspond to changes in exposures to risk factors over time.

2.4.1 Limitations

This review found substantial range in prevalence estimates of MI, attributable to differences in definitions and assessments of MI, study protocols, and sample characteristics. Moreover, some reports were missing key details, including how MI was classified. As a result, the ability to compare the observed prevalence estimates, and identify the true prevalence of MI, was limited due to the presence of many possible sources of bias. Nevertheless, this systematic review provided comprehensive examination of the availability of prevalence data and provides a foundation for future research.

In addition, studies of clinical and specialised populations were excluded. Understanding the prevalence of MI in clinical groups is equally valuable for surveillance of health trends, and given its contribution to the long-term prognosis and outcomes of several psychiatric disorders. Studies of these groups are likely to be rich sources of data on MI. However, MI in clinical samples might be missed due to disengagement from mental health services or a lack of recognition of symptoms. Under ideal conditions, samples from the general population will be unbiased with respect to the presence of mental health status, and therefore, more representative of persons irrespective of diagnosis. For this reason, we selected only non-clinical samples.

Finally, only publications with a full-text available in English were included, and there may be additional data published in other languages.

2.4.2 Implications for Future Research

Critical first steps for future research will be to standardise terminology and produce an operational definition of MI that is precise and quantifiable. Marwaha and colleagues have proposed that MI is a multifactorial construct that includes rapid changes in affect, affect intensity, a deficiency in the capacity to regulate emotions, and whether the changes in affect are precipitated by environmental stimuli. In an effort to unify the field, they provided the following definition of *affective lability*: 'rapid oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioural consequences' (Marwaha, He, et al., 2014). This definition is useful because it is comprehensive and maintains a flexible theoretical framework (Marwaha, He, et al., 2014). However, more work is needed in terms of how to operationalise this definition.

Firstly, measurement tools need to be constructed or revised in order to assess MI in its entirety. Currently, to my knowledge, no single measure of MI assesses all features together. For population research, measurement tools need to be brief, cost efficient, and easy to understand, administer, and score. A good starting point might be to assess and adapt existing instruments. Comparisons of responses from several existing measures might help to better understand their differences and inform potential modifications. Alternatively, factor analysis of responses might be a suitable technique to construct new instruments.

Secondly, methods to dichotomise these improved dimensional measures need to be established. Although dimensional approaches are advantageous in many clinical and

research settings because they provide more detailed information, categorical approaches are better suited in other contexts for their clinical utility, particularly for facilitating decision-making. Signal detection methods, widely used in medical research for establishing accuracy of diagnostic tests, might be an option to find the optimal cut-point on dimensional measures (Kraemer, Noda, & O'Hara, 2004). Although, this requires use of an external referent, typically a gold standard. As no current gold standard exists, one might use, for example, clinical judgement of whether an individual has MI. Importantly, the optimal cut-point on a dimensional measure must be chosen in relation to its purpose. For example, the level that differentiates general population from the ill may be a different cut-point than if the aim is for differential diagnosis (Kraemer et al., 2004).

Thirdly, tools need to have standardised time scales. For example, for prevalence data, tools should align with typical prevalence durations such as point, 12-month or lifetime. This will facilitate consistency and comparability between studies.

Although it is important for future work to improve and refine single assessments of MI, cross-sectional assessments are limited by their reliance on retrospective recall of mood changes and the inability to objectively capture temporal dependencies. An ideal assessment of MI should capture not only variability and intensity of affect, but also how changes occur over time. Ecological momentary assessment (EMA) it a method of real-time, high-frequency data collection that can largely overcoming the shortcomings of cross-sectional research. If used with an appropriate analytic strategy, EMA may also

comprehensively capture MI. Several platforms have already been developed to monitor mood prospectively and remotely using smartphones or computers, such as TrueColours (www.oxfordhealth.truecolours.nhs.uk) and ChronoRecord (www.chronorecord.org). These platforms have been used previously to study MI. For example, remote mood monitoring has been used to study MI in relation to emotional processing (Bilderbeck, Reed, et al., 2016) and cognitive processing (Panchal et al., 2018) in patients with BD, and to examine whether MI can discriminate between BD, BPD, and healthy controls (De Vos et al., 2016). While traditionally used in clinical settings, remote monitoring techniques are more recently being scaled up successfully to large population studies. For example, in a French sample, over 28,000 people provided daily ratings of mood and activities for an average of 27 days using a smartphone application (Taquet, Quoidbach, de Montjoye, Desseilles, & Gross, 2016). Although promising for research at the population level, further work is needed to refine and validate self-report measures of mood designed for use with EMA methods.

2.5 Conclusion

MI is associated with considerable negative health and social impairment (Marwaha, Parsons, et al., 2013a; Patel et al., 2015; Strejilevich et al., 2013), and is a possible prodrome and maintaining factor for psychiatric disease (Howes et al., 2011; Marwaha et al., 2015). Prevalence estimates of MI are useful because they provide a framework to understand and monitor its impact on the population, and to inform decision-making strategies intended to reduce and prevent related morbidity and mortality. This

systematic review found substantial heterogeneity in available data on the prevalence of MI in the general population. Operationalisations of MI, study designs, and sample characteristics were diverse, and as a result, it remains difficult to identify the true population prevalence of MI. A vital area for future research is to establish consensus on the definition of MI, and to produce validated measurement tools that assess all of its components. Currently, the best estimate of prevalence of MI available in the literature is 14%, measured from the APMS 2007. MI has been examined extensively in the APMS 2000 and 2007 (references) and strong and consistent relationships are observed with other highly correlated factors known from the literature such as the presence of diagnosed psychiatric conditions, mental health service utilisation, and treatment with mood stabilisers, particularly antipsychotics, and suicidal ideation.

Chapter Three: Mood instability, sleep disturbance and suicide in the English adult household population.

3.1 Introduction

SD and MI are frequently found in the population, and even more frequently in people with mental disorders. Sleep problems are present in approximately 32–36% of the population (Kerkhof, 2017; Roth et al., 2006; Stein et al., 2008). The odds of SD are three to five times higher in people with mood disorders, anxiety disorders, or impulse control disorders than in those without (Roth et al., 2006). The prevalence of MI in the population is less clear, although the systematic review reported in Chapter 2 suggests that MI is common, with even the lowest prevalence estimate at 6% (Angst, Gamma, & Endrass, 2003). In the APMS 2007, MI was present in approximately 14% of the population, and 49–67% of persons with generalised anxiety disorder, panic disorder, depressive episode, post-traumatic stress-disorder, or obsessive-compulsive disorder (Marwaha, Parsons, et al., 2013b). The high occurrence of MI and SD in a wide range of mental disorders suggest that they may qualify as transdiagnostic processes (Aldao, 2016; A. G. Harvey, Murray, Chandler, & Soehner, 2011b).

Sleep and mood are closely linked. It is proposed that sleep and mood disturbances, particularly emotional dysregulation, are bidirectionally related such that poor mood regulation interferes with sleep, and poor sleep perpetuates difficulties with mood regulation (Espie, 2002; A. G. Harvey, 2008b). The relationship between MI and SD is important because they are both independently associated with poorer outcomes. For

example, a longitudinal study of BD patients (*n*=483) found that the presence of SD was associated with a more severe disease course, including increased risk of relapse, history of psychosis, and a higher number of past suicide attempts (Sylvia et al., 2012). Likewise, another prospective study of patients with BD (*n*=55) showed that intensity and frequency of mood changes predicted poorer functional recovery during interepisode periods (Strejilevich et al., 2013). Furthermore, MI and SD have both been identified as robust predictors of BD onset (Howes et al., 2011; Jackson et al., 2003), and occur at the earliest stages of several other illnesses.

A great deal of the existing evidence on the relationship between MI and SD is based on samples with specific clinical psychiatric disorders, particularly BD. It is unclear whether this association is limited to psychiatric conditions or whether it is a pattern also observed in the population more generally. It is important to study MI and SD in general population samples, because they appear to be not only common symptoms, but also predictors of onset and maintenance of mental illness. Population surveys capture individuals regardless of whether they have been in contact with health services–a portion of the population who are often missed in clinical and administrative databases. By extension, these surveys are also advantageous because they permit the study of persons who are subsyndomal, undiagnosed or at risk of developing clinical disease, as well as those with clinical diagnoses. The APMS is one such national survey that provides an opportunity to study both MI and SD from a transdiagnostic perspective.

3.1.1 Aim

The aim of this study was to assess the association between MI and SD and the link with a single potential outcome–suicide ideation and attempt–in a general population sample.

3.1.2 Hypotheses

(a) SD is positively associated with MI;

(b) Psychotropic medications alter the association between SD and MI; and

(c) SD is positively associated with suicide ideation and attempt, particularly when concurrent with MI.

3.2 Methods

3.2.1 Adult Psychiatric Morbidity Survey

The Adult Psychiatric Morbidity Survey (APMS) 2007 is one of a series of national cross-sectional surveys conducted every 7 years since 1993. Key parameters captured by the survey included demographic features, common psychiatric disorders, utilisation of health services and treatments, and general health. APMS 2007 consisted of two phases; all subjects participated in phase one, and a subset of participants were selected to participate in a second phase to collect more detailed information about possible psychiatric diagnoses. Data used in this thesis are from phase one, therefore all survey details refer to phase one only. Data are available from the UK Data Archive (http://www.hscic.gov.uk/pubs/psychiatricmorbidity07). The Royal Free Hospital and Medical School Research Ethics Committee provided ethical approval for APMS 2007.

The target population was adults aged 16 years and older living in private households in England. The sampling frame was from the Small User Postcode Address file, including delivery points of fewer than 50 pieces of mail daily excluding small businesses. A stratified multi-stage probability sampling procedure was used. First, the national population was stratified by region (Strategic Health Authorities) and socio-economic grouping. Stratification increases the precision of the random sample by ensuring that the sample is representative of known population distributions. After stratification, a sample of addresses was taken from the primary sampling units (postcode sectors). Next, a random sample of delivery points within each selected postcode sector was taken. In households with more than one eligible adult resident, one adult was randomly selected per household to take part in the survey (National Centre for Social Research, 2017).

Data collection occurred between October 2006 and December 2007. A total of 13,171 households were selected and eligible for the study. The response rate for the survey was 57%, yielding a total of 7,461 interviews. Of these, there were 7,353 full interviews, 50 partial interviews and 58 proxy interviews (proxy interviews were omitted from these data). Interviews were fully-structured and conducted in English by trained lay interviewers. The questionnaires were highly branched, meaning that individuals did not answer all possible survey questions–questions identified as irrelevant based on the participants' answers to previous items were omitted. Interviews took on average 1.5 hours to complete.

3.2.2 Measurement

3.2.2.1 Sleep Disturbance

SD was classified based on the sleep section of the Clinical Interview Schedule-Revised (CIS-R; Lewis, Pelosi, Araya, & Dunn, 2009). Trouble falling or staying asleep and sleeping more than usual were measured by the questions 'In the past month, have you been having problems with trying to get to sleep or with getting back to sleep if you woke up or were woken up?', and 'Has sleeping more than you usually do been a problem for you in the past month?', respectively. The label *sleep disturbance* refers to an affirmative response to either item. Notably, the two sleep problems were mutually exclusive–the item about problems with sleeping more than usual was only asked if the participant denied trouble falling or staying asleep. It is possible that some individuals experienced both issues during the previous month, and therefore may not be appropriately represented in one category. Therefore, the aggregate item was produced to address potential misclassification.

3.2.2.2 Mood Instability

MI was assessed using a single item from the Borderline Personality Disorders Module of the Structured Clinical Interview for DSM IV-II (SCID-II): 'The next set of questions are about the kind of person you generally are, that is, how you have usually felt or behaved over the past several years … Do you have a lot of sudden mood changes?' (First et al., 1997).

3.2.2.3 Medication

Prescribed medications were self-reported and verified by the interviewer by examining the medication packages. This included commonly prescribed medications for psychiatric symptoms. Medications were grouped based on whether they have a high risk or low risk of sedating effects (Appendix A).

3.2.2.4 Psychiatric Diagnosis

Participants were asked to provide, from a list, all of their current health conditions. The list included 'anxiety, depression, or other mental health issue'. For each condition, participants were also asked whether it had been diagnosed by a doctor. Only reports of mental health conditions that were diagnosed by a doctor were included in this variable.

3.2.3 Statistical Analysis

Demographic features and possible covariates within the sample were summarised as frequencies and proportions. Prevalence estimates were produced using generalised linear modeling of the binomial family with a log link function. Odds ratios (ORs) were calculated using logistic regression. All models were assessed for age and sex interactions and confounding, including the possible influence of non-linear age trends. Effect modification was assessed using Wald tests, and confounding was assessed by comparing adjusted and crude estimates. Confounding was considered present if the two estimates were deemed meaningfully different. All analyses were weighted, and

statistical tests were conducted at the 5% significance level. Analyses were carried out in Stata version 11 (StataCorp, 2009).

3.2.4 Weighting

Results presented in Chapters 3 and 4 are weighted to account for the complex survey design and non-response, and to ensure that the results are representative of the English private household population aged 16 years and older. Weights, supplied by the UK Data Service, were produced in three main steps: (a) to account for differential selection probabilities between households with different numbers of eligible adults, weights were calculated as the inverse probability of selection within the household; (b) to reduce household non-response bias, household level weights were calculated as the inverse of the probability of response estimated from a logistic regression model (with response as the outcome against a list of potential explanatory variables) multiplied by the household's selection weight; and (c) to ensure results are representative of the structure of the national population, calibration weights were produced based on age, sex, and region. These weights were applied using Taylor linearized variance and scaled variance for singleton strata[h]. Unless otherwise specified, all sample sizes and statistics presented in Chapters 3 and 4 are weighted and sample sizes are rounded to the nearest whole number[i].

[h] Scaled variance assigns each singleton strata the average variance from strata with multiple sampling units.
[i] The application of weights produces non-integer frequency estimates.

3.3 Results

The final weighted sample size was 7,939. There were no missing data for the MI or SD items, and <1% missing data for psychiatric diagnosis, psychotropic medications, and suicide ideation and suicide attempt.

Demographic features and selected potential covariates are summarised in Table 3.1. Both MI and SD were more frequent in subjects who were female, lower income (<£10,575), underweight, and with more hazardous alcohol use. Subjects with MI were more often single, while subjects with SD were more often widowed, divorced or separated.

Table 3.1 Frequency and percent of subjects with mood instability (*n*=1073) or sleep problems (*n*=3299) who reported selected demographic features and possible covariates.

	Mood Instability		**Sleep Problems**	
	n	**%**	***n***	**%**
Age (years)				
16-34	504	22.5	906	39.9
35-54	393	15.1	1084	41.3
55+	176	7.1	1142	45.6
Sex				
Male	409	11.5	1256	35.0
Female	664	17.6	1875	49.3
Ethnicity				
White	958	14.5	2798	42.2
Black	33	14.9	95	42.4
South Asian	42	15.7	111	39.0
Other	34	16.1	102	47.6
Marital Status				
Single	387	23.2	700	41.7
Widowed/Divorced/Separated	136	12.9	529	49.6
Married/Cohabitating	551	12.0	1903	40.9
Employment				
Full-time	411	14.9	1564	42.0
Part-time	198	18.0	638	34.9
Not employed	459	13.2	1564	49.8
Income[a]				
<£10,575	240	22.2	570	52.4
≥£10,575	542	12.0	1838	40.4
Body mass index				
Underweight	46	26.8	88	50.7
Normal weight	461	14.6	1322	41.4
Overweight	287	12.0	985	40.6
Obese	207	16.8	570	45.9
Psychotropic medications				
Any medication	179	41.2	318	72.3
Antipsychotic	25	54.6	32	67.9
Antidepressant	146	42.2	253	72.9
Sedative-hypnotic	39	42.7	71	76.3
Lithium	6	41.6	7	64.9
Audit[b]				
0-7	712	12.8	2345	41.9
8-15	260	17.3	641	42.6
16-40	102	37.1	135	51.4
Alcohol dependence	167	38.7	247	56.9
Substance dependence	108	42.8	142	56.3

[a] Equivalised annual household income; [b] AUDIT=Alcohol Use Disorders Identification Test.

The estimated lifetime prevalence of MI was 14.7% (95% CI: 13.6%–15.7%). Prevalence of MI was significantly higher in females (17.6%, 95% CI: 16.1%–19.1%) than males (11.5%, 95% CI: 10.1%–12.9%), and decreased significantly with age for both genders (b=0.97, SE=0.002, p<0.0001). The estimated prevalence of SD was 42.8% (95% CI: 41.0%–43.7%). Prevalence of SD was significantly higher in females (63.1%, 95% CI: 63.1%–66.9%) than males (35.0%, 95% CI: 33.1%–36.9%) and did not appear to depend on age. The prevalence of SD was also significantly higher in those with MI (69.8%, 95% CI: 66.6%–73.2%), than those without MI (37.6%, 95% CI: 36.2%–39.1%).

The odds of having SD in subjects with MI versus without was modified by sex and linear age (Figure 3.1). Across ages 16 to 94, the OR of SD in males ranged from approximately 1.5 to 8.5, while in females, the OR increased from approximately 2.0 to 3.8.

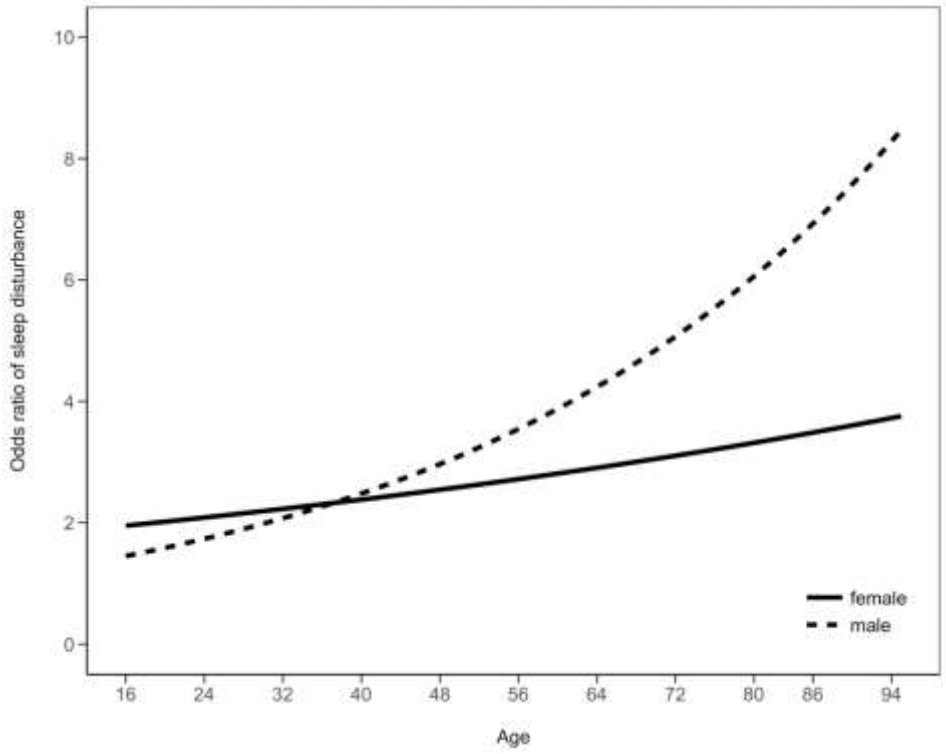


Figure 3.1 Predicted change in the odds ratio of sleep disturbance by age in subjects with mood instability and without mood instability.

The relationships between MI and two SD subtypes were also examined. Trouble falling or staying asleep and sleeping more than usual were each significantly associated with MI. The OR of trouble falling or staying asleep was 3.33 (95% CI: 2.9–3.9) and was significantly higher in males (OR=4.2, 95% CI: 3.2–5.4) than females (OR=2.6, 95% CI: 2.1–3.2). The OR of sleeping more than usual was 4.5 (95% CI: 3.1–6.5) and did not significantly differ by gender (males: OR=6.7, 95% CI: 3.9–11.6; females: OR=3.2, 1.9–5.2 in females). Associations between MI and each SD subtype did not depend on age.

In order to determine if having SD was associated with MI independently of having a psychiatric disorder, we calculated the OR of SD in those with MI and a psychiatric disorder, MI-only, or psychiatric disorder-only versus having neither MI nor a psychiatric disorder. The common reference group allows comparison of the relative influence of MI and psychiatric diagnosis on the odds of having a SD. Compared with the reference group, the OR of SD in those with both MI and a diagnosis was highest, followed by MI without a diagnosis, then a diagnosis without MI (Table 3.2). While similar a trend was observed in both genders, the relationship in males appeared stronger at all levels. Comparisons did not depend on age.

Table 3.2. Estimated odds ratios (ORs) of sleep disturbance comparing three mood instability and psychiatric disorder groups versus a common referent.

	Male		**Female**	
	OR	**95% CI**	**OR**	**95% CI**
MI and diagnosis	11.6	6.7–19.9	3.8	2.8–5.1
MI-only	4.2	3.1–5.8	2.9	2.2–3.8
Diagnosis-only	2.3	1.7–3.1	1.9	1.6–2.3
No MI or diagnosis[a]	1.0		1.0	

[a] Reference group.

The use of psychotropic medications with a high risk of sedation did not significantly modify or confound the association between the odds of SD in those with MI versus those without in either males (p=0.269), or females (p=0.051). Among males taking sedating medication, the OR was 10.13 (95% CI: 2.66–38.62), while in males not taking sedating medication the OR was 4.70, (95% CI: 3.58–6.17). In females taking sedating medication, the OR was 1.39 (95% CI: 0.68–2.84), while in those not using sedating medication the OR was 2.93 (95% CI: 2.36–3.64).

The prevalence of suicide ideation in the total sample was 0.8% (95% CI: 0.6%–1.0%), during the past week, 4.3% (95% CI: 3.7%–4.9%) during the past year, and 13.7% (95% CI: 12.8%–14.7%) during the lifetime. The prevalence of suicide attempt was 0.7% (95% CI: 0.4%–0.9%) during the past year, and 4.8% (95% CI: 4.2%–5.4%) during the lifetime. Too few subjects reported suicide attempt during the past week to estimate prevalence using the weighting procedure. Estimates of the association between suicide ideation or attempt and SD are shown in Table 3.3. Associations were not modified or confounded by age or sex. MI appeared to confound the association such adjusting for MI diminished the strength of the association.

Table 3.3 Estimated odds ratios of suicide ideation or attempt among individuals with any sleep problem versus no sleep problem.

	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
Suicide ideation				
Past week	8.0	3.6–17.8	5.0	2.1–11.8
Past year	5.0	3.6–6.8	3.1	2.2–4.3
Lifetime	3.1	2.6–3.7	2.2	1.8–2.7
Suicide attempt				
Past week[b]				
Past year	2.5	1.2–5.2	1.1	0.4–2.6
Lifetime	3.2	2.4–4.3	2.1	1.5–2.8

[a] Adjusted for mood instability; [b] Estimates unavailable owing to insufficient sample sizes.

3.4 Discussion

The estimated prevalence of MI for the past several years was 14.7%. This is slightly different than prevalence reported in two previous studies based on the same data. Marwaha and colleagues reported a prevalence estimate of 13.9% (Marwaha, Parsons, et al., 2013b), while Peters and colleagues reported a prevalence of 13.8%, and a weighted estimate of 14.5% (Evyn M. Peters et al., 2015). When using data from complex survey designs, it is important to apply weights in order to address bias that results from the complex survey design and produce estimates that are representative of the target population. For APMS 2007, the application of weights produces estimates that better reflect the English residential household population aged 16 years and older. Since the prevalence estimate of 14.7%[j] is weighted, it is a more accurate estimate of the true population prevalence.

[j] Differences between 14.5 and 14.7, and 13.8 and 13.9 were considered due to rounding.

The first hypothesis, that SD is positively associated with MI, was supported. A strong and positive relationship was observed between MI and SD. This is consistent with other research examining the relationship between diurnal rhythms and mood. For example, an observational study of patients with BD, BPD, and healthy controls, also showed that mood variability was significantly positively correlated with physiological measures of diurnal rhythms including heart rate, activity levels, and sleep, and that variations in mood appeared to be more sensitive to variations in sleep phase and depth in patients with BD and BPD than in healthy controls (Carr et al., 2018).

The relationship between MI and SD was modified by age and gender; the ORs of SD in those with MI versus those without were similar in males and females at younger ages, but increased more sharply with age in males than females. This suggests a particularly strong relationship between MI and SD in males of older ages. Gender and age are salient determinants of many mental and physical health problems. Understanding differences between genders and across age might suggest mechanisms that lead to MI and SD and associated complications, and facilitate better diagnosis, treatment, and prevention. Further work is required to clarify the differences between groups, and to gain an understanding of how such differences arise.

MI and SD are not only symptoms shared by several psychiatric disorders, but also may be part of the prodromes of such illnesses. Given the possible predictive value of MI and SD in identifying disease risk, it is critical to examine whether the presence of these factors is driven by having a psychiatric diagnosis, or if they occur independently of

clinical disease. Compared to the common referent, ORs were highest in those with MI and a diagnosis, followed by MI-only, and diagnosis-only. These results suggest that the association may be driven more strongly by the presence of MI than the presence of a psychiatric condition. This aligns with several prominent theories that mental illness may originate from physiological mechanisms shared by mood and sleep disturbances (Espie, 2002; Riemann et al., 2010; Wulff et al., 2010). However, these results should be interpreted with caution because psychiatric diagnosis in this study includes all individuals who have ever been diagnosed, and therefore may not have symptoms of the condition at present.

In relation to the second hypothesis, that the use of medications with a high risk of sedating effects would alter the association between MI and SD, the results remain unclear. The use of sedating medication did not significantly change the association between SD and MI in either males or females. Still, trends in the estimates were apparent. The lack of significant results could be the result of low precision, evident in the wide confidence intervals. In females, the Wald test for effect modification was borderline (p=0.51) and those taking sedating medication had a small non-significant association (OR=1.39), while the OR of SD in those not taking sedating medication (OR=2.93) was significantly increased. On the other hand, in males, the OR of SD in those taking sedating medication (OR=10.13) was substantially, but not significantly, higher than the OR in those not taking sedating medication (OR=4.70). Together, these results provide mixed evidence in terms of the influence of taking sedating medications on the relationship between MI and SD.

Finally, in line with the third hypothesis, suicidal ideation and attempt were significantly and positively associated with SD, and the presence of MI influenced the magnitude of association. Estimated unadjusted ORs were significant for both suicide ideation and attempt at all three time periods. The significant association between suicidality and SD is consistent with previous research, showing that the risk of suicidal ideation and behaviour is increased by insomnia, nightmares and other sleep disorders (Bernert, Kim, Iwata, & Perlis, 2015; Pigeon et al., 2012). A temporal trend in the relationship between SD and suicide ideation was also apparent, such the OR was highest for past week, followed by past year, and lifetime suicide ideation. However, this trend was not observed for suicide attempt. Lastly, for all available estimates, MI appeared to positively confound the associations, meaning that the presence of MI increased the association between suicidality and SD. This provides evidence that both MI and SD are also positively associated with suicide ideation and behaviour, and importantly, the presence of MI and SD together increase the odds of suicidality even further.

3.4.1 Limitations

This study was a cross-sectional design; therefore, causality cannot be inferred for any of the associations assessed. It is unclear whether the presence of SD leads to MI or whether the occurrence of MI causes SD. Likewise, the temporality between MI, SD and other factors considered, medication and suicidality, is also unclear. Nevertheless, this study shows that there is a strong relationship between MI and SD that warrants further study.

The measurement of MI in this survey relies on a single subjective question about the frequency of sudden mood changes extracted from the SCID-II. As detailed in Chapter 2, the reliability and validity of this tool for classifying MI have not been evaluated, and the item does not capture MI in its entirety. Furthermore, a duration of 'several years or longer' may have led to some misclassification of participants if they have forgotten symptoms that occurred in the past. While this study represents a cautious estimate of MI, it is useful for creating a foundation for future research and generating hypotheses.

SD was measured using a retrospective assessment of problems with falling or staying asleep or sleeping more than usual during the past month, and included no information about the frequency or severity of symptoms. Some individuals may have responded affirmatively to having SD, even if they experienced only a single or a few nights of SD or if the SD was minor. In this case, an otherwise 'good sleeper' may have been misclassified as having SD. This non-specificity of the measure may have led to an overestimate of the frequency of SD. In fact, previous epidemiological research has typically found the prevalence to be slightly lower, approximately 32–36% versus 43% in this study (Kerkhof, 2017; Roth et al., 2006; Stein et al., 2008).

Comparing MI and SD occurring over different time periods might also be considered a limitation. While the MI item specified a duration of the past several years or longer, SD included only the past month. Comparing MI based on a long time period with more proximal SD could be problematic if symptoms of MI are not currently present. In such cases, any relationship observed between MI and SD is likely due to an alternative

explanation. However, the different time periods for MI and SD is unlikely to result in large bias. The 'peak-end phenomenon', originally observed in pain research, suggests that individuals' aggregate judgments about their symptoms are often weighted by their most intense and recent experiences (Stone et al., 2000). This suggests that participants' evaluations of their experiences of MI and SD are likely to be based on similarly recent periods, and therefore, appropriate for comparison.

The influence of psychotropic medications on the association between MI and SD requires further clarification. The current study did not find an effect of medications with a high risk of sedation on the association between MI and SD, despite rather large differences in the ORs between sedating and non-sedating medications, particularly in males. Many psychotropic medications, including mood stabilisers, have profound effects on sleep. For example, a sample of young patients with anxiety, depression, and BD (n=146) were recruited to examine the relative effects of psychiatric symptoms and psychotropic medications on the sleep-wake cycle. After controlling for symptoms severity, researchers found that medications from all classes under study (antidepressants, anticonvulsants, and antipsychotics) significantly influenced sleep-wake times and/or sleep duration. There may be several reasons for the absence of a relationship in the current study. The associated estimates were imprecise (with wide confidence intervals), suggesting the inability to detect a significant difference even if one exists. In addition, the classification of medications into high risk of sedation and low risk of sedation could have been too broad. Narrowing the classifications to include medications with more specific effects on sleep may improve control. However, due to

insufficient power, narrower classifications were not possible. Moreover, some mood stabilising medications, such as anticonvulsants, were not assessed in this survey. In sum, it is likely that the influence of medications on the association between SD and MI were underestimated.

3.4.2 Implications for Future Research

MI and SD appear to be important in the risk and maintenance of psychiatric disorders, and strongly related irrespective of diagnosis. Several theories exist such that MI and SD share a common mechanistic origin. For example, Wulff has theorised that a range of psychopathologies, including MI, arise from dysregulation of sleep and circadian timings that destabilise physiology. She further posits that stabilisation of such disturbances to sleep and circadian rhythms may be an effective avenue for early intervention in all psychiatric and neurodegenerative diseases (Wulff et al., 2010). However, the proposed mechanism has not been fully elucidated. To aid in clarifying these potential mechanisms, future research should aim to study the association between MI and SD more rigorously.

Foremost, it remains indefinite whether SD is a cause or effect of MI. While it is proposed that pathophysiology associated with SD may also be the origin of MI, it is also suggested that MI promotes further SD, thereby propagating a mutually maintaining relationship. However, very few studies have examined both MI and SD prospectively. More work is needed to determine the temporality between MI and sleep and SD, which is a prerequisite for establishing causality.

Furthermore, it is unclear whether MI and SD are universal processes or if they are unique to specific mental illnesses. Based on these data, it appears that the relationship between MI and SD is present regardless of diagnosis. Much of the existing research on the association between MI and MI has be confined to small studies of specific psychiatric disorders. To better understand MI and SD as possible transdiagnostic factors, more research is needed in larger representative samples of persons with a range of disorders as well as individuals without mental illness.

In addition, it is unclear which aspects of SD are most strongly tied to MI. Sleep is closely linked to circadian rhythm. Although both have been implicated in mental illness, SD and circadian rhythm disturbance are two different processes. Apparent differences between disorders may arise from slight differences in the underlying mechanisms (A. G. Harvey, 2008a). Future research should investigate the relative contributions of SD and circadian rhythm in relation to MI, as well as their interactions with other factors such as age and gender, to better understand disorder-specific mechanisms.

Finally, if MI and sleep and circadian rhythm disturbances (SCRD) are transdiagnostic processes, then their treatment may have widespread public health implications. SCRD may be a particularly modifiable risk factor for psychiatric illness, and therefore a worthwhile target for treatment. Transdiagnostic therapies may be advantageous for at least three reasons. First, a single treatment protocol may be effective in a wide range of disorders. Second, psychiatric disorders are often comorbid, and treatment of a co-

occurring mechanism may simultaneously treat symptoms of each disorder. Third, advances in relation to one illness may propagate knowledge and treatment of other illnesses. If MI and SD are bi-directionally related as proposed, then treating SD should also alleviate symptoms of MI. Equally, both MI and SD have independently been associated with poorer functional outcomes in several disorders, therefore treatment of SCRD may also improve functioning. Future research should aim to develop transdiagnostic sleep therapies, and to evaluate their effectiveness in a wide range of disorders.

3.5 Conclusion

The results of this study suggest that MI and SD are common in the general population, and closely linked. The association between MI and SD appears to transcend diagnostic boundaries. Suicide ideation and behaviour may represent potential complications of MI and SD. SD represents a modifiable risk factor and potentially salient transdiagnostic therapeutic target for a wide range of mental disorders. Further work is needed to examine the association between MI and SD more rigorously. The emergence of digital health introduces new opportunities to study the association on an epidemiological scale, with the accuracy of deep phenotyping.

Chapter Four: Clinical and Social Associations with Mood Instability and Sleep Disturbance

4.1 Introduction

MI and SD are common in many mental disorders and in the population. Among a sample of patients referred to one of two community mental health teams in Derby City (*n*=421), the first and third most common mood symptoms reported by patients were MI (83%) and SD (70%), respectively (Gilbert et al., 2005). In Chapter 3 it was observed that MI and SD are also prevalent in the general population, irrespective of mental health status. MI was present in approximately 15% of the population, while SD during the past month was reported by approximately 43% of individuals.

MI and SD are also independently associated with poor health. In the general population, MI is associated with increased suicidal ideation, independent of neuroticism and a range of psychiatric disorders and socio-demographic variables (Marwaha, Parsons, & Broome, 2013). In a large clinical sample of patients with a psychotic, affective or personality disorder, MI was associated with significantly more frequent and longer hospitalisation and more prescriptions of mood stabilising medications (Patel et al., 2015). MI is also considered a core feature of BD and is associated with a more severe illness course and poorer long-term clinical and functional outcomes (O'Donnell et al., 2018; Strejilevich et al., 2013). Importantly, evidence suggests that MI is not only a symptom of mental illness, but may also be involved in the origins of several psychiatric

disorders, including BD (Howes et al., 2011), depression (Marwaha et al., 2015), and psychosis (Marwaha, Broome, et al., 2014).

There is also extensive evidence for the negative effects of SD, both physical and mental. SD has been associated with increased symptom severity in BD (Gruber et al., 2009a), attention deficit hyperactivity disorder (Wynchank et al., 2018), and psychosis (Waters et al., 2010). BD patients with SD also show poorer functioning and quality of life relative to those without SD (Gruber et al., 2009a). Adding to this, SD in the general population has been associated with suicidal ideation and behaviour (see Chapter 3), impaired cognition (Kyle et al., 2017), loss of productivity (Rosekind et al., 2010), cardiovascular disease (Michal et al., 2014), cancer risk (Schernhammer et al., 2001), diabetes risk (Leng et al., 2016), and mortality (Cappuccio, D'Elia, et al., 2010; Kripke, Garfinkel, Wingard, Klauber, & Marler, 2002).

Given their high frequency and evident impact on health and well-being, MI and SD may be responsible for a considerable portion of the burden attributable to mental illness. Although MI and SD are shown to be independently related to negative outcomes, little is known about the effect of co-occurring MI and SD in relation to health and social functioning. A main strength of the APMS and other large population surveys is the capability to study a wide range of possible health and social factors in the population.

4.1.1 Aim

The aim of this study was to examine the association of MI and SD independently and together, with possible health and social covariates in the following domains:

(a) General health;

(b) Education, employment and income;

(c) Difficulties with activities of daily living;

(d) Diagnosed health conditions;

(e) Mental health services use; and

(f) Cognitive functioning.

4.1.2 Hypotheses

(a) Persons reporting MI and SD, alone or together, will have poorer health and social functioning than persons without either MI or SD.

(b) Co-occurring MI and SD will be associated with poorer health and social functioning than either symptom alone.

4.2 Methods

Data were from the APMS 2007. Details about the survey, sampling, and weighting procedures are provided in Chapter 3.

4.2.1 Measures

The primary exposures of interest were MI and SD (see Chapter 3). Additional social and health covariates assessed in the current study are described in Table 4.1.

Table 4.1 Measurement details of social and health covariates.

Variable	Measurement	Tool
Body mass index	Calculated from self-reported height and weight (kg/m^2).	
Annual gross personal income	Annual personal income before taxes.	
General health	'How is your health in general?'	SF-12
Health limits for moderate activities	'Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?'	SF-12
Health limits for social activities	'During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends or relatives, etc.)?'	SF-12
Self-rated happiness	'Taking all things together, how would you say you are these days? Would you say you're very happy, fairly happy, or not too happy these days?'	SF-12
Work in the past 7 days	Did paid work in the past 7 days.	
Activities of daily living	Self-reported difficulty with personal care, getting out and about or using transport, medical care, household activities, practical activities, paperwork or money management.	
Diagnosed health conditions	Any health conditions (from a list) that they ever had since the age of 16, present in the last 12 months, and diagnosed by a doctor.	
Mental health service use	Outpatient visits and inpatient stays, during the past 3 months for mental, nervous or emotional health problem.	
Cognitive functioning	A measure of premorbid intelligence for use in neuropsychiatric research comprised of 50 written English words with irregular spellings. A total score is produced by summing the number of correctly pronounced words. To permit estimation of an OR, a binary variable was created using the median of the sample–29 or below and 30 or above. The questionnaire was completed by all respondents whose first language was English.	NART

[a] Standardised questionnaires only; SF-12=Short Form 12 Health Survey; NART=National Adult Reading Test.

4.2.2 Statistical Analysis

Analyses were carried out in STATA 15 (StataCorp, 2017). Odds ratios (OR) and standard errors were calculated using logistic regression. Subjects were grouped based on whether they experienced (1) concurrent MI and SD; (2) MI and no SD (MI-only); (3) SD and no MI (SD-only); or (4) neither MI nor SD. Specifically, the odds of selected covariates in each study group (MI and SD, MI-only, SD-only) versus the common reference group (no MI or SD) were calculated. For each OR, additive and multiplicative interactions of ORs between MI and SD were also assessed. Multiplicative interactions were estimated using logistic regression with the addition of an interaction term. Additive interactions were estimated as the relative excess risk due to interaction on the odds ratio scale ($RERI_{OR}=OR_{MI\&SD}-OR_{MI}-OR_{SD}+1$; VanderWeele, 2015). All analyses were weighted as described in Chapter 3.

The Benjamini-Hochberg procedure was used to control the false discovery rate (expected proportion of Type I errors), which is increased with multiple comparisons (Benjamini & Hochberg, 1995). In this procedure, rather than adjusting the p-values, Benjamini-Hochberg critical values are produced. This procedure consisted of four main steps: (a) The individual *p*-values for all tests were ranked in ascending order; (b) Ranks were assigned to the *p*-values (the lowest is 1, the second lowest is 2, and so on); (c) The Benjamini-Hochberg critical value associated with each rank was calculated as $(i/m)*Q$ where i is the rank, m is the total number of comparisons, and Q is the false discovery rate; and (d) Each *p*-value was compared with its associated Benjamini-Hochberg

critical value. The largest rank for which the *p*-value is less than the critical value was considered significant, and all *p*-values with a lower rank were also significant–even if they were not less than the Benjamini-Hochberg critical value. The false discovery rate, *Q*, was set at 0.05.

4.3 Results

Few participants (<1%) declined to answer the items about MI and SD. Of the remaining sample (*n*=7,321), 10.2% (*n*=750) reported both MI and SD, 4.4% (*n*=324) reported MI-only, 32.1% (*n*=2,352) reported SD-only, and 53.2% (*n*=3,895) reported neither MI nor SD.

4.3.1 General Health

The ORs of selected general health outcomes in the MI and SD, MI-only, and SD-only study groups compared with the reference group without MI or SD are presented in Table 4.2. Particularly strong associations were observed for perceived happiness and self-reported mental and physical health limits for social activities. Males and females in all three study groups showed significantly decreased odds of being very or fairly happy these days, and significantly increased odds of limits for social activities some, a good bit, most, or all of the time. Similar associations were significant for males and females, with the exception of being overweight or obese. In females, MI and SD and SD-only were associated with significantly increased odds of being overweight or obese, while in males having MI-only was associated with significantly decreased odds of being overweight or obese, and no association was found for MI and SD or SD-only.

Table 4.2 General health: Odds ratios with standard errors comparing selected covariates between three study groups versus the reference group without mood instability or sleep disturbance, by gender.

	Male			Female		
	OR	**SE**	***p***	**OR**	**SE**	***p***
Overweight or obese[a]						
MI and SD	0.86	0.12	0.338	1.32	0.17	0.013*
MI-only	0.52	0.12	0.005*	1.10	0.20	0.579
SD-only	0.92	0.09	0.390	1.25	0.10	0.004*
no MI or SD	1.00			1.00		
Current smoker						
MI and SD	3.05	0.46	<0.001*	2.04	0.28	<0.001*
MI-only	2.31	0.56	0.001*	1.64	0.29	0.006*
SD-only	1.24	0.13	0.039	1.02	0.10	0.812
no MI or SD	1.00			1.00		
Excellent, very good or good perceived general health						
MI and SD	0.24	0.04	<0.001*	0.25	0.03	<0.001*
MI-only	1.03	0.29	0.921	0.66	0.14	0.049
SD-only	0.67	0.04	<0.001*	0.38	0.04	<0.001*
no MI or SD	1.00			1.00		
Health limits for moderate activities						
MI and SD	2.77	0.49	<0.001*	2.02	0.26	<0.001*
MI-only	1.25	0.41	0.499	1.15	0.26	0.535
SD-only	2.47	0.26	<0.001*	2.63	0.23	<0.001*
no MI or SD	1.00			1.00		
Health limits for social activities some, a good bit, most, or all of the time						
MI and SD	9.95	1.65	<0.001*	5.66	0.74	<0.001*
MI-only	3.56	0.96	<0.001*	2.05	0.38	<0.001*
SD-only	3.31	0.38	<0.001*	2.86	0.26	<0.001*
no MI or SD	1.00			1.00		
Very or fairly happy these days						
MI and SD	0.06	0.01	<0.001*	0.08	0.01	<0.001*
MI-only	0.19	0.07	<0.001*	0.20	0.05	<0.001*
SD-only	0.22	0.04	<0.001*	0.24	0.04	<0.001*
no MI or SD	1.00			1.00		

[a] Overweight or obese=body mass index >25 kg/m^2; * Indicates significant in relation to Benjamini-Hochberg critical value.

4.3.2 Employment, Education, and Income

Comparisons of MI and SD, MI-only, and SD-only versus no MI or SD for selected employment, education and income variables are presented in Table 4.3. Having MI and SD or SD-only was associated with significantly increased odds of an annual gross personal income in the lowest quintile (<£10,400) for both males and females. Study group was not related to being in full-time employment, however, having MI and SD and SD-only was associated with significantly decreased odds of having done paid work in the previous seven days. In females, having MI and SD and SD-only were associated with significantly decreased odds of having a degree, while the association was only significant for males with MI-only.

Table 4.3 Employment, education and income: Odds ratios with standard errors comparing selected covariates between three study groups versus the reference group without mood instability or sleep disturbance, by gender.

	Male			Female		
	OR	**SE**	***p***	**OR**	**SE**	***p***
Gross personal income <£10,400						
MI and SD	2.54	0.43	<0.001*	1.55	0.19	<0.001*
MI-only	1.41	0.36	0.180	1.16	0.20	0.402
SD-only	1.54	0.16	<0.001*	1.23	0.09	0.007*
no MI or SD	1.00			1.00		
Highest educational qualification, degree						
MI and SD	0.69	0.15	0.096	0.59	0.10	0.001*
MI-only	0.29	0.11	0.001*	0.93	0.20	0.717
SD-only	0.86	0.10	0.217	0.75	0.08	0.005*
no MI or SD	1.00			1.00		
Did paid work in past 7 days						
MI and SD	0.34	0.05	<0.001*	0.66	0.08	<0.001*
MI-only	1.20	0.34	0.522	1.23	0.22	0.252
SD-only	0.5	0.06	<0.001*	0.78	0.07	0.003*
no MI or SD	1.00			1.00		
Full-time employment[a]						
MI and SD	1.01	0.28	0.966	1.00	0.12	0.992
MI-only	0.70	0.25	0.317	0.70	0.12	0.036
SD-only	0.95	0.14	0.747	0.92	0.08	0.341
no MI or SD	1.00			1.00		

[a] Excludes respondents over 70 years of age; * Indicates significant in relation to Benjamini-Hochberg critical value.

4.3.3 Activities of Daily Living

Associations between study group and activities of daily living are presented in Table 4.4. Having MI and SD and SD-only versus neither MI nor SD were significantly associated with increased odds of difficulties with all activities of daily living for both genders. MI-only was associated with significantly increased odds of difficulties with managing money (males and females) and paperwork (males only).

Table 4.4 Activities of daily living: Odds ratios with standard errors comparing selected covariates between three study groups versus the reference group without mood instability or sleep disturbance, by gender.

	Male			Female		
	OR	**SE**	***p***	**OR**	**SE**	***p***
Personal Care						
MI and SD	3.70	0.80	<0.001*	2.20	0.35	<0.001*
MI-only	1.06	0.47	0.905	1.52	0.43	0.139
SD-only	2.68	0.38	<0.001*	2.53	0.33	<0.001*
no MI or SD	1.00			1.00		
Getting out and about						
MI and SD	5.77	1.06	<0.001*	2.51	0.38	<0.001*
MI-only	1.75	0.73	0.176	1.06	0.29	0.821
SD-only	2.78	0.38	<0.001*	2.47	0.28	<0.001*
no MI or SD	1.00			1.00		
Medical care						
MI and SD	4.71	1.45	<0.001*	4.72	1.28	<0.001*
MI-only	2.57	1.42	0.088	1.16	0.62	0.782
SD-only	2.08	0.53	0.004*	2.55	0.62	<0.001*
no MI or SD	1.00			1.00		
Household activities						
MI and SD	6.26	1.19	<0.001*	2.79	0.40	<0.001*
MI-only	1.26	0.57	0.609	1.27	0.31	0.331
SD-only	3.02	0.42	<0.001*	2.71	0.27	<0.001*
no MI or SD	1.00			1.00		
Practical activities						
MI and SD	4.14	0.65	<0.001*	2.35	0.28	<0.001*
MI-only	1.44	0.42	0.223	1.12	0.20	0.533
SD-only	3.03	0.30	<0.001*	2.46	0.21	<0.001*
no MI or SD	1.00			1.00		
Paperwork						
MI and SD	5.51	0.95	<0.001*	4.39	0.65	<0.001*
MI-only	2.57	0.72	0.001*	1.25	0.34	0.409
SD-only	1.93	0.45	<0.001*	2.15	0.24	<0.001*
no MI or SD	1.00			1.00		
Managing money						
MI and SD	6.64	1.15	<0.001*	4.46	0.85	<0.001*
MI-only	4.26	1.26	<0.001*	2.41	0.64	0.001*
SD-only	2.42	0.38	<0.001*	1.46	0.27	0.038
no MI or SD	1.00			1.00		

* Indicates significant in relation to Benjamini-Hochberg critical value.

4.3.4 Diagnosed Health Conditions

The ORs for diagnosed health conditions in subjects with MI and SD, MI-only, and SD-only versus neither MI nor SD are shown in Table 4.5. In both males and females, ORs of mental health conditions were significantly increased for all three study groups. In males, particularly strong relationships were also found for epilepsy in all three study groups, and liver problems and migraines in MI and SD. In females, associations were particularly strong for incontinence and bladder problems in MI and SD and SD-only, and infectious disease in MI and SD.

Table 4.5 Diagnosed Health Conditions: Odds ratios with standard errors comparing selected covariates between three study groups versus the reference group without mood instability or sleep disturbance, by gender.

	Male			**Female**		
	OR	**SE**	***p***	**OR**	**SE**	***p***
Cancer						
MI and SD	1.36	0.79	0.595	1.12	0.56	0.825
MI-only	—	—	—	—	—	—
SD-only	2.50	0.73	<0.001*	2.58	0.91	0.008*
no MI or SD	1.00			1.00		
Diabetes						
MI and SD	0.28	0.13	0.007*	0.91	0.29	0.761
MI-only	0.40	0.23	0.109	1.15	0.45	0.731
SD-only	1.28	0.23	0.167	1.88	0.36	0.001*
no MI or SD	1.00			1.00		
Epilepsy/fits						
MI and SD	12.30	10.44	0.003*	2.12	1.52	0.300
MI-only	14.80	15.22	0.009*	4.79	3.36	0.027
SD-only	7.45	5.93	0.012*	1.32	0.70	0.596
no MI or SD	1.00			1.00		
Migraine/frequent headaches						
MI and SD	3.04	0.86	<0.001*	3.32	0.47	<0.001*
MI-only	1.76	0.89	0.270	1.81	0.45	0.018
SD-only	1.66	0.35	0.015	1.70	0.24	<0.001*
no MI or SD	1.00			1.00		
Anxiety/ depression/ other mental health issues						
MI and SD	21.45	4.84	<0.001*	10.10	1.43	<0.001*
MI-only	5.50	2.23	<0.001*	4.88	1.03	<0.001*
SD-only	3.27	0.75	<0.001*	2.31	0.31	<0.001*
no MI or SD	1.00			1.00		
Cataracts/eyesight problems						
MI and SD	0.91	0.19	0.666	1.08	0.18	0.670
MI-only	0.59	0.22	0.164	0.91	0.22	0.716
SD-only	0.93	0.11	0.540	1.43	0.13	<0.001*
no MI or SD	1.00			1.00		
Ear/hearing problems						
MI and SD	1.00	0.25	0.999	1.65	0.36	0.021
MI-only	1.72	0.60	0.122	0.79	0.29	0.522
SD-only	1.75	0.25	<0.001*	1.64	0.24	0.001*
no MI or SD	1.00			1.00		

	Male			Female		
	OR	**SE**	***p***	**OR**	**SE**	***p***
Cardiovascular						
MI and SD	0.80	0.16	0.256	0.84	0.12	0.228
MI-only	0.81	0.24	0.479	0.70	0.16	0.128
SD-only	1.54	0.17	<0.001*	1.51	0.13	<0.001*
no MI or SD	1.00			1.00		
Bronchitis/emphysema						
MI and SD	2.74	0.99	0.006*	1.62	0.53	0.135
MI-only	1.20	0.90	0.807	0.15	0.16	0.072
SD-only	2.03	0.55	0.009*	2.15	0.51	0.001*
no MI or SD	1.00			1.00		
Asthma						
MI and SD	2.10	0.55	0.004*	2.53	0.42	<0.001*
MI-only	0.70	0.34	0.462	2.02	0.63	0.024
SD-only	1.34	0.22	0.079	1.87	0.25	<0.001*
no MI or SD	1.00			1.00		
Allergy						
MI and SD	1.17	0.38	0.620	1.66	0.29	0.005*
MI-only	0.90	0.45	0.827	0.77	0.23	0.391
SD-only	1.40	0.26	0.072	1.20	0.15	0.152
no MI or SD	1.00			1.00		
Stomach ulcer/other digestive problems						
MI and SD	2.19	0.59	0.004*	2.25	0.45	<0.001*
MI-only	1.92	0.80	0.119	2.25	0.62	0.003*
SD-only	1.56	0.30	0.020*	2.04	0.33	<0.001*
no MI or SD	1.00			1.00		
Liver problems						
MI and SD	3.97	1.69	0.001*	4.10	2.69	0.032
MI-only	1.60	1.67	0.651	2.81	2.59	0.264
SD-only	2.03	0.76	0.061	3.44	2.14	0.048
no MI or SD	1.00			1.00		
Bowel/colon problems						
MI and SD	2.76	0.80	0.001*	2.52	0.50	<0.001*
MI-only	0.34	0.35	0.292	1.56	0.47	0.145
SD-only	2.38	0.51	<0.001*	2.29	0.35	<0.001*
no MI or SD	1.00			1.00		
Incontinence/bladder problems						
MI and SD	0.75	0.32	0.494	3.89	1.03	<0.001*
MI-only	0.74	0.54	0.677	2.99	1.15	0.005*
SD-only	2.16	0.42	<0.001*	2.80	0.60	<0.001*
no MI or SD	1.00			1.00		

	Male			Female		
	OR	**SE**	***p***	**OR**	**SE**	***p***
Arthritis						
MI and SD	1.28	0.26	0.245	1.43	0.23	0.026
MI-only	0.80	0.30	0.547	0.94	0.23	0.797
SD-only	2.01	0.24	<0.001*	2.20	0.23	<0.001*
no MI or SD	1.00			1.00		
Bone/back/joint/muscle problems						
MI and SD	1.99	0.32	<0.001*	1.88	0.24	<0.001*
MI-only	1.66	0.45	0.062	1.06	0.22	0.777
SD-only	1.77	1.19	<0.001*	1.81	0.16	<0.001*
no MI or SD	1.00			1.00		
Infectious disease						
MI and SD	3.62	3.15	0.142	6.92	3.88	0.001*
MI-only	—	—	—	—	—	—
SD-only	0.59	0.51	0.542	1.85	0.97	0.240
no MI or SD	1.00			1.00		
Skin problems						
MI and SD	1.47	0.36	0.112	2.12	0.36	<0.001*
MI-only	0.71	0.32	0.446	1.29	0.32	0.303
SD-only	1.66	0.27	0.002*	1.62	0.20	<0.001*
no MI or SD	1.00			1.00		

— Insufficient sample size for estimation; * Indicates significant in relation to Benjamini-Hochberg critical value.

4.3.5 Use of Mental Health Services

Table 4.6 shows the relationships between study group and use of mental health services. ORs were significantly increased for MI and SD for all types of mental health service use that were examined. MI-only was associated with lifetime hospital admission for males and females and visit to GP in the last 2 weeks for females.

Table 4.6 Mental health service use: Odds ratios with standard errors comparing selected covariates between three study groups versus the reference group without mood instability or sleep disturbance, by gender.

	Male			Female		
	OR	**SE**	***p***	**OR**	**SE**	***p***
Outpatient stay last quarter, mental health						
MI and SD	22.81	12.81	<0.001*	15.20	8.63	<0.001*
MI-only	—	—	—	6.62	5.01	0.013
SD-only	4.05	2.54	0.026	1.27	0.82	0.712
no MI or SD	1.00			1.00		
Spoken with GP last 2 weeks, mental health						
MI and SD	40.78	16.61	<0.001*	10.91	3.34	<0.001*
MI-only	16.14	9.82	<0.001*	3.44	1.67	0.012
SD-only	5.71	2.44	<0.001*	3.57	0.99	<0.001*
no MI or SD	1.00			1.00		
Admitted to hospital ever, mental health						
MI and SD	6.58	2.47	<0.001*	5.72	1.58	<0.001*
MI-only	6.09	3.16	0.001*	5.77	2.30	<0.001*
SD-only	1.43	0.52	0.318	2.49	0.69	0.001*
no MI or SD	1.00			1.00		

— Insufficient sample size for estimation; * Indicates significant in relation to Benjamini-Hochberg critical value.

4.3.6 Cognitive Functioning

Table 4.7 displays the ORs of scoring below the median (30) on the NART. The odds of scoring below the median were significantly increased for males and females with MI and SD and MI-only but not significantly associated with SD-only.

Table 4.7 Cognitive Functioning: Odds ratios with standard errors comparing selected covariates between three study groups versus the reference group without mood instability or sleep disturbance, by gender.

	Male			Female		
	OR	**SE**	***p***	**OR**	**SE**	***p***
NART<30[a]						
MI and SD	2.12	0.37	<0.001*	2.04	0.23	<0.001*
MI-only	1.96	0.51	0.010 *	1.71	0.30	0.003 *
SD-only	0.94	0.09	0.476	0.08	0.08	0.648
no MI or SD	1.00			1.00		

[a] Median score of the total sample; * Indicates significant in relation to Benjamini-Hochberg critical value.

4.3.7 Additive and Multiplicative Interactions

Additive and multiplicative interactions were assessed for MI and SD on each social and health covariate. Among females, significant positive additive interactions were observed for health limits for social activities (RERI=2.43, SE=0.69, $p<0.001$), difficulties with activities of daily living including managing money (RERI=2.90, SE=4.64, $p<0.001$) and paperwork (RERI=1.69, SE=0.52, $p=0.001$), and diagnosed mental health conditions (RERI=4.64, SE=1.30, $p<0.001$). Among males, significant positive additive interactions were observed for health limits for social activities (RERI=5.68, SE=1.75, $p=0.001$), and diagnosed mental health conditions (RERI=14.80, SE=4.11, $p<0.001$). Significant negative additive interactions were also observed for self-reported happiness in females (RERI=0.62, SE=0.07, $p<0.001$) and males (RERI=0.64, SE=0.08, $p<0.001$).

4.4 Discussion

This study adds to existing literature providing evidence for strong associations between each of MI and SD and poorer health and social functioning. It also extends current evidence by showing that concurrent MI and SD may be associated with greater dysfunction than either factor alone. A primary strength of this study is the use of a large epidemiological sample. The APMS was designed, among other objectives, to collect data on potential risk and protective factors of mental illness (National Centre for Social Research and University of Leicester, January 2011). Therefore, these data are well designed to assess health and social covariates. In addition, studies of MI are often conducted in relatively small cohorts of patients with specific psychiatric diagnoses, and few studies have examined MI and SD concurrently. These data permit the examination of MI and SD irrespective of diagnostic status or engagement with health services.

This study provides evidence that MI and SD frequently occur together. Approximately 16% of the sample reported both MI and SD, and SD-only was substantially more frequent (38%) than MI-only (8%). These relative frequencies are consistent with the hypothesis that mood disturbance emerges from abnormalities in neural and endocrine pathways involved in the regulation of sleep and circadian rhythms (Wulff et al., 2010). There is considerable variability in the manifestation of abnormal sleep in the population, and the pathways underlying these differences may also produce differential outcomes.

As expected, all three study groups–MI-only, SD-only, and MI and SD together–were associated with poorer health and social functioning in a wide range of domains compared to the reference group with neither MI nor SD. Concurrent MI and SD showed the strongest associations, relative to MI-only and SD-only. Particularly strong associations were apparent for self-reported happiness, difficulties with activities of daily living, mental health services use, and diagnosed mental health conditions.

A few additive interactions of the ORs for MI and SD were also observed. In both genders, significant positive additive interactions were observed for health limits for social activities and diagnosed mental health conditions, and negative additive interactions were observed for self-reported happiness. In females, positive additive interactions were also significant for difficulties with activities of daily living including managing money and paperwork. No Significant multiplicative interactions were observed.

An interaction between two exposures (in this case MI and SD) occurs when the observed effect of one exposure depends on the presence or absence of the second exposure. Whether an interaction is observed or not (and whether it is a positive or negative interaction) depends on if it is examined on an additive or multiplicative scale. An interaction on an *additive* scale indicates that the combined effect of two exposures departs from the *sum* of the individual effects of the two exposures. An interaction on a *multiplicative* scale indicates that the combined effect of the two exposures departs from the *product* of the individual effects. An interaction is *positive* if the combined effect of

the two exposures is *larger* than the sum (or product) of the individual effects, while a *negative* interaction indicates that combined effect is *smaller* than the sum (or product) of the individual effects. Additive interactions are assessed using risk differences, while multiplicative interactions are assessed based on risk ratios (VanderWeele, 2015).

Historically, it has been debated which scale is the most appropriate or meaningful to assess an interaction (Blot and Day, 1979; Rothman et al., 1980; Saracci, 1980). It is suggested that when interactions are assessed, both additive and multiplicative interactions should be reported (VanderWeele, 2015). Generally, it is believed that multiplicative interactions are more useful for suggesting etiological associations, while additive interactions are said to have public health importance. Interactions on the additive scale permit discrimination of effects in different subgroups (Rothman et al., 1980). In this study, MI and SD showed a significant positive interaction effect on the presence of diagnosed mental disorders for males (and females); the estimated excess risk due to the interaction was 14.80. In a public health framework, this is useful because it indicates that, for example, removal of SD (or MI) should result in a reduction of mental disorders in the population. Furthermore, the presence of a positive interaction, implies that the public health consequence of removing one exposure will be larger in those exposed to the other factor. That is to say, removing SD will have a larger effect on mental illness in those with MI than those without MI. On the other hand, the presence of a negative additive interaction for self-reported happiness may indicate that removing SD from the population will have a larger impact in those without MI than those with MI in terms of perceived happiness.

Interestingly, a greater number of significant ORs and stronger associations were observed for SD-only than for the MI-only group, particularly for paid work, annual income, and difficulties with activities of daily living. However, MI-only did show some associations not present for SD-only, such as utilisation of mental health services, difficulties with managing money, and cognitive functioning. The stronger and more widespread associations of health and social covariates with SD than with MI, also appears to fit within Wulff's disease model (Wulff et al., 2010). If MI represents only one of many possible complications of SD, it may be more commonly associated with only a subset of outcomes that involve similar pathways.

There were some gender differences in terms of the types and strengths of associations present in males and females. Males with MI and/or SD appeared to have stronger associations than females for several domains, such as difficulties with activities of daily living and use of mental health services. ORs between MI and SD and some diagnosed health conditions also appeared to depend on gender. For example, strong significant associations with epilepsy and liver problems were present for males, while significant associations were found for infectious disease, skin problems, and incontinence or bladder problems in females. Some differences in associations, such as these, may be partly explained by known differences in gender distributions of various health problems. For example, excessive alcohol use and related adverse consequences are more frequent in males than females (Wilsnack et al., 2000), and males are more likely to die of alcohol-related cirrhosis of the liver (Leon & McCambridge, 2006). Likewise,

eczema is closely linked with increased symptoms of depression and anxiety, particularly in females (Marron et al., 2018).

This study further supports the connection between mental and physical well-being. MI and SD were related to a wide range of somatic, cognitive, and psychiatric disturbances. Connections between the mind and body have been extensively documented, often illustrated by high rates of comorbidity between psychiatric and other medical diagnoses. Comorbidities of gastrointestinal problems with depression (Hochstrasser, 1996), BD with metabolic syndrome (McIntyre, 2010), and excess mortality due to somatic causes in psychotic disorders (Laursen, 2011) are only a few examples. These results further highlight the need for physical complaints to be assessed in psychiatric patients and psychiatric symptoms in patients with other medical conditions in order to mitigate the occurrence and consequences of multiple comorbidities. In particular, the strong associations with MI, SD, and poor health observed in this study suggest that MI and SD should not only be routinely assessed during clinical consultations, but that they should also be taken in earnest and treated promptly.

4.4.1 Limitations

Some limitations of this study are acknowledged. Weaknesses in the measurements of MI and SD and have been detailed in Chapter 3. In addition, this study was founded on an assumption that MI and SD represent exposures to the health and social outcomes. However, these data cannot imply causality due to the cross-sectional survey design. For example, based on these data, it cannot be determined whether MI and SD *cause* specific

health conditions or if the health conditions lead to MI and SD. Some of the factors assessed are well known determinants of health and may be both a risk factor for and result of mental illness.

The interaction analyses are also limited by the absence of temporality. While MI and SD were treated as exposures, it is not clear based on these data whether they preceded the health and social outcome of interest or not. Assessments of interaction effects aid in the analysis of causal relationships and are usually measured in terms of RERI. In cases where risk ratios are inappropriate due to a lack of clear directionality–like this study–ORs may be directly substituted into the equation. This requires caution, however, because ORs approximate risk ratios only when the outcome is rare, and the larger the baseline risk, the more the two measures diverge. Since some of the outcome measures may not be rare, interpretations of the interactions in terms of risk should be made with care.

In addition, this study did not account for the effect of some potentially important covariates, which may influence some of the associations. For example, many social and health outcomes may vary with age. Persons of older age may have more difficulties with some activities of daily living such as getting out and about or housework or they may be more likely to have age-related health problems such as cardiovascular conditions. The effect of confounding (shifting the estimated OR further away from or towards the null value of 1) by age may vary depending on the outcome of interest. Given the large number of associations examined, it was not feasible to also examine the

influences of potential confounders, however, it is recognised that this is an important aim for future research.

Finally, a large number of potential health and social covariates were examined, which may have resulted in some spurious relationships. The nature of the study involved selecting only a subset of potential outcomes associated with MI and SD. The presence of multiple comparisons can result in an increased type I error rate (probability of finding a relationship when one does not actually exist). However, all results were adjusted for an increased false discovery rate, and a stringent criteria of 5% was used. Therefore, concerns about the presence of significant results due to chance are minimal.

4.4.2 Directions for Future Research

The present study provides a broad foundation for future research. Several directions for future research have already been suggested in Chapter 3, including more rigorous examination of MI and SD in order to better elucidate their underlying mechanisms.

The current study includes no information about frequency or severity of MI and SD, which are important dimensions to consider in future research. Research needs to distinguish symptoms that are clinically significant from normal variations in experiences. While a great deal of research has gone into identifying these differences for sleep problems, there exists little evidence to distinguish clinically significant MI from lesser mood swings that may be part of a normal emotional experience. Further work should aim to identify such differences.

Several potentially important relationships have been observed in this study that warrant more detailed examination. Some relationships showed an interaction effect of MI and SD; however, it is important to distinguish mechanistic interaction from statistical interaction (Rothman et al., 1980). The mechanism by which psychiatric disturbances, like MI, and SD are connected and produced have not been fully elucidated, but Wulff (2009) suggests that there are four possibilities: (1) Psychiatric disturbances lead to SD by way of heightened arousal; (2) SD is concurrent with psychiatric disturbances due to shared neural circuitry and molecular pathways; (3) Certain individuals are predisposed to specific psychiatric disturbances due to abnormalities in neural circuits and molecular pathways; or (4) Social and environmental demands lead to SD, which in turn alters neural circuits and molecular pathways involved in psychiatric health (Wulff et al., 2009). None of these alone appear to be a sufficient explanation–it is more likely that they each play a role, which contributes to the large heterogeneity in SD and symptoms observed in different psychiatric diseases. Additional research, particularly that involving prospective data collection with deep phenotyping, is needed to clarify these processes and how they are linked, which may aid in the identification of possible etiological pathways and defining subgroups for treatment or prevention.

Interventions to treat and prevent MI and SD, even in the absence of psychiatric diagnosis, may also be a worthwhile area for future research. In terms of MI, several treatments have been developed for use in specific clinical populations, but to my knowledge, there are currently no known treatments of MI used at the community-level. SD has been long-recognised as a concern and several means for public health

intervention have been suggested. If SD is at the origin of many psychiatric disorders, then it may be particularly worthwhile target, as treatment of SD may not only improve sleep, but also alleviate or prevent downstream complications.

Due to increasing recognition of SD as a public health problem, population-level interventions for sleep are emerging. For example, Sleepio (www.sleepio.com), is a fully-automated, digital cognitive behavioural therapy for Insomnia (dCBT). The program is comprised of six sessions delivered weekly with behavioural, cognitive and educational components. The content is personalised based on the participant's baseline, adherence, and progression. Participants have access to their program history, an online community forum, and a digital library of information about sleep (Espie et al., 2012). This form of treatment has been shown to improve sleep and daytime functioning in both community and clinical populations. A randomised controlled trial of Sleepio versus treatment as usual at 26 UK universities found that Sleepio showed sustained reductions in insomnia, hallucinations, paranoia, and other psychological symptoms, superior to treatment as usual (Freeman et al., 2017). Another study, based on a sample of patients referred from a community-based psychological therapy group[k], showed marked improvements in depression and anxiety in patients who took part in dCBT (Luik et al., 2017). This suggests that sleep treatments, such as dCBT, can be used at the community-level as a cost-effective strategy to treat SD along with some psychiatric symptoms. Future research may aim to evaluate the effectiveness of the program for improving SD other than insomnia, in addition to MI. Further, given the strong links

[k] Patients referred to the study had poor sleep as well as symptoms of depression and anxiety.

with physical health, future research may see to assess improvement in physical health outcomes, and whether the effects are sustained long term.

4.5 Conclusion

This study shows that MI and SD are common in the general population and frequently occur together. The impacts of MI and SD are substantial and widespread, particularly in the domains of diagnosed mental and physical health conditions, use of mental health services, perceived health and happiness, and difficulties with daily activities. Importantly, the combined effect of MI and SD appears to be greater than either factor alone. Given the high frequency and apparent impact of MI and SD on functioning, further research is required to better understand their natures and correlates, and to determine the directionality of associations. As SD may be part of the origin of many of the relationships observed in this study, then it may be a particularly worthwhile target for community-level interventions. Some interventions have already been developed, such as dCBT for insomnia, which is able to reach many individuals and may be more accessible and less resource-intensive than traditional psychotherapies when carried out on a large-scale. More work is needed to examine the breadth of benefits from dCBT beyond insomnia, such as whether improvements are also seen in other mental health domains, like MI, as well as physical health outcomes.

Chapter Five: Mood Instability and Sleep Disturbance in Secondary Mental Health Care

5.1 Introduction

MI and SD are clinically important. Although part of the diagnostic criteria for only some conditions, they are present in a wide range of mental disorders and have been regarded individually as potential transdiagnostic processes in the origin and maintenance of mental illness (Aldao, 2016; A. G. Harvey, 2008a). MI and SD may be part of a set of symptoms that share a common physiological pathway, such as dysregulation of stress-related pathways, which transcend diagnostic boundaries (Gilbert, 2001). However, clinical evidence of the relationship between MI and SD is limited, and research has been mostly confined to small samples of specific mental disorders with limited generalisability.

In chapters 3 and 4, I examined the relationship between MI and SD in a representative sample of the general population in England. Results showed that MI and SD are closely linked and common in the general population, irrespective of mental illness. Furthermore, MI and SD were associated with extensive use of resources for mental health care, and their co-occurrence may be related to poorer health and social outcomes than either symptom alone.

To further investigate the relationship between MI and SD as transdiagnostic features within the clinical population, this study examines data from a large sample of electronic health records (EHRs) from secondary mental health care. EHRs contain a wealth of

clinical information, often recorded as text. Recently, novel natural language processing (NLP) approaches have been developed that enable efficient identification of clinical information from text within EHRs, thereby permitting the secondary analysis of large quantities of data not typically feasible by manual review. This study makes use such novel NLP approaches to study MI and SD in a large sample of individuals aged 16 to 65 years presenting to a secondary mental health care service.

5.2 Aims

The specific aims of this study were to:

(a) Examine the validity of NLP approaches for identifying selected clinical features–MI, SD, and prescribed medication–from text within EHRs.

(b) Describe the demographic and clinical features of persons with MI and/or SD documented within one month of presenting to secondary mental health services.

(c) Estimate the incidence density rates of clinical features within persons with MI-only, SD-only, and MI and SD relative to a common reference group of persons with neither symptom.

5.3 Methods

5.3.1 Data

Data from the EHRs of all individuals aged 16 to 65 years who presented to the Oxford Health NHS Foundation Trust (OHFT) between 31 December 2007 and 1 January 2016.

The date of first presentation to OHFT (study entry) was defined as the date of the patients' first clinical progress note. Study end for each participant was defined as the date of their most recent clinical progress note or 31 January 2018, whichever occurred first. Based on the assumption that patients hospitalised long-term are not representative of the clinical psychiatric population, individuals were excluded if they had a hospital duration greater than two standard deviations above the mean number of days in hospital for the total patient sample.

5.3.1.1 Oxford Health Foundation Trust

The Oxford Health NHS Foundation Trust (OHFT) provides comprehensive mental health care to a geographical catchment area of approximately 1.6 million residents in Oxfordshire, Buckinghamshire, Swindon, Wiltshire, Bath and North East Somerset. OHFT delivers care at multiple levels including community bases, hospitals, clinics and individuals' homes (https://www.oxfordhealth.nhs.uk/).

5.3.1.2 Clinical Research Interactive Search

Trust EHRs contain extensive information recorded by health care providers over the course of service provision to patients. Extensive information is documented within the EHR, such as patient details, diagnoses, clinical history, assessments of mental state and functioning, and care plans. Clinical Research Interactive Search (CRIS; https://crisnetwork.co.uk), is an information technology system developed at South London and Maudsley (SLaM) NHS Foundation Trust and King's College London with the National Institute for Health Research (NIHR). CRIS transforms the EHR system

into an accessible pseudo-anonymised database, consisting of structured (for example, numbers and dates) and unstructured text (for example, clinical progress notes and correspondence) data fields.

5.3.1.3 Natural Language Processing

Due to the large amount of unstructured data contained within EHRs, it is not often feasible to manually read and extract all relevant information from free text for secondary data analysis. The use of NLP techniques has permitted efficient and automatic processing of EHR data. In this study, NLP applications were used to extract information about MI, SD, and prescribed medications from EHRs.

5.3.2 Development of NLP Applications

The NLP methodologies were developed by SLaM in collaboration with University of Sheffield Department of Computer Science, and the details of their development have been published previously (Patel et al., 2015; Perera et al., 2016). The main NLP technique used was information extraction, whereby structured information is produced from unstructured or semi-structured text (Liu et al., 2013). This section describes the general processes involved in the development of the NLP applications used in the current study to derive the presence or absence of MI, SD, and prescribed medication.

Given the large volume of data contained within UK CRIS and the need to transfer these data securely to SLaM, only clinical progress notes and correspondence containing one

or more specific keywords–mood, affect, emotion, sleep, or insomnia–were extracted for processing through the NLP applications[l].

The NLP software package, TextHunter (R. G. Jackson; R. G. Jackson et al., 2014) was used to extract documentation of each target feature. Two primary methods of information extraction were used to develop the NLP applications. The first used support vector machines[m] to develop the MI and SD applications. The other was rule-based pattern matching of key concepts used to develop the medication application.

The development of applications that used support vector machines consisted of three general steps. First, keywords (sometimes called a 'bag of words') associated with each target feature are identified. Second, using the keywords, manual annotations (or labelling) of each target feature were performed in a random sample of sentences. Three sets of manually annotations were produced; a training set (for use in the machine learning stage), validation set (for use in refining the application, and testing set (for use in precision testing of the final application). Third, supervised machine learning with active learning was carried out on labelled and unlabelled data from the training set, from which the support vector machine learns the classification function. Lastly, precision testing was performed by comparing the classifications of the final application to the testing set of manual annotations.

[l] Including variable word suffixes, such as 'affective' or 'emotional'.
[m] A support vector machine is a supervised machine-learning technique, whereby algorithms that analyse data for classification are produced using statistical learning. For the current NLP applications, the occurrence of single words within a sentence were used to distinguish the various classes.

The development of the rule-based pattern matching application also involved three main steps. First, a random sample of sentences were manually annotated with simple linguistic information (for example, words or sentences). Second, keywords were used to identify sentences that possibly contained the target feature for information extraction. Third, a set of patterns (templates against which expressions can be matched) were run over the previously generated annotations to produce a final annotation with all information in a structured format.

The accuracy of the NLP applications was assessed by comparing the classification produced by the final applications to the manually annotated testing set. Given that the target feature may occur multiple times within the same document, the NLP applications were developed to maximise specificity in order to reduce the probability of false-positives. Thus, a minimum threshold for specificity was set for each NLP application. Additional details of the development of the NLP applications for MI, disturbed sleep, insomnia, and prescribed medications are available in Appendix C.

5.3.3 Measures

5.3.3.1 Mood instability

The MI application was comprised of three separate NLP applications to extract documentation of MI, affective instability, and emotional instability (jointly referred to as the MI application in this thesis). The ‘bag of words’ included frequently used combinations of mood, affect, instability and modifier terms such as dysfunction, instability, and lability.

5.3.3.2 Sleep Disturbance

SD was based on two separate NLP applications designed to identify the presence of disturbed sleep and insomnia. The disturbed sleep application is intended to identify documentation of problems with sleep, while the insomnia application extracted mentions of insomnia, more specifically.

5.3.3.3 Prescribed Medication

The medication application was designed to extract documentation of medications prescribed to the patient and the dose from free text. The application ignores medications that might be prescribed in the future (for example, a medication to be considered if the patients' condition worsens). The NLP application extracts the name of any medication identified within the text. For the current study, medications within the classes: antidepressants, antipsychotics, mood-stabilising antiepileptics, lithium, sedative-hypnotics, sympathomimetics, amphetamines, and sedating antihistamines were included.

5.3.3.4 Diagnosis

Diagnoses are recorded as ICD-10 codes and descriptions (World Health Organization, 1992) within structured fields. This study examines primary diagnoses of organic mental disorders (F00-F09), substance use disorders (F10-F19), schizophrenia and related (F20-F29), mood disorders (F30-F39), anxiety disorders (F40-F49), behavioural syndromes (F50, F52-F59), personality disorders (F60-F69), mental retardation (F70-F79),

disorders of psychological development (F80-F89), behavioural and emotional disorders with onset usually in childhood and adolescence (F90-F98), and unspecified mental disorders (F99). Given the specific interest in SD, sleep disorders were examined separately, including any sleep disorder (F51, G47), insomnia (F51.0, G47.0), hypersomnia (F51.1, G47.1), sleep-wake disorders (F51.2, G47.2), sleep apnoea (G47.3), narcolepsy and cataplexy (G47.4), and other/unspecified sleep disorders (F51.3-F51.9, G47.8-G47.9). Sub-classifications of mood disorders included BD or mania (F30-F31), unipolar depression (F32-F33), and other mood disorders (F34, F38, F39)[n].

5.3.3.5 Events

The frequency of contacts (events) with mental health services for each patient was identified from dates of clinical notes, diary and clinic appointments, and participation in group therapies. Events that were cancelled or scheduled in error were excluded. Missed appointments and appointments including staff only were included. Some patients had multiple appointments within the same day, in these cases, each appointment was included as a separate event.

5.3.3.6 Hospitalisation

The frequency and duration of hospitalisation were extracted based on hospital admission and discharge dates recorded in structured fields. Some individuals were in

[n] Mood disorder sub-classifications were mutually exclusive. For example, persons with unipolar depression must not have had any diagnosis of bipolar disorder or mania.

hospital at the time of study entry; in these instances, hospitalisation start dates were the date of study entry.

5.3.3.7 Health of the Nation Outcome Scale

The health of the Nation Outcome Scale (HoNOS) is an assessment tool used to measure the health and social functioning of people of working age with severe mental illness (Wing et al., 1998). HoNOS was developed by the Royal College of Psychiatrists Research Unit to provide a routine outcome measure for the NHS, and ratings from the HoNOS are used to assist with offering patients the care and interventions to meet their individual needs (NHS England, 2016). Twelve items are rated on a scale of 0 (no problem) to 4 (severe to very severe problem). Responses to twelve items can be summed for an overall measure of severity. A total score is produced by summing responses to individual items, with possible total scores ranging 0 to 48. To account for the presence of missing responses the individual items, an adjusted total score is calculated as 12*total score/number of responses. If more than 3 responses were missing from an assessment, it was omitted from the analysis.

5.3.4 Statistical Analysis

Data were analysed in R (R Development Core Team, 2017). The NLP applications were validated comparing manual classifications to those produced by the application. From all extracted clinical notes and attachments, a random sample of 100 documents were extracted. I reviewed all 100 documents manually and classified each feature (MI, disturbed sleep, insomnia, and psychotropic medication) as present or absent from the

document. Some documents contained more than one mention of a feature. If the feature was identified as present anywhere within the document, then the feature was classified as present. For the 100-document sample, the manual classifications were compared with the NLP classifications. Validation metrics consisted of sensitivity, specificity, positive predictive value, and negative predictive value (Appendix C).

For the main analysis, study groups were defined based on the presence or absence of MI and/or SD (MI-only, SD-only, MI and SD, no MI or SD). Prevalence estimates of MI and SD were calculated as proportions with 95% confidence intervals. Selected demographic and clinical features within each study group (MI-only, SD-only, MI and SD, no MI or SD) were described using estimates of frequencies, proportions, and means and standard deviations. Incidence density rates (IDRs) of selected clinical outcomes were estimated using approximation. Specifically, these were calculated as the incidence density of selected outcome each study group (MI-only, SD-only, MI and SD) versus that in the common referent (neither MI nor SD). The Bonferroni-Holm procedure was used to control the family-wise error rate, which is increased due to multiple comparisons (Holm, 1979).

In a follow-up analysis, patients were grouped according to whether they received a specified primary diagnosis (for example, any diagnosis, organic disorder or substance use disorder) within the first month of presenting to OHFT. Within diagnostic subgroups, the proportions of patients who presented with MI-only, SD-only, both MI

and SD, or neither symptom were calculated. These proportions were also examined among all individuals with a specified diagnosis during the study period.

5.4 Results

A total of 31912 patients aged 16 to 65 years presented to OHFT between 31 December 2007 and 1 January 2016. There were 521 patients with hospital durations greater than two standard deviations above the mean (*mean*=19.80, *sd*=120.12 days). After exclusion, the final sample included 31391 patients.

5.4.1 Validation of the NLP Outputs

The accuracy of the NLP applications in relation to manual annotation were estimated based on the presence or absence of each feature at the document level for a random sample of 100 documents. Table 5.1 summarises the estimated sensitivity, specificity, positive predictive value, and negative predictive value of each NLP application. Specificity was found to be better than sensitivity for all applications. Negative predictive values were higher than positive predictive values for the insomnia and sleep problems applications, whereas positive predictive values were higher for the MI and medication applications.

Table 5.1 Estimates of sensitivity, specificity, positive predictive value, and negative predictive value for each NLP classifier against manual annotation.

	Mood Instability		Disturbed Sleep		Insomnia		Medication	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Se	70.31	57.58–81.09	80.00	64.35–90.95	84.00	70.89–92.83	85.94	74.98–93.36
Sp	91.67	77.53–98.25	88.33	77.43–95.18	90.00	78.19–96.67	86.11	70.50–95.33
PPV	93.75	82.80–98.69	82.05	66.47–92.46	89.36	76.90–96.45	91.67	81.61–97.24
NPV	63.46	48.96–76.38	86.89	75.78–94.16	84.91	72.41–93.25	77.50	61.55–89.16

Se=sensitivity; Sp=specificity; PPV=positive predictive value; NPV=negative predictive value.

5.4.2 Prevalence of Mood Instability and Sleep Disturbance

The prevalence estimates for MI and SD documented within one month of presenting to OHFT are shown in Table 5.2. For MI, the overall prevalence was approximately 9.58% (95% CI: 9.25%–9.90%), and prevalence was higher in females than males and decreased with age. The overall prevalence of SD was approximately 26.26% (95% CI: 25.77–26.75). Prevalence of SD was higher in males than females and appeared to increase with age, except among the oldest age group for whom prevalence was lowest. The overall prevalence estimates of sleep problems and insomnia were 24.88% (95% CI: 24.40%–25.35%) and 4.04% (95% CI: 3.82%–4.25%), respectively. Both disturbed sleep and insomnia showed similar gender and age-specific trends in prevalence.

Table 5.2 Crude, gender-specific, and age-specific prevalence estimates for mood instability, sleep problems, insomnia, and combined sleep problems and insomnia.

		Mood Instability			Sleep Disturbance			Disturbed Sleep			Insomnia		
	N	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Crude	31391	3006	9.58	9.25-9.90	8243	26.26	25.77-26.75	7809	24.88	24.40-25.35	1267	4.04	3.82-4.25
Gender													
Female	17204	1700	9.88	9.44-10.33	4347	25.27	24.62-25.92	4139	24.06	23.42-24.70	639	3.71	3.43-4.00
Male	14134	1303	9.22	8.74-9.70	3884	27.48	26.74-28.22	3658	25.88	25.16-26.60	627	4.44	4.10-4.78
Age													
16–25	3029	340	11.22	10.10-12.35	743	24.53	23.00-26.06	701	23.14	21.64-24.64	114	3.76	3.09-4.44
26–35	9599	1004	10.46	9.85-11.07	2544	26.50	25.62-27.39	2408	25.09	24.22-25.95	385	4.01	3.62-4.40
36–45	8676	833	9.60	8.98-10.22	2380	27.43	26.49-28.37	2244	25.86	24.94-26.79	392	4.52	4.08-4.96
46–55	7085	675	9.53	8.84-10.21	2063	29.12	28.06-30.18	1965	27.73	26.69-28.78	293	4.14	3.67-4.60
56–65	3002	154	5.13	4.34-5.92	513	17.09	15.74-18.44	491	16.36	15.03-17.68	83	2.76	2.18-3.35

The frequencies of insomnia and disturbed sleep were cross-tabulated in order to more fully understand the relative classifications of disturbed sleep/insomnia and the implications of using a combined SD group. While 73.74% (*n*=23148) of patients were similarly classified as having neither sleep problems nor insomnia, 22.22% (*n*=6976) of patients with sleep problems did not have insomnia, 1.38% (*n*=434) of patients with insomnia did not have sleep problems, and only 2.65% (*n*=833) of patients had documentation of both insomnia and sleep problems within one month of presenting to OHFT.

5.4.3 Demographic and Clinical Features of the Sample at Baseline and 2-years Follow-up

For the remaining analyses, patients were grouped based on the presence of MI and/or SD documented within one month of presenting to OHFT. Of the total sample, 4.22% (*n*=1322) had MI-only, 20.94% (*n*=6559) had SD-only, 5.38% (*n*=1684) had MI and SD, and 69.69% (*n*=21,826) had neither MI nor SD.

Table 5.3 summarises selected demographic and clinical features of patients with MI-only, SD-only, MI and SD, and neither feature documented within one month of presenting to OHFT. SD-only had a higher proportion of males than females, while the remaining groups had higher proportion so females than males. Age distributions were similar across all groups. Patients with MI and SD were most often diagnosed with any psychiatric disorder (29.87%), particularly mood disorders (16.27%), substance use disorders (3.15%), personality disorders (4.63%), and schizophrenia and related

disorders (3.44%). Persons with MI-only showed the highest proportion of behavioural syndromes (1.89%), while individuals with SD-only had the highest proportion of anxiety disorders (5.50%). Individuals without either MI or SD had a considerably lower proportion of any psychiatric disorder (11.73%). Patients with both MI and SD were also most often prescribed any medication, and more frequently prescribed two or more medications. SD-only also showed higher proportion taking multiple medications, with a particularly high number of patients prescribed sedative-hypnotics (24.35%). Patients with neither MI nor SD were taking the fewest medications, with only 19.62% of patients prescribed a medication from any class. A higher proportion of patients with MI and SD were hospitalised within one month of presenting to OHFT compared with the other three groups. Approximately 24.23% of patients with MI and SD were hospitalised at least once within the first month of presenting to OHFT, followed by SD-only (8.54%), MI-only (6.66%) and no MI or SD (1.66%). The mean number of days spent in hospital and mean adjusted total HoNOS scores were similar across the four groups.

Table 5.3 Descriptive features of the sample with MI-only, SD-only, MI and SD, and no MI or SD within one month of presenting to OHFT.

Feature	1 Month (*N*=31391)							
	MI-only (*n*=1322)		SD-only (*n*=6559)		MI and SD (*n*=1684)		No MI or SD (*n*=21826)	
	n	%	n	%	n	%	n	%
Age								
16-25	164	12.41	567	8.64	176	10.45	2122	9.72
26-35	426	32.22	1966	29.97	578	34.32	6629	30.37
36-45	360	27.23	1907	29.07	473	28.09	5936	27.20
46-55	315	23.83	1703	25.96	360	21.38	4707	21.57
56-65	57	4.31	416	6.34	97	5.76	2432	11.14
Gender, female	761	57.56	3408	51.96	939	55.76	12096	55.42
Diagnosis								
Any	231	17.47	1460	22.26	503	29.87	2560	11.73
Organic	3	0.23	11	0.17	1	0.06	71	0.33
Substance use	24	1.82	143	2.18	53	3.15	166	0.76
Schizophrenia and related	29	2.19	208	3.17	58	3.44	470	2.15
Mood	90	6.81	719	10.96	274	16.27	919	4.21
Anxiety	48	3.63	361	5.50	88	5.23	484	2.22
Behavioural syndrome	25	1.89	83	1.27	19	1.13	346	1.59
Personality	37	2.80	120	1.83	78	4.63	254	1.16
Mental retardation	0	0.00	3	0.05	0	0.00	3	0.01
Developmental	3	0.23	5	0.08	2	0.12	32	0.15
Behavioural and emotional	4	0.30	9	0.14	2	0.12	43	0.20
Unspecified	3	0.23	22	0.34	12	0.71	61	0.28
Any sleep disorder	0	0.00	2	0.03	0	0.00	0	0.00
Medication								
1	283	21.41	1241	18.92	268	15.91	1990	9.12
2	208	15.73	1063	16.21	243	14.43	1171	5.37
3+	232	17.55	1944	29.64	836	49.64	1038	4.76
Any	724	54.77	4251	64.81	1347	79.99	4203	19.26
Antidepressant	475	35.93	3158	48.15	901	53.50	2973	13.62
Antipsychotic	255	19.29	1529	23.31	642	38.12	1395	6.39
Antiepileptic[a]	62	4.69	181	2.76	114	6.77	225	1.03
Sedative hypnotic	183	13.84	1597	24.35	673	39.96	912	4.18
Lithium	26	1.97	86	1.31	57	3.38	115	0.53
Sedating antihistamine	6	0.45	57	0.87	32	1.90	20	0.09
Sympathomimetic	3	0.23	21	0.32	7	0.42	42	0.19
Amphetamine	0	0.00	0	0.00	0	0.00	6	0.03
Events								
1	117	8.85	493	7.52	59	3.50	4694	21.51
2	159	12.03	658	10.03	99	5.88	4466	20.46
3+	1002	75.79	5200	79.28	1449	86.04	11777	53.87

Feature	1 Month (*N*=31391)							
	MI-only (*n*=1322)		SD-only (*n*=6559)		MI and SD (*n*=1684)		No MI or SD (*n*=21826)	
	n	%	n	%	n	%	n	%
Hospitalisation								
Days in hospital[b]	89	17.40 (11.04)	580	14.73 (10.72)	429	16.92 (10.15)	374	16.43 (11.67)
1	88	6.66	560	8.54	408	24.23	363	1.66
2	1	0.08	20	0.30	20	1.19	11	0.05
3+	0	0.00	0	0.00	1	0.06	0	0.00
HoNOS adjusted total score[b,c]	69	10.45 (5.16)	377	11.94 (6.67)	114	12.12 (6.10)	427	11.02 (5.87)

[a] antiepileptic taken as a mood stabiliser; [b] *mean(sd);* [c] Health of the Nation Outcome Scale.

Only individuals with at least two years of follow-up data (*n*=14351) were included in the subsequent analyses. The proportions of patients in each study group remaining at 2-years follow-up were: MI-only (*n*=627, 47.43%), SD-only (*n*=2793, 42.58%), MI and SD (*n*=835, 49.58%), no MI or SD (*n*=10096, 46.26%).

To examine whether patients with at least two years of follow-up were different from patients without at least 2 years of follow-up, demographic and clinical features were summarised among the subset of patients remaining after 2 years (Table 5.4). Age distributions remained similar at baseline and 2-years follow-up for all study groups, but a slightly higher proportion of females than males remained in the sample. Between 51.62% and 74.49% had a diagnosis at 2-years follow-up (versus 11.73% and 29.87% at 1-month follow-up). The proportion of patients prescribed three or more medications at 2-year follow-up was highest among persons with MI and SD (66.23%), followed by SD-only (56.53%), MI-only (51.04%), and individuals with neither feature (45.02%) HoNOS scores remained stable, with a slight increase in MI-only. Hospitalisation

remained the most frequent in persons with MI and SD. Patients with no MI or SD had the fewest hospitalisations, but spent, on average, approximately 6 to 14 days longer in hospital than the patients from the other three groups. HoNOS scores increased, but remained comparable across the four groups.

Table 5.4 Descriptive features of the sample with MI-only, SD-only, MI and SD, and no MI or SD within two-years of presenting to OHFT.

Feature	2 Years (*N*=14351)							
	MI-only (*n*=627)		SD-only (*n*=2793)		MI and SD (*n*=835)		No MI or SD (*n*=10096)	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Age								
16-25	81	12.92	248	8.88	90	10.78	1000	9.90
26-35	190	30.30	816	29.22	286	34.25	2962	29.34
36-45	190	30.30	848	30.36	242	28.98	2916	28.88
46-55	140	22.33	712	25.49	180	21.56	2252	22.31
56-65	26	4.15	169	6.05	37	4.43	966	9.57
Gender, female	373	59.49	1512	54.14	491	58.80	5480	54.28
Diagnosis								
Any	377	60.13	1775	63.55	622	74.49	5212	51.62
Organic	4	0.64	15	0.54	5	0.60	131	1.30
Substance use	24	3.83	165	5.91	48	5.75	338	3.35
Schizophrenia and related	73	11.64	377	13.50	110	13.17	1459	14.45
Mood	191	30.46	952	34.09	382	45.75	1993	19.74
Anxiety	56	8.93	395	14.14	92	11.02	925	9.16
Behavioural syndrome	21	3.35	68	2.43	18	2.16	328	3.25
Personality	86	13.72	256	9.17	141	16.89	821	8.13
Mental retardation	0	0.00	5	0.18	1	0.12	18	0.18
Developmental	4	0.64	12	0.43	2	0.24	77	0.76
Behavioural and emotional	8	1.28	11	0.39	5	0.60	101	1.00
Unspecified	5	0.80	16	0.57	9	1.08	63	0.62
Any sleep disorder	0	0.00	1	0.04	1	0.12	0	0.00
Medication								
1	1	0.16	0	0.00	0	0.00	3	0.03
2	188	29.98	777	27.82	184	22.04	2431	24.08
3+	294	46.89	1600	57.29	584	69.94	2955	29.27
Any	483	77.03	2377	85.11	768	91.98	5389	53.38
Antidepressant	352	56.14	1924	68.89	583	69.82	3781	37.45
Antipsychotic	286	45.61	1380	49.41	517	61.92	3044	30.15
Antiepileptic[a]	76	12.12	248	8.88	134	16.05	632	6.26
Sedative hypnotic	192	30.62	1224	43.82	462	55.33	1960	19.41
Lithium	49	7.81	172	6.16	99	11.86	393	3.89
Sedating antihistamine	9	1.44	104	3.72	38	4.55	122	1.21
Sympathomimetic	7	1.12	20	0.72	8	0.96	94	0.93
Amphetamine	0	0.00	1	0.04	0	0.00	5	0.05
Events								
12-23	95	15.15	400	14.32	104	12.46	1681	16.65
24-35	83	13.24	313	11.21	91	10.9	1273	12.61
36+	320	51.04	1579	56.53	553	66.23	4550	45.02

Feature	2 Years (*N*=14351)							
	MI-only (*n*=627)		SD-only (*n*=2793)		MI and SD (*n*=835)		No MI or SD (*n*=10096)	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Hospitalisation								
Days in hospital[b]	88	34.38 (42.51)	510	38.25 (50.54)	298	36.42 (45.75)	903	48.77 (55.88)
1	63	10.05	364	13.03	205	24.55	629	6.23
2	22	3.51	83	2.97	55	6.59	175	1.73
3+	3	0.48	63	2.26	38	4.55	99	0.98
HoNOS adjusted total score[b,c]	75	13.24 (11.60)	426	13.01 (10.603)	142	11.43 (6.73)	716	12.56 (6.99)

[a] antiepileptic taken as a mood stabiliser; [b] *mean(sd)*; [c] Health of the Nation Outcome Scale.

5.4.4 Incidence Density Rates of Clinical Features in Patients Presenting with Mood Instability and Sleep Disturbance

IDRs of diagnoses, prescribed medications, and first episode of hospitalisation within two years of presenting to OHFT are shown in Table 5.5. After adjusting for multiple comparisons, the IDR of any diagnosis was significantly increased in persons with MI and SD (IDR=1.82, 05% CI:1.66–1.96, p<0.0001) and SD-only (IDR=1.44, 95% CI: 1.36–1.52, p<0.0001), but not MI-only (IDR=1.16, 95% CI:1.04–1.28, p<0.007) compared to those without either MI or SD. The IDR for substance use was particularly strong among those with SD-only (IDR=1.50, 95% CI: 1,26–1.79, p<0.001), while the IDR for mood disorder was particularly strong for those with MI and SD (IDR=1.77, 95% CI: 1.59–1.97, p<0.0001). All three groups showed significantly increased IDRs for any prescribed medication (IDR=2.26–7.04), particularly those with MI and SD. SD-only was associated with significantly increased IDR of antidepressants and sedative-hypnotics. IDRs for all medication classes were similar in MI-only versus the referent.

MI and SD was the only group to have significantly increased IDR for lithium. Patients with MI and SD had the highest rate of first hospitalisation within 2 years of follow-up (IDR=5.32, 95% CI: 4.67–6.07, p <0.0001), followed by SD-only (IDR=1.98, 95% CI: 1.77–2.21, p<0.0001), and MI-only (IDR=1,61, 95% CI: 1.30–2.01, p<0.0001).

Table 5.5 Estimated incidence density rates of diagnoses, prescribed medications and first hospitalisation within 2 years of presenting to OHFT in MI-only, SD-only, and MI and SD versus no MI or SD.

	MI-only			SD-only			MI and SD		
	IDR	**95% CI**	***p***	**IDR**	**95% CI**	***p***	**IDR**	**95% CI**	***p***
Diagnosis									
Any	1.16	1.04-1.28	0.007	1.44	1.36-1.52	<0.0001*	1.81	1.66-1.96	<0.0001*
Organic	1.16	0.43-3.13	0.772	0.93	0.55-1.56	0.772	1.45	0.59-3.53	0.414
Substance use	1.45	0.97-2.17	0.071	1.50	1.26-1.79	<0.0001*	1.57	1.20-2.06	0.001*
Schizophrenia and related	1.18	0.93-1.49	0.177	1.35	1.20-1.51	<0.0001*	1.57	1.29-1.90	<0.0001*
Mood	1.04	0.90-1.20	0.617	1.41	1.31-1.53	<0.0001*	1.77	1.59-1.97	<0.0001*
Anxiety	1.26	0.96-1.64	0.089	1.31	1.17-1.47	<0.0001*	1.50	1.22-1.86	<0.0001*
Behavioural syndrome	1.11	0.89-1.38	0.362	1.16	1.00-1.33	0.042	1.57	1.31-1.88	<0.0001*
Personality	0.78	0.50-1.19	0.247	1.11	0.86-1.43	0.442	1.38	0.86-2.21	0.186
Mental retardation				1.20	0.45-3.24	0.713	0.36	0.05-2.71	0.301
Developmental	0.79	0.32-1.95	0.610	0.88	0.49-1.58	0.672	0.63	0.23-1.73	0.367
Behavioural and emotional	1.79	0.87-3.67	0.109	0.77	0.42-1.39	0.380	2.23	0.91-5.48	0.072
Unspecified	2.14	0.86-5.33	0.093	0.98	0.57-1.70	0.941	0.77	0.38-1.55	0.465
Medication									
Any	2.26	2.06-2.48	<0.0001*	3.58	3.41-3.76	<0.0001*	7.04	6.53-7.59	<0.0001*
Antidepressant	1.73	1.55-1.93	<0.0001*	2.34	2.21-2.47	<0.0001*	3.21	2.94-3.50	<0.0001*
Antipsychotic	1.56	1.39-1.77	<0.0001*	1.94	1.82-2.07	<0.0001*	3.13	2.85-3.44	<0.0001*
Antiepileptic[b]	1.67	1.32-2.12	<0.0001*	1.44	1.25-1.67	<0.0001*	1.31	1.09-1.58	0.004
Sedative hypnotic	1.31	1.13-1.52	<0.0001*	2.35	2.19-2.52	<0.0001*	4.73	4.27-5.23	<0.0001*
Lithium	1.03	0.76-1.38	0.867	1.09	0.91-1.31	0.325	1.78	1.43-2.22	<0.0001*
Sedating antihistamine	1.14	0.58-2.24	0.708	1.21	0.93-1.57	0.150	1.68	1.17-2.42	0.005
Sympathomimetic	1.29	0.60-2.78	0.514	1.84	1.14-2.99	0.012	1.48	0.72-3.04	0.288
Amphetamine									
First Hospitalisation	1.61	1.30-2.01	<0.0001*	1.98	1.77-2.21	<0.0001*	5.32	4.67-6.07	<0.0001*

*Indicates significance in relation to the Bonferroni-Holm critical value.

5.4.5 Presenting Symptoms by Primary Diagnosis

Table 5.6 shows the distributions of initial symptoms (MI and SD, MI-only, SD-only, neither) among individuals who received a specified primary diagnosis at baseline. A total of 5,863 patients had received a diagnosis within 1-month of presentation to OHFT. Of these, most had presented with neither MI nor SD (53.06%), followed by SD-only (30.97%), both MI and SD (11.05%), and few had MI-only (4.91%). Distributions of presenting symptoms varied considerably across diagnostic groups. MI and SD were not frequently observed in patients with organic mental disorders, behavioural syndromes, developmental disorder, and behavioural and emotional disorders with onset usually in childhood. Relative to other diagnostic groups, persons with BD/mania and other mood disorders had the highest frequencies of both MI and SD at baseline (22.39% and 18.82%, respectively). This was followed by personality disorders (13.96%) and substance use disorders (14.96%). Relative to other diagnostic groups, persons with other mood disorders also had a high frequency of presenting with MI-only (16.47%). SD-only was particularly frequent among persons with unipolar depression (39.06%) and neurotic disorders (36.86%).

Table 5.7 shows the distribution of initial symptoms (MI-only, SD-only, both or neither) among individuals who received a specified primary diagnosis at any time during the study follow-up. Among all patients with any primary diagnosis during study follow-up (*N*=26,803), most had presented with neither MI nor SD (64.09%), followed by SD-only (23.12%), both MI and SD (8.11%) and few had MI-only (4.67%). SD-only was particularly frequent among patients with unipolar depression (30.91%), substance use (27.21%), and neurotic disorders (27.41%). Approximately 16.19% of patients with BD/mania presented with both MI and SD (versus 10%

or fewer patients among other diagnostic groups), and approximately 10.17% of patients with other mood disorder presented with MI-only (versus 7% or less in other diagnostic groups).

Table 5.6 Proportion of individuals with a specified primary diagnosis within 1 month of first visit to OHFT who presented with MI and SD, MI-only, SD-only or neither symptom.

		Both		MI-only		SD-only		None	
	N	n	%	n	%	n	%	n	%
Any	5863	648	11.05	288	4.91	1816	30.97	3111	53.06
Organic	90	<5	–	<5	–	11	12.22	75	83.33
Substance Use	468	70	14.96	32	6.84	175	37.39	191	40.81
Schizophrenia & related	848	67	7.90	32	3.77	221	26.06	528	62.26
Mood	2136	301	14.09	92	4.31	762	35.67	981	45.93
Bipolar/Mania	469	105	22.39	21	4.48	126	26.87	217	46.27
Unipolar depression	1582	180	11.38	57	3.60	618	39.06	727	45.95
Other mood disorder	85	16	18.82	14	16.47	18	21.18	37	43.53
Neurotic	1058	94	8.88	52	4.91	390	36.86	522	49.34
Behavioural syndromes	490	20	4.08	26	5.31	90	18.37	354	72.24
Personality	566	79	13.96	41	7.24	127	22.44	319	56.36
Mental retardation	6	<5	0.00	<5	–	<5	–	<5	–
Developmental	44	<5	–	<5	–	5	11.36	34	77.27
Behavioural and emotional	58	<5	–	<5	–	9	15.52	43	74.14
Unspecified	99	12	12.12	<5	3.03	23	23.23	61	61.62
Sleep disorder	<5	<5	–	<5	–	<5	–	<5	–

<5 = cell counts suppressed due to small numbers.

Table 5.7 Proportion of individuals with a specified primary diagnosis at any time during study follow-up that presented with MI and SD, MI-only, SD-only or neither symptom.

		Both		**MI-only**		**SD-only**		**None**	
	N	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any	26803	2175	8.11	1252	4.67	6198	23.12	17178	64.09
Organic	516	18	3.49	12	2.33	60	11.63	426	82.56
Substance Use	1834	153	8.34	79	4.31	499	27.21	1103	60.14
Schizophrenia & related	5139	308	5.99	193	3.76	973	18.93	3665	71.32
Mood	9509	1025	10.78	504	5.30	2516	26.46	5464	57.46
Bipolar/Mania	3157	511	16.19	221	7.00	618	19.58	1807	57.24
Unipolar depression	5939	475	8.00	241	4.06	1836	30.91	3387	57.03
Other mood disorder	413	39	9.44	42	10.17	62	15.01	270	65.38
Neurotic	4017	239	5.95	146	3.63	1101	27.41	2531	63.01
Behavioural syndromes	1474	47	3.19	69	4.68	235	15.94	1123	76.19
Personality	3392	342	10.08	210	6.19	685	20.19	2155	63.53
Mental retardation	42	<5	–	<5	–	6	14.29	33	78.57
Developmental	279	5	1.79	16	5.73	36	12.90	222	79.57
Behavioural and emotional	324	13	4.01	15	4.63	34	10.49	262	80.86
Unspecified	277	22	7.94	8	2.89	53	19.13	194	70.09
Sleep disorder	<5	<5	–	<5	–	<5	–	<5	–

<5 = cell counts suppressed due to small numbers.

5.5 Discussion

This study examined MI and SD documented in EHRs from a large sample of patients in secondary psychiatric clinical care. The results add to evidence that psychiatric symptoms can be identified from EHRs using NLP applications with reasonable accuracy. Previous validation of the MI applications was carried out within a sample of EHRs from patients who presented to SLaM. The mood, affective, and emotional instability applications were observed to have specificity of approximately 91% each, and positive predictive values ranging between approximately 46% and 73% (Patel et al., 2015). The current study examined the combined accuracy of these three applications and found a similar estimate of specificity (92%), but considerably higher positive predictive value (94%). Specificity–not reported in the original validation–was approximately 70% in this study. The other applications for identifying sleep problems, insomnia, and prescribed medications also showed good accuracy; sensitivity estimates ranged between 80% and 86%, while specificity ranged between 86% and 90%.

Specificity exceeded sensitivity for all of the NLP applications. For any test or classification tool (such as the NLP applications), there is usually a trade-off between sensitivity and specificity, such that increasing sensitivity results in decreased specificity (or vice versa), and the preferred balance is usual related to the purpose of the tool. In the current study, specificity was more critical than sensitivity in order to minimise the false positive rate, and limits minimal heterogeneity within the sample, which may dilute the estimates of association. However, the lower sensitivity may have resulted in underestimated prevalence of MI and SD.

The current study adds to robust evidence that MI and SD are commonly found in a wide range of psychiatric disorders (Marwaha, Parsons, & Broome, 2013; Ohayon, Caulet, & Lemoine, 1998; Roth et al., 2006). The prevalence of MI observed in this study (9.58%) was slightly lower than that reported based on a previous study using the MI application in data from SLaM NHS Trust (12.1%; Patel et al., 2015). The higher prevalence in the previous study likely reflects a difference in sample selection; Patel *et al.* restricted their sample to individuals with affective, psychotic or personality disorders, many of which are often characterised by MI (Bopp et al., 2010; Marwaha, Broome, et al., 2014; Trull et al., 2008). Like the current study, Patel *et al.* observed higher prevalence of MI in females and persons of younger age (Patel et al., 2015). This also aligns with patterns observed in the general population (Chapter 3).

The prevalence of SD was approximately 26.26% (95% CI: 25.77%–26.75%), comprised of individuals with insomnia (4.04%) and disturbed sleep (24.88%). Patters in the age and gender-specific prevalence estimates for SD, aligned with the wider literature, which tends to show increased prevalence with age and female gender (Arber et al., 2009; Ohayon, 2002).

The study groups had similar age distributions, and all were comprised of more females than males. The most frequent diagnoses were mood, anxiety, personality and schizophrenia and related disorders, regardless of the presence of MI and/or SD. However, individuals with MI and SD had the highest proportion of diagnoses, followed by SD-only, MI-only and neither MI nor SD. Although there were some differences in the frequencies of diagnoses between the study groups, there were no clear trends in their relationships with specific diagnostic categories. Together, this supports the hypothesis MI and SD are transdiagnostic processes given their presence in nearly all classes of primary mental disorders.

Notably, the number of sleep disorder diagnoses was negligible (<0.5%), despite the frequent documentation of SD in clinical notes and correspondence. Although many individuals may have symptoms below the threshold for formal diagnosis of a sleep disorder, the frequency of sleep disorders in this sample was considerably lower than reported in the wider literature. For example, Ohayon *et al*. reported that the prevalence of insomnia, defined according to the DSM-IV, is approximately 6% (Ohayon, 2002). The low frequency of sleep disorders may reflect a common view that SD is an epiphenomenon of the *primary* psychiatric disorder, and in turn, may not be the initial focus of treatment (A. G. Harvey, 2009). However, the proportion of sedative-hypnotic prescriptions was nearly two times higher in SD-only than MI-only, which may suggest recognition of SD as an important focus of treatment may be improving. Nevertheless, given extensive evidence that SD maybe an underlying or maintaining factor in mental illness, a shift toward better recognition of SD will provide important benefits to treatment.

In keeping with the findings reported in Chapter 4, persons with MI and SD appeared to be among the most extensive users of mental health services. This is a striking finding given that all individuals within the current study, including those in the reference group, had clinically significant mental health symptoms and were in secondary mental health care. Individuals with both MI and SD documented within 1 month of presentation to OHFT had the highest proportions of events and hospitalisation compared with the other three groups. Over 85% of those with MI and SD had three or more contacts with services within their first month of presentation. These frequencies appeared to remain higher across 2-years; over 65% had 36 or more visits over the 2-year period (equating to approximately more 1.5 visits per month). MI and SD also showed significantly increased incidence rates of these features in relation to that of

persons without MI or SD, and IDRs in MI and SD were considerably higher than in MI-only or SD-only. For example, rates of hospitalisation were over five times higher in MI and SD than the referent, and nearly two times higher in MI-only and SD-only versus the referent.

HoNOS scores were similar across the four groups, both at 1-month and 2-years follow-up, and therefore, do not appear to explain the increased service use and prescribed medications in those with MI and SD. However, an unexpectedly small proportion of individuals in the sample had HoNOS ratings, and therefore this assessment may not be representative of each study group. The low frequency of HoNOS assessments within this sample is surprising. HoNOS has been widely implemented as the main routine outcome measure of health and social functioning in patients with mental illness in England. HoNOS ratings comprise part of the Mental Health Minimum Data Set. These data are important not only for planning individualised patient care, but also more widely for surveillance of health, monitoring policies, planning services, and allocating financial resources across NHS Trusts. The absence of these data has important implications for resource allocation to OHFT and also for the implementation of mental health care in England.

Distributions of presenting symptoms appeared to vary considerably across diagnostic groups. Between 17% and 43% of all patients with a primary psychiatric diagnosis during the study presented with at least one of MI or SD. SD was a common presenting symptom across all disorder groups, although particularly frequent among unipolar depression (30.91%), neurotic (27.41%), and substance use disorders (27.21%). Similar to the findings in Chapter 3, MI in the absence of SD was relatively infrequent, while the frequency of both MI and SD was higher than MI-only, but less that SD-only.

Differences in distributions of presenting symptoms were more apparent in patients with a diagnosis at baseline compared with those among patients with a diagnosis at any point during the study period. Importantly, the presence of MI and SD rely on documentation by the health care provider, which may reflect inherent biases in therapeutic practice. For example, clinicians might be more likely to ask about MI in patients with diagnoses that are traditionally associated with the symptom, such as BD or BPD, and less likely to ask about MI in patients with other diagnoses not typically characterised by MI.

Nevertheless, the results suggest that mood disorders may be differentiated, to some degree, by the presence of both MI and SD or MI-only. Among patients with a diagnosis at baseline, presentation with both MI and SD was more frequent in patients with BD/mania or other mood disorders (22.39% and 18.82%, respectively) compared with unipolar depression (11.38%). However, after including diagnoses at any time during study follow-up, the frequency of both MI and SD in other mood disorder looked more similar to unipolar depression (decreasing to approximately 10%). The high frequency of both MI and SD at presentation among patients with BD is expected given that MI is a core feature of BD and SD is also common and a well-known risk factor for relapse. Therefore, it is expected that both MI and SD are discussed during treatment, and for a high proportion of patients to experience the symptom, particularly at the beginning of treatment before symptoms have been stabilised.

Initial symptoms of MI in the absence of SD also appeared to differentiate BD/mania and other mood disorders. Among patients with a diagnosis at baseline, the presence of MI in the absence of SD was more frequent in other mood disorders (16.47%) compared with BD/mania (4.48%). Although smaller, these differences remained after including diagnoses at any time; the

frequency of MI-only in other mood disorder (10.17%) remained higher than in BD/mania (7.00%).

5.5.1 Limitations

Some limitations to this study are acknowledged. First, EHRs represent only information documented during service provision and missing data cannot be quantified. For example, it is unclear whether a missing diagnostic code reflects the absence of a diagnosis or just no record of a diagnosis within that field. Additionally, MI, SD and prescribed medications were identified from clinical progress notes and correspondence, and therefore, reflect only information documented during routine care. Specific symptoms may not be discussed uniformly or routinely in each patient, but rather in relation to a number of other factors, such as the patient's diagnosis or medication. For example, MI is not routinely assessed in clinical settings, and may be particularly overlooked within disorders for which these symptoms are seen as uncommon.

The limitation of missing data is evident in the small proportion of patients with HoNOS assessments. For example, within 2-years of presentation, HoNOS scores were only available approximately 9.5% of the sample[o]. HoNOS is a national health indicator recommended by the NHS for routine assessment. It is used in planning individualised care for patients, and therefore, one would expect most patients to have at least one assessment during 2-year period upon entering care.

[o] At 2-years follow-up:
n/N=75 (MI-only)+426 (SD-only)+42 (MI and SD)+716 (no MI or SD)=359/14351*100=9.47%.

Second, the NLP applications have some degree of inaccuracy, which may have introduced bias into the prevalence and IDR estimates. For example, the specificity of the MI applications in relation to the manual annotations was approximately 88%, which implies a false positive rate of 12%. This means that for every 1000 individuals in the sample, approximately 120 individuals without MI were incorrectly classified as having the symptom. It should be noted that the validation of the NLP applications in this study was based on a relatively small number of manual annotations carried out by a single human annotator. Ideally, the validation process should include at least two independent annotators and agreement between annotators should be considered. In addition, the size of the sample should be large enough to provide better precision than was available in the current study.

Third, the medication application was only run over documents containing the keywords mood, affect, emotion, sleep, or insomnia and therefore medications were missed from any documents not containing those keywords. Since any documents without the respective keywords are unlikely to have MI or SD, the proportions of prescribed medications may have been underestimated in the MI-only, SD-only, and no MI or SD groups. However, very few documents had none of the keywords, therefore, any bias due to misclassification is likely to be minimal.

Finally, the study did not account for changes in MI and SD symptoms over time. Patients were classified according to of MI and SD documented within 1 month of presenting to OHFT. This time period was selected to facilitate comparability with previous examination of MI by Patel *et al.* (Patel et al., 2015*).* However, individuals may have previously experienced MI symptoms that resolved prior to entering care by OHFT or they may have developed MI the study period.

Additionally, the NLP classification tool did not account for the duration or severity of symptoms, which may be important confounders to consider in future research.

5.5.2 Future Research Directions

The results of the current study highlight several important avenues for future work. Foremost, interventional research may help to better understand and improve the effectiveness of transdiagnostic treatments (both pharmacological and psychosocial treatments) of MI and SD. Additionally, many pharmacological treatments that target mood disturbances also have secondary effects that may exacerbate or improve symptoms of SD. Further research is needed to clarify which treatments may be most effective in persons with both MI and SD.

Future research should also seek to clarify factors that influence the incidence of poor clinical outcomes, such as hospitalisation, in individuals with MI and SD. Early intervention targeted at modifiable risk-factors may help to reduce complications and improve quality of life in persons with mental illness.

Finally, EHRs hold a wealth of clinically relevant information and NLP applications offer a novel method to examine these data. More work is needed to refine and validate NLP methods for eliciting symptoms from EHRs.

5.6 Conclusion

The findings of this study suggest that MI and SD may contribute to the high cost of mental disorders, especially when the two symptom co-occur. MI and SD are present in a wide range of psychiatric disorders and are associated with considerably increased use of services and

prescribed medications. Furthermore, individuals who present to secondary mental health services with MI and SD have significantly higher rates of hospitalisation within 2-years than individuals without these symptoms. These findings have important implications for clinical practice. One possible reason for the poor outcomes associated with MI and SD may be that they are often overlooked during care. Both MI and SD are often seen as epiphenomena of the underlying disorder. However, growing evidence that they are transdiagnostic features and involved in the origins and maintenance of mental disorders implies that routine assessment and prompt treatment may help to improve prognosis in individuals with a wide range of mental disorders.

Chapter Six: The Directionality Between Mood and Sleep in Patients with Bipolar Disorder

6.1 Introduction

BD is a severe mood disorder often characterised by chronic MI. MI is important because it is associated with increased morbidity. In a sample of adolescents with BDI and BDII diagnoses, baseline MI predicted greater time spent ill at 3-months follow-up (O'Donnell et al., 2018). A prospective study of BD patients versus healthy controls also examined affective lability and affective intensity in relation to illness severity. Both dimensions of MI were significantly increased in BD patients, and MI was associated with earlier age of onset and increased comorbidity with anxiety and substance use disorders (Henry et al., 2008). MI is also associated with significantly poorer functional recovery during interepisode periods (Strejilevich et al., 2013).

SD is another common and important characteristic of BD, and one that is closely linked with mood. BD patients often experience significant problems with sleep onset latency, duration, fragmentation, and efficiency (Geoffroy et al., 2015). In a prospective study comparing sleep patterns in euthymic BD patients, insomnia patients and healthy controls, approximately 70% of BD patients showed clinically significant SD. BD patients also reported more anxiety, fear and misperceptions about sleep, and lower daytime activity levels compared with the insomnia and control groups (A. G. Harvey, Schmidt, Scarna, Semler, & Goodwin, 2005). BD patients with SD also show more pervasive impairments in domains such as quality of life, and cognitive and psychosocial functioning (Boland et al., 2015; Giglio et al., 2009; Gruber et al., 2009b; Lunsford-Avery, Judd, Axelson, & Miklowitz, 2012). SD is not only a symptom of BD, but also

a risk factor for onset and relapse. According to a systematic review of early symptoms of BD, SD is the most common prodrome of mania and the sixth most common prodrome of bipolar depression (Jackson et al., 2003).

The link between SD and mood variation is supported by several lines of evidence. For example, mood changes correlate with diurnal rhythms (Boivin et al., 1997), and mood appears to more sensitive to changes in sleep in BD patients than in healthy individuals (Carr et al., 2018). In addition, manipulations of sleep duration and timing are shown to produce changes in valence and intensity of affect. Experimental sleep deprivation can precipitate mania in patients with BD (Barbini, Bertelli, Colombo, & Smeraldi, 1996; Wehr et al., 1982), while prolonged darkness may alleviate mood elevation (Barbini et al., 2005). Furthermore, light–the main environmental zeitgeber[p] for circadian rhythms–is used therapeutically to alleviate seasonal and non-seasonal depressive symptoms (Al-Karawi & Jubair, 2016; Glod, 2017).

Although the presence of a relationship between SD and mood has been well established in existing literature, the nature of the relationship in terms of the directionality and polarity of mood changes in relation to SD requires further clarification. Few studies have directly assessed the temporality between mood and sleep changes. A prospective study of patients with BD receiving standard treatment collected self-reported mood durations of sleep and bedrest to investigate the latency between changes in sleep duration and mood. After examining time shifts between +7 days and 7 days, duration of sleep plus bedrest was most often inversely correlated with mood change, and mood changes in relation to sleep duration typically occurred with 1-day

[p] A zeitgeber is an endogenous or exogenous agent that acts to entrain the biological clock to approximately 24-hour cycle.

latency. This means that short sleep duration significantly predicted more elevated mood the following day and longer sleep duration predicted next day depressive mood (Bauer et al., 2006). Another study examined the relationships between self-reported positive and negative mood and SD (defined as total time spent awake) in patients with interepisode BD, insomnia, and healthy controls. In BD, SD was associated with more negative mood the next morning, while evening negative mood significantly predicted increased subsequent total wake time. The same relationship was not apparent for positive mood (Talbot et al., 2012). Different types of SD may be differentially related to alterations in positive and negative affect (Gershon et al., 2012; Gruber et al., 2011), but evidence of different forms of SD is very limited.

This chapter describes a study which aimed to clarify the relationship between mood and sleep in BD, and to extend evidence by assessing the relationship between SD and MI.

6.1.1 Aim

The aim of this study was to characterise the association between MI and sleep in a sample of patients with BD, and to evaluate whether an integrated mood management intervention, demographic or clinical features influence the observed associations.

6.2 Methods

This study was a retrospective analysis of data from a randomised controlled trial in diagnosed BD patients (OXTEXT-6). Details of the trial have been published previously (Bilderbeck, Atkinson, et al., 2016). OXTEXT-6 was approved by UK NHS Ethics Committees (REC reference: OXTEXT-6, 10/H0604/13). All participants provided written informed consent.

6.2.1 OXTEXT-6 Trial

OXTEXT-6 was a two-armed randomised controlled trial designed to compare two integrated mood management (IMM) interventions, facilitator-supported integrated mood management (FIMM) and manualised integrated mood management (MIMM), in the reduction of depressive symptom severity at 12 and 24-months follow-up.

6.2.1.1 Participants

Participants were recruited from an ongoing observational study (OXTEXT-1) if they had previously expressed an interest to participate in further research studies and were actively participating in True Colours mood monitoring (https://truecolours.nhs.uk).

Inclusion Criteria:

(a) Able and willing to provide informed consent for participation;

(b) Aged 16 years or older;

(c) Diagnosed with DSM-IV bipolar I (BDI) or bipolar II (BDII) disorder;

(d) Current and reliable participation in mood monitoring (True Colours) for at least 4 weeks and having completed at least 3 out of 4 of the weeks;

(e) Sufficient understanding of verbal and written English for participation in trial procedures;

(f) Current patient of Oxford Health NHS Foundation Trust (OHFT); and

(g) Appropriate for psychoeducational intervention with mood monitoring by a treating psychiatrist, with no need for more acute treatment.

Exclusion criteria:

(a) Concurrent participation in OXTEXT-2 or previous participation in OXTEXT-4[q];

(b) Participation in intensive mood monitoring within the past 3 months;

(c) Acutely unwell such that they cannot participate as judged by a treating psychiatrist or the research team; or

(d) Integrated mood management has been deemed inappropriate for the patient by the treating psychiatrist.

Participants were randomised to each trial arm in blocks, stratified by illness type (BDI or BDII), and clinical status (major mood episode or euthymia) at the time of randomisation.

6.2.1.2 Interventions

All participants received standard medication management and weekly mood monitoring in addition to their IMM intervention.

Facilitator-supported Integrated Mood Management (experimental intervention). Facilitator-supported integrated mood management (FIMM) consisted of 5 x 50 minutes individual face-to-face sessions with a facilitator (trained clinician) plus weekly mood monitoring. Participants received an outline of the IMM manual upon randomisation. Each session corresponded to a chapter in the IMM manual, and participants were sent a hardcopy of the chapter to be covered prior to each session. The five sessions covered (1) identifying the relapse signature; (2) reviewing risk and protective factors; (3) daily rhythm and sleep/wake regulation; (4) the role of

[q] OXTEXT-2 was a health economics study that exampled the resource impact of mood monitoring. OXTEXT-4 included the development and initial evaluation of the psychoeducational intervention evaluated in OXTEXT-6.

medications and substance/alcohol abuse; (5) and finalising the mood management plan. All five sessions were aimed to be delivered within 12-weeks of entering the study. Any sections still incomplete after week 12 were conducted over the telephone. Participants in the FIMM group also received follow-up phone calls at weeks 15, 17, 21 and 29. These provided support for implementation of core mood management techniques but did not contain novel therapeutic material. In addition to weekly mood, participants were invited to participate in daily monitoring of symptoms for the duration of the trial intervention. Information about the development and implementation of FIMM is available (Miklowitz et al., 2012).

Manualised Integrated Mood Management (control intervention). Manualised integrated mood management (MIMM) was identical to FIMM, except the full manual was provided at randomisation and participants could work through the manual at their own pace during the 12-week period without any face-to-face or telephone support from facilitators.

6.2.2 Measures

6.2.2.1 Weekly Monitoring

True Colours (https://truecolours.nhs.uk) is a platform for real-time, remote monitoring of symptoms and clinical outcomes. Patients are prompted by two separate weekly text messages (or emails) separately for the monitoring of depressive and elevated (manic) mood. Alternatively, patients can opt to communicate securely via email and online (Simon, Budge, Price, Goodwin, & Geddes, 2017). Prompts were sent from first assessment up to 24-months follow-up.

Depressive mood symptoms. The Quick Inventory of Depressive Symptomatology 16-item self-rated version (QIDS) is a validated rating scale that measures depressive symptoms during the

past seven days (Rush et al., 2003). For each item, participants select one of four possible responses (ordered 0 least severe to 3 most severe symptoms) that best describes how they have been feeling during the past 7 days. Questions inquire about SD, change in appetite or weight, sad mood, concentration, self-criticism, suicide ideation, psychomotor agitation or retardation, general interest, and energy levels. Higher scores on the QIDS represent more severe symptoms of depression. The QIDS shows good psychometric properties, including high internal consistency and consistency with the 30-item Inventory of Depressive Symptomatology (IDS-SR; Rush et al., 1986; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996) and Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960, 1967), two other widely accepted measures of depressive symptoms (Rush et al., 2003).

Elevated mood symptoms. The Altman Mania Rating Scale (ASRM). The ASRM consists of 5-items designed to screen for the presence and severity of manic symptoms (Altman, Hedeker, Peterson, & Davis, 1997). For each item, participants select one of five possible statements that best describe how they have been feeling during the past week. Items include feelings of happy/cheerful mood, self-confidence, need for sleep, talking more than usual, and activity levels. Scores on the five items may be summed to produce a total mood score (with possible total scores ranging between 0 and 20); a higher total score indicates a greater degree of manic or hypomanic symptoms. The scale was developed and validated using a sample of patients with mania, schizophrenia, schizoaffective, and depressive disorders during a washout period and after pharmacotherapy treatment. ASRM has high concurrent validity with the Clinician Administered Rating Scale for Mania (CARS-M; Altman, Hedeker, Janicak, Peterson, & Davis,

1994). A cut-off score of greater than five on the ASRM was found to have 85.5% specificity and 87.3% sensitivity for discriminating mania from non-mania on the CARS-M.

Sleep disturbance. Items to measure SD are embedded within the QIDS and ASRM. Four items in the QIDS ask directly about sleep including initial insomnia (falling asleep), middle insomnia (sleep during the night), terminal insomnia (early waking), and hypersomnia (sleeping too much). A single sleep item is embedded in the ASRM, which asks about decreased need for sleep.

To produce overall measures of depressive and elevated mood that are independent of the sleep items, revised total mood scores were calculated using the respective published scoring methods (Altman et al., 1997; Rush et al., 2003), but omitting the sleep items. Total scores on the QIDS ranged between 0-24 after removing the sleep items (rather than 0 to 27 according to the published scoring method (Rush et al., 2003). Total scores on the ASRM ranged between 0 and 16 (rather than 0 to 20 according to the published scoring method (Altman et al., 1997).

6.2.2.2 Daily Monitoring

Mood ratings and nightly sleep durations were collected for the duration of IMM intervention (approximately 5 weeks/35 days).

Mood. Participants are prompted each afternoon to complete daily mood ratings[r]. MZ consists of five mood terms: irritable, anxious, depressed, elated, and energised. Participants are asked to

[r] The questionnaire used to obtain the daily ratings was altered slightly and named Mood Zoom (MZ) after completion of the trial.

rate, to what degree they experienced each mood over the last 24 hours, on a 7-point scale from 1 'not at all' to 7 'very much' (Tsanas et al., 2016).

Sleep Duration. Participants are also prompted each morning to report the total number of hours (to the nearest half-hour) slept the previous night.

6.2.2.3 Mood Instability

MI was quantified using the Teager-Kaiser Energy Operator (TKEO) from daily mood ratings. TKEO is a measure of instantaneous amplitude and frequency changes of a signal (Kaiser, 1990, 1993). It has been used previously in a variety of applications in addition to MI (Carr et al., 2018; Tsanas et al., 2016), such as detection of muscle activity onset (Li, Zhou, & Aruin, 2007), and speech signal processing (Maragos, Kaiser, & Quatieri, 1993).

The calculation of TKEO results in a vector. To summarise MI for each week, mean TKEO was estimated for each 7-day period (for the 5 weeks of daily mood ratings).

6.2.3 Statistical Analysis

All analyses were conducted in *R* version 3.4.3 (R Development Core Team, 2017). Demographic and clinical features of the sample were summarised as frequencies, proportions, and means and standard deviations. Differences in demographic and clinical features between FIMM and MIMM and males and females were assessed using Fisher's exact tests and two-sample t-tests.

6.2.3.1 Data Screening

Some subjects provided more than one response to the same prompt. It was assumed that repeated responses during the same period were sent to correct earlier responses, therefore only the most recent response within the same response interval was retained. Participants were permitted to continue daily and weekly self-monitoring following the trial, however, responses after 5 weeks (daily) and 12 months (weekly) were omitted from the current analysis due large amounts of missing data during the optional response period.

6.2.3.2 Principal Component Analysis of the MZ Questionnaire

Principal Component Analysis (PCA) was carried out on the daily ratings to identify its underlying structure and to reduce the number of variables. PCA is a procedure that transforms a number of possibly correlated variables into a smaller set of *principal components,* while still accounting for as much variability in the data as possible. PCA has been used previously on the Mood Zoom (MZ) questionnaire in a cohort of patients with BD (Tsanas et al., 2017; Tsanas et al., 2016). Prior to the analysis, the MZ items were standardised with a mean of zero and standard error of one. This ensures that the variances of each variable provide equal weight to the analysis.

6.2.3.3 Cross-Correlation Function Analysis

The primary analysis consisted of calculations of cross-correlation functions (CCF), which were used to quantify the relationship between mood and sleep disturbance as a function of lag (time shift between the two series). The CCF can be used to determine lags at which one time series may be a predictor of another time series. Prior to calculation of the CCF, missing data must

either be removed or replaced. Missing values were imputed using a simple moving average (imputeTS; Moritz & Bartz-Beielstein, 2017). Data must also be *prewhitened* (detrended) prior to calculation of the CCF because the presence of autocorrelations or shared trends between the two time series can produce spurious correlations (Dean & Dunsmuir, 2016). Time series were filtered using an auto-regressive moving average ARIMA (*p, d, q*) model, where *p* is the lag order, *d* is the degree of differencing, and *q* is the order of the moving average. For each subject, the model of best fit for the mood time series was determined using plots of the time series, autocorrelation and partial autocorrelation functions, as well as the *auto.arima* function (forecast; Hyndman et al., 2018). Next each pair of time series were passed through the identified model, and the residuals were retained. The residual time series were used to calculate the CCF at lags -7 to +7 days daily mood and sleep, -12 to +12 weeks for weekly mood and sleep ratings, and -5 to +5 for MI and mean sleep duration per week. Cross-correlations at each lag were determined significant if the CCF exceeded two times the standard error (SE), where $SE=1/\sqrt{n}$ and *n* is the length of the time series. A positive CCF indicates that the time series are in phase, while a negative CCF indicates an inverse phase relationship between the paired time series. Negative lag values indicate that sleep changes precede mood changes, positive lag values indicate that mood changes precede sleep changes, and a lag of zero indicates no time shift between mood and sleep ratings.

To explore whether differences between participants with significant CCFs and non-significant CCFs may be due to the intervention or differences in demographic and clinical features, a follow-up analysis was performed. Comparisons were carried out using Fisher's exact tests and two-sample t-tests.

6.3 Results

Participants (*n*=121) were randomised to FIMM (*n*=60) or MIMM (*n*=61). Three subjects withdrew prior to completing the study, and 21 participants did not complete any daily ratings, yielding a final sample size of 97 for analysis. A flow diagram of participant selection is presented in Figure 6.1.

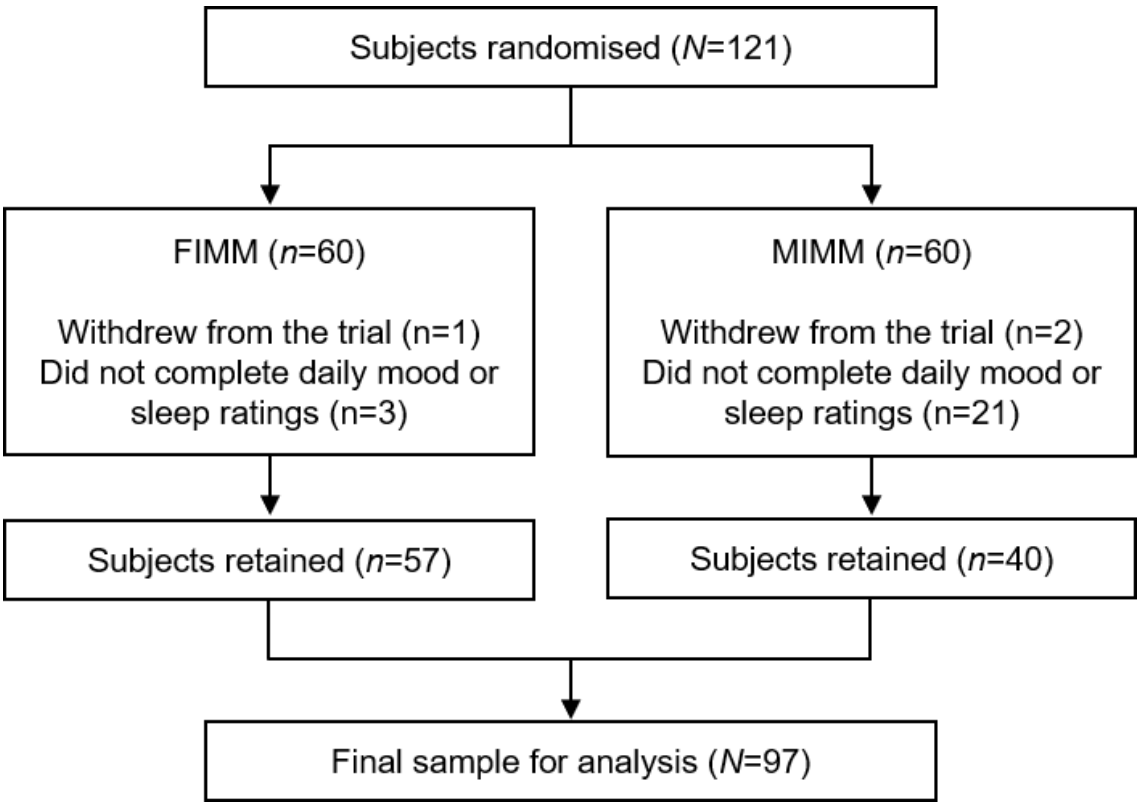


Figure 6.1 Flow diagram of participant selection.

Demographic and clinical features of the sample are shown in Table 6.1. None of the demographic and clinical features differed significantly between treatment (FIMM versus MIMM, gender (male versus female), or diagnostic groups (BDI versus BDII). Participant response rates to weekly QIDS and ASRM prompts over the 52 weeks were 72.9% (*SD*=19.7%) and 73.0% (*SD*=19.6%), respectively. Response rates to daily mood and sleep duration prompts over the 5 weeks were 81.8% (*SD*=17.4%) and 86.0.0% (*SD*=14.6%), respectively.

Table 6.1 Demographic and clinical features of the study sample.

	Total Sample (*n*=97)	
	n	**%**
Age[a]		44.52(13.75)
Male	24	24.74
BDI	65	67.01
FIMM	57	58.76
Any psychotropic medication	91	93.81
Lithium	36	37.11
Anticonvulsant	40	41.67
Antipsychotic	48	49.48
Antidepressant	32	32.99
Anxiolytic	20	21.05
Hypnotic	8	8.25
Other	4	4.21
Rapid cycling	7	7.22

[a] *m*ean(*sd*); BDI=bipolar I disorder; FIMM=facilitator-supported integrated mood management.

6.3.1 Principal Component Analysis

PCA was used to identify the underlying structure of the MZ questionnaire. Table 6.2 shows the Spearman's correlation matrix for the five MZ items. All items showed significant pairwise correlations with each other, except anxious, which was not significantly associated with either

elated or energised. Elated and energised showed the strongest pairwise correlation (r=0.64), followed by depressed and anxious (r=0.56), anxious and irritable (r=0.49), and depressed and irritable (r=0.44). The remaining correlation coefficients were weak.

Table 6.2 Spearman correlation matrix for Mood Zoom items.

	Anxious	Depressed	Irritable	Elated	Energised
Anxious	1.00				
Depressed	0.56*	1.00			
Irritable	0.49*	0.44*	1.00		
Elated	-0.01	-0.13*	0.09*	1.00	
Energised	-0.03	-0.10*	0.07*	0.64*	1.00

*Indicates significant pairwise correlation ($p<0.05$).

A scree plot of the eigenvalues for each principal component is displayed in Figure 6.2. Components one and two had eigenvalues greater than one, and there is a steep drop in eigenvalues between components two and three. Table 6.3 shows the factor loadings and percent of variance explained by each component. The first two components explained approximately 76% of the variance in MZ. Based on these results, the first two components were retained for further analyses. The dominant factor loadings for component one included the anxious, depressed and irritable items, and for component two included the elated and energised items. For ease of reference and to reflect their dominant loadings, component one was labelled *negative emotions* and component two was labelled *positive emotions*. Likewise, estimates of MI calculated based on these two components were labelled *negative MI* and *positive MI*.

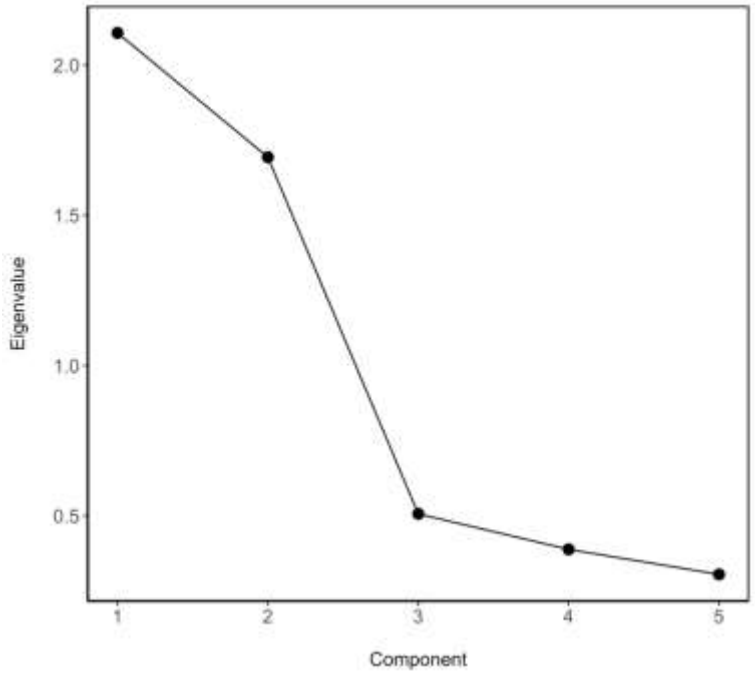


Figure 6.2 Scree plot showing the eigenvalues for each component from principal component analysis of the Mood Zoom.

Table 6.3 Results of the principal component analysis of the Mood Zoom questionnaire.

	Component 1	**Component 2**	**Component 3**	**Component 4**	**Component 5**
Factor loadings					
Anxious	**0.58**	0.14	0.16	**-0.74**	-0.26
Depressed	**0.58**	0.02	**0.59**	**0.52**	0.21
Irritable	**0.52**	0.24	**-0.77**	0.27	0.06
Elated	-0.16	**0.68**	0.08	-0.21	**0.68**
Energised	-0.16	**0.68**	0.14	0.26	**-0.65**
% of cumulative variance explained	42.16	76.00	86.12	93.88	100.00

Bolded entries indicate dominant factor loadings (>0.4) for each principal component.

6.3.2 Cross-Correlation Function Analysis

6.3.2.1 Pre-processing

Figure 6.3 shows time series data for weekly depressive mood and initial insomnia ratings from a single participant at different stages of pre-processing. The result of the CCF analysis between depressive mood and initial insomnia for the same patient is shown in Figure 6.4. There is a significant positive CCF of approximately 0.3 at lag 0, indicating that more depressive mood was correlated with higher SD ratings during the same week (or less depressive mood was correlated with lower SD ratings). The CCF at lag 0 is significant because it is greater than two times the standard error (*se*). No other lags show significant CCFs.

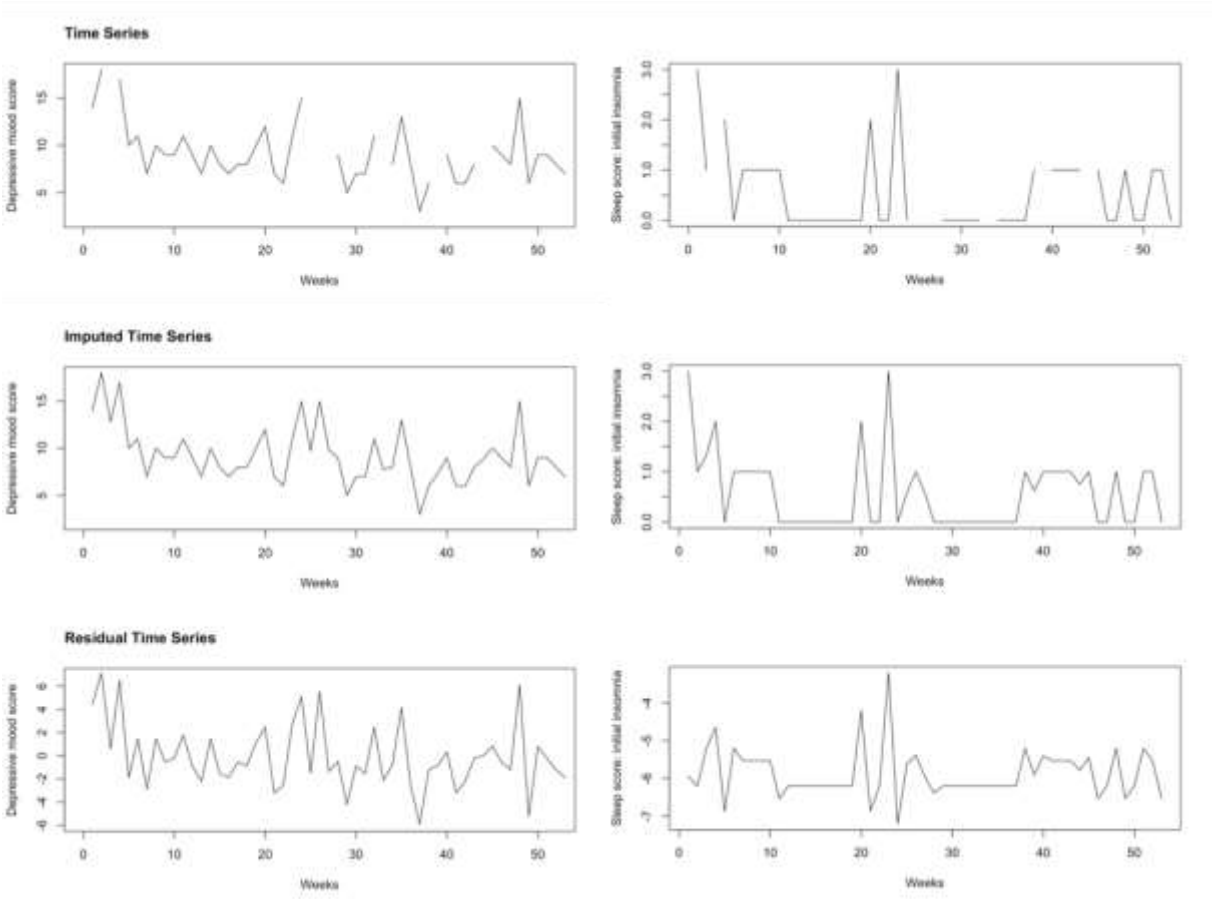


Figure 6.3 Raw, imputed, and residual time series for depressive mood and initial insomnia for a single subject.

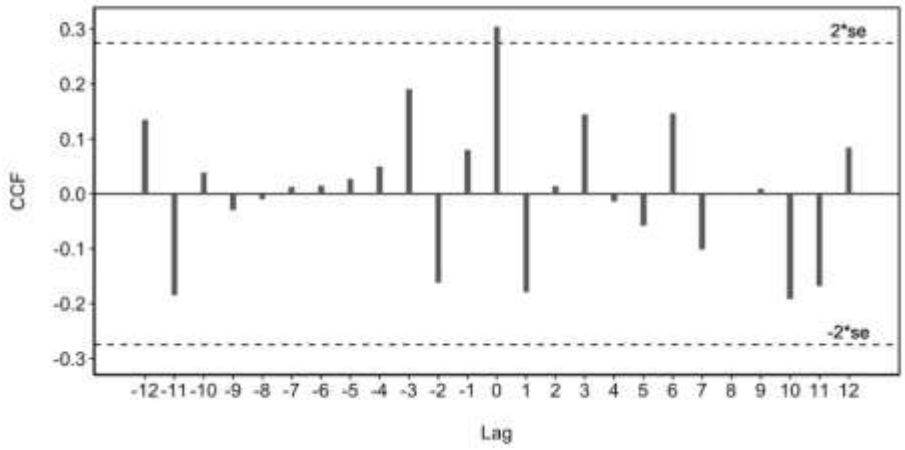


Figure 6.4 Plot of cross-correlation function for weekly measures of depressive mood versus initial insomnia for a single patient. Negative lag values indicate that sleep ratings preceded mood ratings by one or more weeks, positive lag values indicate that mood ratings preceded sleep ratings by one or more weeks, and a lag of zero represents mood and sleep ratings during the same week. Positive CCF values indicate that more depressive mood was associated with more severe SD (or less depressive mood was associated with less severe SD), while negative CCF values indicate that more depressive mood was associated with less severe SD (or less depressive mood was associated with more severe SD). CCFs are considered significant if they are greater than two times the standard error (se).

6.3.2.2 Weekly Mood Versus Sleep Disturbance

A summary of the CCF analysis for depressive mood versus initial insomnia, middle insomnia, terminal insomnia, and hypersomnia is shown in Figure 6.5. For all comparisons, the highest proportion of participants with significant positive relationships between mood and SD ratings during the same week, suggesting that increased depressive mood is associated with more SD (or

decreased depressive mood is associated with less SD). The highest proportion occurred between depressive mood and hypersomnia (38.37%, *n*=33), followed by initial insomnia (30.77%, *n*=28), middle insomnia (25.53%, *n*=24), and terminal insomnia (23.60%, *n*=21). The number of participants with significant relationships at all other time shifts was uniformly small, but proportions appeared to decrease with longer time shifts between the two series'. A higher proportion of significant relationships were positive than inverse

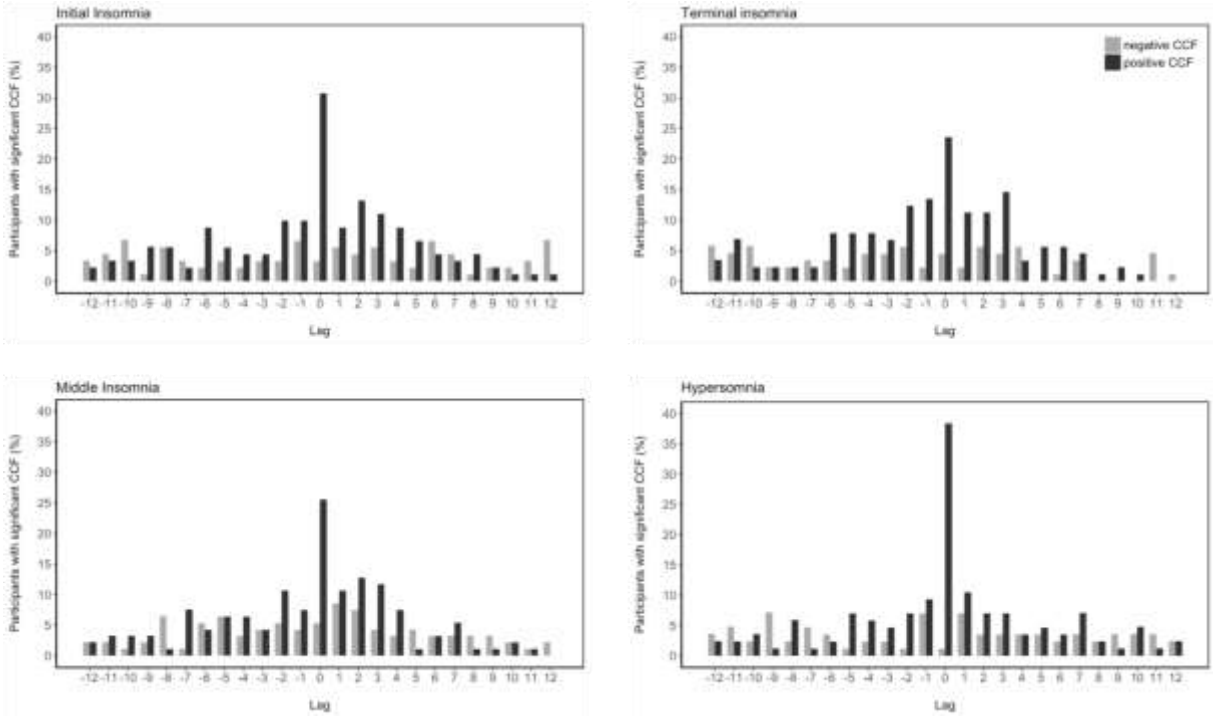


Figure 6.5 Bar plots showing the percent of participants (*n*=97) with significant CCFs at each lag for weekly measures of depressive mood versus initial insomnia, middle insomnia, terminal insomnia, and hypersomnia. Negative lag values indicate that sleep ratings preceded mood ratings by one or more weeks, positive lag values indicate that mood ratings preceded sleep ratings by one or ore weeks, and a lag of 0 represents mood and sleep ratings made during the same week. Positive CCF values indicate that higher ratings of depressive mood were associated with more SD (or less depressive mood was associated with less SD). Negative CCF values indicate that more depressive mood was associated with less SD (or less depressive mood was associated with more SD).

Results of the CCF analysis between elevated mood and decreased need for sleep are shown in Figure 6.6. Five subjects reported the same level of elevated mood across all weeks, therefore did not contribute to the CCF analysis. The highest proportion of participants with a significant CCF (62.20%, *n*=51) showed a positive correlation between elevated mood and decreased need for sleep during the same week. Proportions of significant CCFs for all other lags were uniformly small

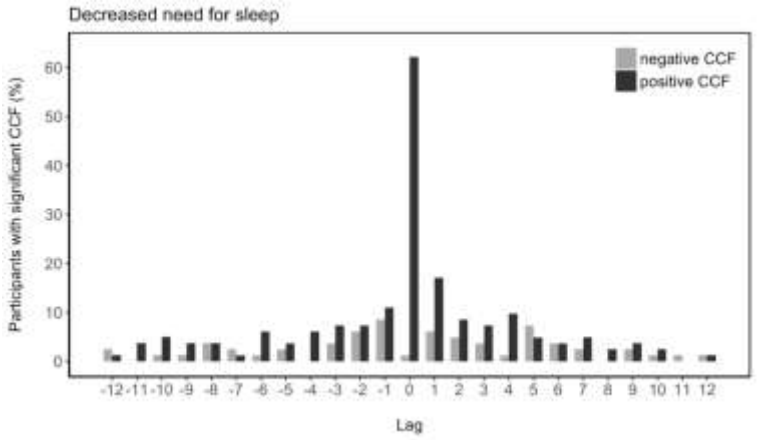


Figure 6.6 Bar plot showing the percent of participants (*n*=92) with significant CCFs at each lag for elevated mood versus decreased need for sleep. Negative lag values indicate sleep ratings preceded mood ratings by one or more weeks, positive lag values indicate that mood ratings preceded sleep ratings by one or more weeks, and a lag value of zero represents mood and sleep ratings from the same week. Positive CCF values indicate that more elevated mood was correlated with more decreased need for sleep (or less elevated mood was correlated with less decreased need for sleep). Negative CCF values indicates that more elevated mood was associated with less decreased need for sleep (or less elevated mood was associated with more decreased need for sleep).

6.3.2.3 Daily Mood Versus Sleep Duration

The results of the CCF analysis comparing daily ratings of negative emotions with sleep duration are summarised in Figure 6.7. The most commonly observed association was a significant positive relationship was observed between nighttime sleep duration and next day negative emotions (9.28%; *n*=9). This was followed closely by an inverse relationship between daytime negative mood and nighttime sleep duration (7.22%, *n*=7) and a positive relationship between sleep duration and negative mood two days later (7.22%; *n*=7). Significant positive and inverse relationships between negative emotions and sleep duration occurred at approximately similar frequencies. For the CCF analysis between positive emotions and sleep duration, approximately 12.37% (*n*=12) of participants showed a significant inverse relationship between nighttime sleep duration and next day positive emotions, followed by 7.22% (*n*=7) with a significant inverse relationship between daytime positive emotions and night time sleep duration. Inverse relationships occurred more frequently than positive relationships.

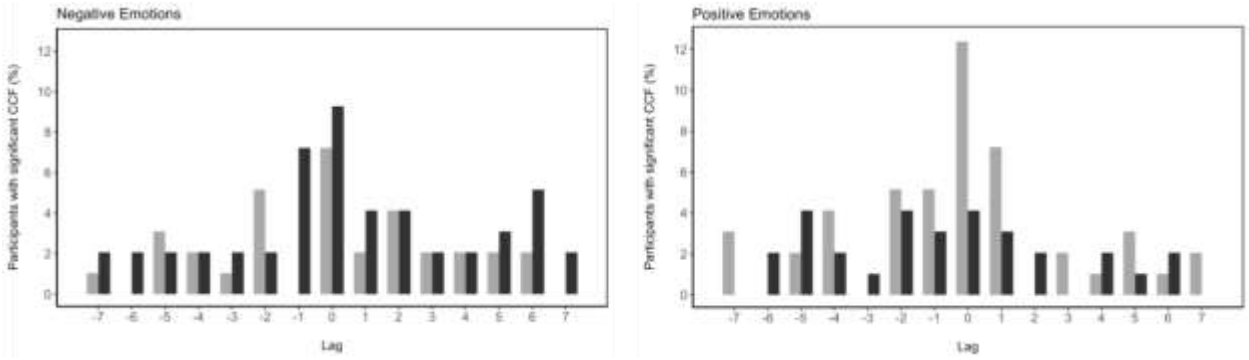


Figure 6.7 Bar plots showing the percent of participants (*n*=97) with significant CCFs at each lag for daily measures of negative emotions versus sleep duration and positive emotions versus sleep duration. Positive lag values indicate that MZ ratings preceded sleep by one or more days, while negative lag values indicate that sleep preceded MZ ratings by one or more days. A lag of 0 represents nighttime sleep duration was correlated with next day MZ ratings. Positive CCF values indicate that higher MZ ratings were associated with longer sleep duration (or lower MZ ratings were associated with shorter sleep duration). Negative CCF values indicated that higher MZ ratings were associated with shorter sleep duration (or lower MZ ratings were associated with longer sleep duration).

6.3.2.4 Weekly Mood Instability Versus Mean Sleep Duration

The CCF analysis of weekly negative MI and positive MI versus mean sleep duration is shown in Figure 6.8. For negative MI versus mean sleep duration, the highest proportions of significant CCFs included a positive relationship (6%, *n*=6) and an inverse relationship (5%, *n*=5) between negative MI and mean sleep duration during the same week. For positive MI versus mean sleep duration, approximately 5% (*n*=5) showed a significant positive relationship indicating that more

positive MI was associated with longer mean sleep duration (less positive MI was associated with shorter mean sleep duration). Approximately 3% (*n*=3) showed a significant inverse relationship between positive MI and mean sleep duration during the same week, indicating that more positive MI was associated with shorter mean sleep duration (or less positive MI was associated with longer mean sleep duration).

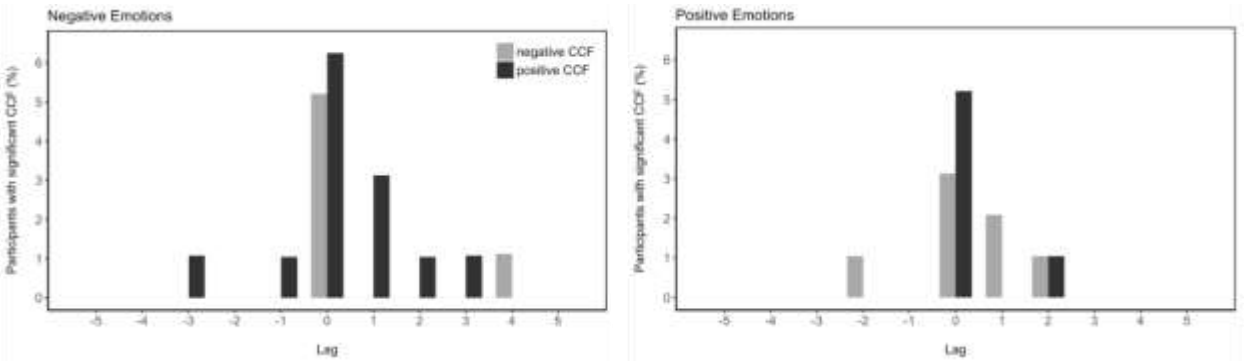


Figure 6.8 Bar plots showing the percent of participants (*n*=97) with significant CCFs at each lag for negative MI versus mean sleep duration and positive MI versus sleep duration. Positive lag values indicate that mood ratings (from which MI was calculated) preceded sleep by one or more weeks. Negative lag values indicate that sleep preceded mood by one or more weeks. A lag of 0 represents sleep and mood reported during the same week. Positive CCF values indicate that higher MI was associated with longer mean sleep duration (or lower MI was associated with shorter mean sleep duration), while negative CCF values indicate that higher MI was associated with shorter mean sleep duration (or lower MI was associated with longer mean sleep duration).

6.3.2.5 Influence of Demographic and Clinical Covariates

Given the most consistent relationships were observed between ratings of mood and SD during the same week, the results were used in a further analysis to explore the possible influence of demographic and clinical features. Selected demographic and clinical features were compared between participants with and without significant positive relationships. To examine the effect of IMM treatment in more detail, the CCF analysis between weekly mood and SD ratings was repeated by treatment group (Figure 6.9). A significant positive relationship was most frequently observed between depressive mood and all types of SD during the weak. A greater proportion of significant relationships were present for MIMM than FIMM. For MIMM, the proportions were: initial insomnia (42.11%, *n*=16), middle insomnia (30.77%, *n*=12), terminal insomnia: (31.43%, *n*=11), hypersomnia (47.06%, *n*=16). In FIMM, the proportions were: initial insomnia (22.64%, *n*=12), middle insomnia (21.82%, *n*=12), terminal insomnia (18.52%, *n*=10), hypersomnia (32.69%, *n*=17).

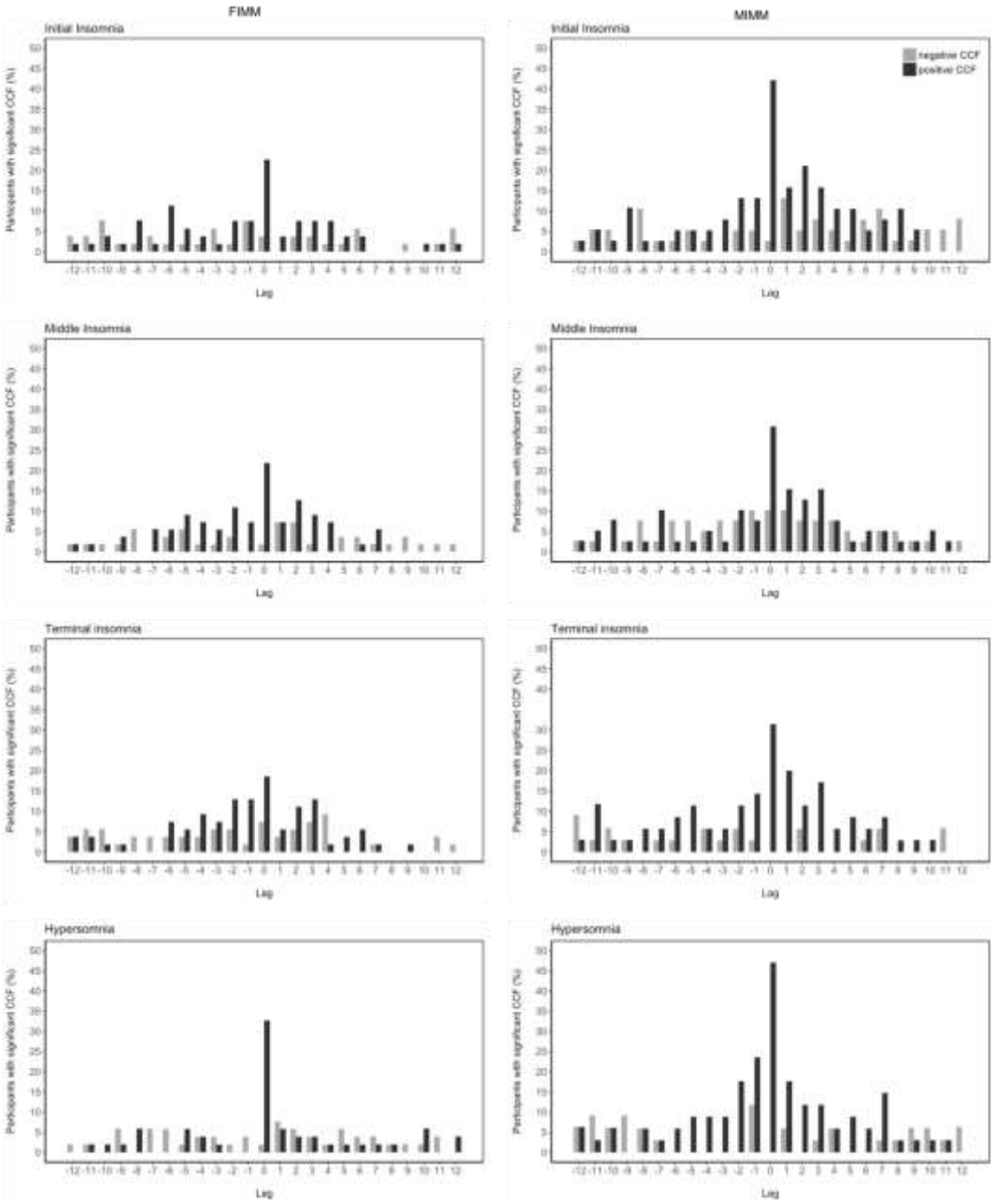


Figure 6.9 Bar plots showing the percent of participants (*n*=97) with significant CCFs at each lag for depressive mood versus initial insomnia, middle insomnia, terminal insomnia, and hypersomnia, by treatment group. Positive lag values indicate that mood ratings preceded sleep ratings by one or more weeks, while negative lag values indicate that sleep ratings preceded

mood ratings by one or more weeks. A lag of 0 represents mood and sleep ratings for the same week. Positive CCFs indicate more severe depressive mood was associated with more SD (or less severe depressive mood was associated with less SD), while negative CCFs indicate more severe depressive mood was associated with less SD (ore less severe depressive mood was associated with more SD).

A summary of the CCF analysis between elevated mood versus decreased need for sleep, stratified by treatment group, is presented in Figure 6.10. The most frequently observed CCF was a positive relationship between elevated mood and decreased need for sleep during the same week, and proportions were similar for FIMM (63.27%, *n*=31) and MIMM (60.61%, *n*=20). The positive CCF indicates that more elevated mood was associated with a higher severity of decreased need for sleep (or less elevated mood was associated with less severe decreased need for sleep).

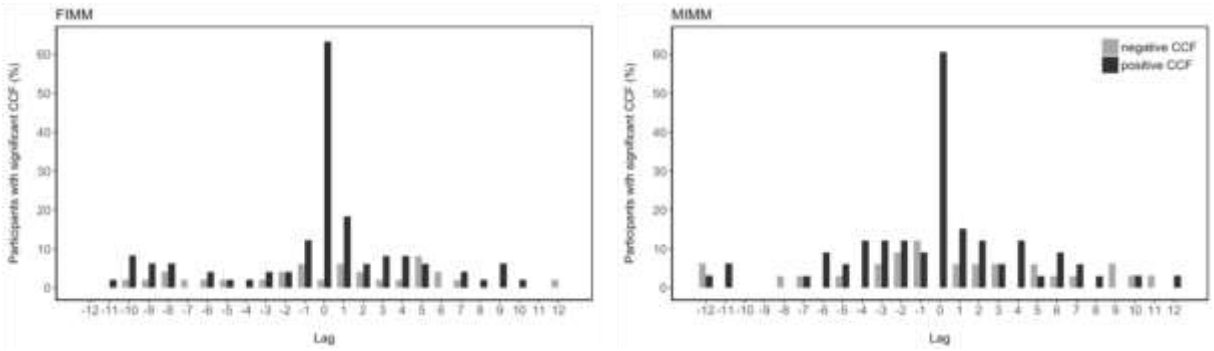


Figure 6.10 Bar plots showing the percent of participants (*n*=97) with significant CCFs at each lag for depressive mood versus initial insomnia, middle insomnia, terminal insomnia, and hypersomnia, by treatment group. Positive lag values indicate that mood ratings preceded sleep ratings by one or more weeks, while negative lag values indicate that sleep ratings preceded mood ratings by one or more weeks. A lag of 0 represents mood and sleep ratings for the same week. Positive CCFs indicate more elevated mood was associated with more SD (or less elevated mood was associated with less SD), while negative CCFs indicate more elevated mood was associated with less SD (ore less severe elevated mood was associated with more SD).

Table 6.4 summarises the results of the comparisons of demographic and clinical features between patients with significant and non-significant CCFs mood and SD ratings during the same week. None of the demographic or clinical features significantly influenced the presence of a significant relationship, apart from diagnosis. Patients with a diagnosis of BDI were more likely than BDII to have a significant positive relationship between negative mood and terminal insomnia (p=0.036). Although not significant, patients in FIMM were less likely to have a significant relationship between negative mood and initial insomnia (p=0.065).

Table 6.4 Comparisons of demographic and clinical features between patients with and without significant cross-correlations between mood and sleep disturbance ratings during the same week.

	Initial Insomnia			**Middle Insomnia**			**Terminal Insomnia**		
	Sig.	**Not sig.**		**Sig.**	**Not sig.**		**Sig.**	**Not sig.**	
	***n*=28**	***n*=63**		***n*=24**	***n*=70**		***n*=21**	***n*=68**	
	***n*(%)**	***n*(%)**	***p***	***n*(%)**	***n*(%)**	***p***	***n*(%)**	***n*(%)**	***p***
Age[a]	28(42,15)	63(46,13)	0.313	24(42,16)	70(45,13)	0.387	21(43,15)	68(45,14)	0.684
Male	6(17.65)	16(23.19)	0.794	6(22.22)	16(21.92)	0.788	5(17.24)	16(21.05)	1.000
BDI	18(52.94)	41(59.42)	1.000	16(59.26)	46(63.01)	1.000	18(62.07)	41(53.95)	0.036
FIMM	12(35.29)	41(59.42)	0.065	12(44.44)	43(58.9)	0.347	10(34.48)	44(57.89)	0.204
Medication	28(82.35)	57(82.61)	0.172	22(81.48)	66(90.41)	0.643	20(68.97)	63(82.89)	1.000
Any	10(29.41)	25(36.23)	0.817	6(22.22)	28(38.36)	0.225	9(31.03)	22(28.95)	0.436
Lithium	11(32.35)	28(40.58)	0.819	9(33.33)	31(42.47)	0.637	8(27.59)	29(38.16)	0.803
Anticonvulsant	7(20.59)	24(34.78)	0.243	5(18.52)	27(36.99)	0.139	6(20.69)	24(31.58)	0.792
Antipsychotic	16(47.06)	28(40.58)	0.364	9(33.33)	38(52.05)	0.237	10(34.48)	34(44.74)	1.000
Antidepressant	9(26.47)	11(15.94)	0.169	7(25.93)	13(17.81)	0.385	7(24.14)	11(14.47)	0.119
Anxiolytic	2(5.88)	6(8.7)	1.000	2(7.41)	5(6.85)	1.000	3(10.34)	4(5.26)	0.349
Hypnotic	1(2.94)	3(4.35)	1.000	1(3.7)	3(4.11)	1.000	1(3.45)	3(3.95)	1.000
Other	4(11.76)	3(4.35)	0.196	2(7.41)	5(6.85)	1.000	2(6.9)	5(6.58)	0.666
Rapid cycling	28(42,15)	63(46,13)	0.313	24(42,16)	70(45,13)	0.387	21(43,15)	68(45,14)	0.684

	Hypersomnia			Decreased Need for Sleep		
	Sig.	**Not sig.**		**Sig.**	**Not sig.**	
	***n*=33**	***n*=53**		***n*=51**	***n*=31**	
	***n*(%)**	***n*(%)**	***p***	***n*(%)**	***n*(%)**	***p***
Age[a]	33(44,15)	53(45,13)	0.633	51(42,14)	31(46,13)	0.232
Male	5(11.36)	17(26.56)	0.126	14(22.95)	8(19.51)	1.000
BDI[b]	22(50)	36(56.25)	1.000	32(52.46)	25(60.98)	0.137
FIMM	17(38.64)	35(54.69)	0.257	31(50.82)	18(43.9)	0.821
Medication	31(70.45)	49(76.56)	1.000	46(75.41)	30(73.17)	0.401
Any	9(20.45)	22(34.38)	0.249	16(26.23)	13(31.71)	0.351
Lithium	14(31.82)	22(34.38)	1.000	24(39.34)	11(26.83)	0.361
Anticonvulsant	9(20.45)	21(32.81)	0.352	15(24.59)	10(24.39)	0.809
Antipsychotic	16(36.36)	27(42.19)	1.000	24(39.34)	17(41.46)	0.649
Antidepressant	5(11.36)	13(20.31)	0.415	13(21.31)	5(12.2)	0.414
Anxiolytic	1(2.27)	4(6.25)	0.645	3(4.92)	5(12.2)	0.147
Hypnotic	2(4.55)	2(3.12)	0.636	1(1.64)	3(7.32)	0.149
Other	1(2.27)	5(7.81)	0.399	3(4.92)	2(4.88)	1.000
Rapid cycling	33(44,15)	53(45,13)	0.633	51(42,14)	31(46,13)	0.232

[a] *n(mean,sd);* BDI=bipolar I disorder; FIMM=facilitator-supported integrated mood management; Sig=participants with significant CCF; Not sig.=participants without a significant CCF.

6.4 Discussion

Given its severity and chronicity, treatment for BD requires not only acute stabilisation during mood episodes, but also long-term, ongoing management of symptoms (Geddes & Miklowitz, 2013). Regular monitoring of symptoms is often encouraged with the aim of self-monitoring of symptom severity in patients and improve recognition of prodromal symptoms to prevent relapse. Real time assessment techniques are often preferred to traditional assessments in order to address issues of recall bias, which often cited as a limitation of research in this field. These techniques also permit the assessment of temporality between symptoms, which is widely regarded among the criteria critical for establishing causality. Understanding the directionality of related symptoms may be useful in order to better understand underlying mechanisms of illness, prevent or mitigate complications, and to identify risk factors for relapse. This study aimed to further clarify the nature of the relationship between SD and mood changes, specifically, to determine if existing evidence is replicable, and to extend evidence by examining the relationship between MI and SD.

The most consistent associations observed in this study occurred between weekly measures of mood and sleep. The highest proportion of subjects with significant cross-correlations for both elevated and depressive moods were positive and occurred for mood and sleep ratings during the same week. For depressive mood ratings versus disturbed sleep, proportions of patients with significant cross-correlations ranged between 23% and 40%. For elevated mood versus decreased need for sleep,

approximately 60% of participants had significant cross-correlations at lag 0, suggesting a particularly strong relationship between sleep loss and elevated mood. Using weekly assessments, the capability of predicting pending changes in mood or sleep at any positive or negative time shifts appears to be limited given uniformly low proportions of significant cross-correlations (<20%) for any degree of time shift between mood and sleep ratings. Although, as expected, the distributions appear to show approximate normality, indicating that proximal mood and sleep measurements are more strongly related than distant ones. Furthermore, similar proportions of significant cross-correlations were observed for positive and negative lags, which perhaps suggests a degree of bidirectionality between sleep and mood changes. This aligns with results of the study by Talbot *et al*, which similarly observed a bidirectional relationship between SD and changes in intensity of positive and negative affect (Talbot et al., 2012).

Cross-correlations between daily mood and sleep ratings produced considerably less consistent results; fewer subjects had significant cross-correlations at any lag for both positive emotions and negative emotions with sleep duration. The most frequent cross-correlations occurred for sleep duration the night before mood change, with a significant CCF in approximately 9% of patients. Similar proportions of positive and negative cross-correlations were observed for negative emotions and sleep at all lags, indicating that both longer and shorter sleep durations were related to more negative emotions. On the other hand, inverse correlations were predominant for positive emotions, suggesting that shorter sleep duration predicts more positive emotions (or longer sleep duration predicts lower ratings of positive emotions). Given the small proportions of significant

CCFs, it is possible that these findings merely represent normal variations within the subjects. However, these findings show some consistency with prior research. The observed pattern of significant CCFs is consistent with a similar study conducted by Bauer *et al.*, which also found that the most common CCF between mood and sleep occurred at 1-day latency in approximately 40% of participants. (Bauer et al., 2006). Notably, the smaller proportion of significant CCFs observed in this study (9%) may be the result of lower power due to fewer mood and sleep pairs included in the CCF analysis; while Bauer *et al.* followed participants for on average 169 days, this analysis only included a maximum of 35 daily mood and sleep assessments. In addition, differences in the polarity of mood changes is relation to sleep duration are also largely consistent with existing evidence of the association, such that elevated mood is predominantly related to sleep loss, whereas both insomnia and hypersomnia are evident in depression (Barbini et al., 1996; Gershon et al., 2017; Steinan et al., 2016; Wehr et al., 1982).

Additionally, very few significant CCFs between MI and mean weekly sleep duration were observed for all lags, providing little evidence about the direction of relationship between MI and sleep duration. Although not clearly present in this study, some preliminary evidence for the relationship between MI and sleep in BD has been published previously. Carr and colleagues studied patients with BD, BPD, and healthy controls to investigate correlations between mood and diurnal rhythms. Mood was measured 10 times per day using the MZ, and physiological measures of diurnal rhythms were collected using a portable electrocardiogram (ECG) device and actigraphy. They

examined several indicators of diurnal rhythms in relation to MI summarised over 4-day intervals. In general, BD patients showed weak correlation with diurnal rhythms, however, a relationship was evident between MI and variability in sleep phase (Carr et al., 2018). This highlights the importance for future research to differentiate the effects of different sleep parameters on mood variation across different psychiatric conditions. In this case, it is possible that sleep duration is less important than changes in sleep phase in terms of MI within patients with BD.

It is notable that the principal components derived from the daily mood ratings were comparable those observed previously. The current study identified positive emotions and negative emotions as the two principal components based on the cumulative variance explained. Previously, PCA was conducted the MZ in patients with BD, BPD and healthy controls. The MZ questionnaire used in their study was comprised of six items (rather than 5 in this study), which included *sad* instead of *depressed* and added *angry*. Researchers found that the components differed between participant groups, and in BD, the first two components were also comprised of predominantly 'positive feelings' and 'negative feelings', which explained 58% and 20% of the total variance, respectively (Tsanas et al., 2017).

Finally, it was also important to determine whether specific patient features influenced the presence or absence of the observed associations. Given that the most consistent relationship was observed for the CCF analysis of weekly ratings at lag 0, it was used for further assessment. The patterns of results of the CCF analysis were similar for FIMM

and MIMM, although a consistently higher proportions of patients in MIMM had significant CCFs across all comparisons between depressive mood and SD, particularly the association between depressive mood and insomnia for which the comparison neared significance (p=0.065). The primary analysis of these randomised-controlled trial data revealed minimal differences between the FIMM and MIMM interventions. Patients in FIMM and MIMM showed no significant differences in manic or depressive symptoms and neither group showed a change in manic or depressive symptoms over time. However, the IMM interventions were associated with increased knowledge of BD[s] at 3 months, particularly FIMM, and improved knowledge was associated with more weeks spent well (Bilderbeck, Atkinson, et al., 2016). Increased BD literacy in FIMM relative to MIMM may be one possible explanation for the smaller proportions of significant CCFs in FIMM observed in this study. Knowledge about BD may indirectly affect the relationship between mood and sleep through any of several means, such as greater adherence to medication, engagement in health-promoting activities, or improved mood regulation skills.

The remaining comparisons of demographic and clinical features of the patients showed little difference between patients with and without significant CCFs for weekly ratings. However, more patients with BDI than BDII showed a significant relationship between depressive mood and terminal insomnia during the same week (p=0.036).

[s] Assessed using the Oxford Bipolar Knowledge Questionnaire (OBQ), which enquires about patients' knowledge of risk factors and risk markers for impending mood changes, as well as behaviours (such as sleep-wake cycles) and medicines that may contribute to MI.

Interestingly, the study by Bauer and colleagues, found that a significantly higher proportion of patients taking benzodiazepines had significant CCFs between sleep plus bedrest and mood. They cite several possible reasons for this, including self-medication in response to SD, possible phase-shifts in the sleep-wake cycle due to the medication, or interactions between the medications and *CLOCK* gene variants to alter diurnal rhythms (Bauer et al., 2006). This was not supported by the current study, which found no significant differences between patients with and without significant CCFs in terms of prescribed medications. However, the sample sizes in the comparisons were very small (for example, only 8 patients in the sample were taking anxiolytics), and there was unlikely sufficient power to detect an effect.

6.4.1 Limitations

The current study was limited by a number of factors. First, mood and sleep data were collected only daily and weekly, which limited the depth at which the relationship could be studied. For example, mood later in the evening and mood earlier in the day may be differently related to nighttime sleep. However, mood assessments were prompted during the afternoon, and therefore, may not have represented evening mood. In addition, aggregate estimates of SD may not be representative of the entire week. In fact, it has been observed that ratings of weekly symptoms may more closely represent a patients most recent experiences than an average of the week (Tsanas et al., 2016). Furthermore, the estimation of MI based on daily assessments resulted in relatively few intervals for use in the CCF analysis. While the CCF analyses on weekly assessments

included up to 52 pairs of mood and sleep assessments, the maximum number of possible pairings for daily ratings was only 35, resulting in only 5 pairs for the comparison between MI and average sleep duration. Consequently, the examination of MI and mean sleep duration had limited reliability, and it may be naïve to discount an association between MI and sleep duration based on the lack of a clear relationship observed in the current study. More frequent assessments combined with longer follow-up may provide clearer results.

Second, sleep parameters were assessed using self-report, which may not align with participants' actual sleep patterns. In patients with BD, weak correlations are often observed between subjective ratings of sleep and objective measures such as actigraphy (A. G. Harvey et al., 2005; Krishnamurthy et al., 2018; Ritter et al., 2012). In addition, several potentially important aspects of sleep were not measured, for example, sleep phase and bedrest–both of which have been identified as salient considerations in BD and health more generally (Carr et al., 2018; Tsanas et al., 2016).

Third, the current analysis did not account for the symptom status of patients, and the relationship may be different during major mood episodes (hypomania, mania, depression) and euthymia. Although still present to a significant degree during euthymia, SD often escalates just prior to and during major mood episodes (Plante & Winkelman, 2008). The relative severity and characteristics of MI during mania, hypomania, and depression and euthymia are less well known.

Fourth, the potential confounding effects of individual psychotropic medications were not assessed. Many mood stabilising medications also have sleep-related side effects. Adding to this, medications within the same class may have very different effect on sleep, while several individual medications can have either sedating or alerting effects. For example, possible side effects of quetiapine include both insomnia and drowsiness (Joint Formulary Committee, 2018). Given the large amount of heterogeneity in prescribed medications and the presence of polypharmacy within the sample, it was not feasible to control for individual medications in the analysis.

Finally, between 15% and 30% of responses were missing on the daily and weekly ratings, and the effect of missing data on the results is unclear. Non-response may produce bias if it is systematically related to either MI, SD or both. For example, patients may fail to respond because they are feeling particularly well or unwell in terms of their mood or if they are experiencing substantial mood fluctuations. A previous study of daily MZ ratings in patients with BD examined whether there were systematic differences between mood ratings before and after missing responses. Researchers found no evidence that failure to respond was related to mood (Tsanas et al., 2016).

6.4.2 Directions for Future Research

Based on the current study, there are several key areas for future research. As identified in previous chapters (see Chapter 2 and Chapter 3), understanding of the nature of MI and its measurement needs refinement. Of particular relevance in the current chapter is a poor understanding of the adequacy of different MI measures under different conditions.

This study quantified MI using TKEO because it was identified as the comprehensive, representing both instantaneous changes in amplitude and frequency of the time series. There are other methods previously used to summarise MI based on time series mood data including the root mean-squared successive difference (RMSSD), standard deviation (SD), and entropy (Carr et al., 2018; Tsanas et al., 2016), and the suitability of different MI measures may depend on the context in which it is used. However, the differences between different MI measures have not been well studied. Likewise, each measure differs in the characteristics it summarises, and it is currently unclear whether any one measure is superior to others under certain circumstances. For example, the frequency, rapidity, and intensity (amplitude) of mood changes may have different relative contributions to the poor outcomes associated with MI. Therefore, future research should seek to identify similarities and differences between the measures of MI and their relative applicability for assessing particular objectives in order to advance research into MI and to facilitate comparability between studies.

In addition, while it is clear that sleep plays a critical role in BD and in MI more generally, future work is needed to parse the relative contributions of different sleep and circadian abnormalities in relation to MI (see also Chapter 3). In BD, many different types of sleep and circadian disturbances have been identified (Murray & Harvey, 2010), and they may have different origins and play different roles in the genesis of MI and other complications. For example, REM sleep is posited to be particularly important for emotional regulation (Murray & Harvey, 2010), and warrants further investigation. Additionally, disturbances in the sleep-wake cycle may be manifestations of

abnormalities in either the circadian rhythm or sleep homeostat or both (A. G. Harvey, 2008b). Assessing a range of sleep and circadian indices within the same sample may allow for isolation of specific parameters in order to identify their relative salience in relation to MI. In order to achieve these objectives, future research should employ standardised evidence-based indices of SD to facilitate comparability within the literature (D. J. Buysse et al., 2006).

A major possible confound in this area of research, is the presence of psychotropic medications. Since many medications have effects on both mood and sleep, they have potential to bias study results. In BD, the use of mood-stabilising medications is often the primary treatment for both acute and long-term maintenance of symptoms. While this study found that none of the classes of medications examined significantly influenced the presence of a significant CCF, the comparisons were likely underpowered, and it is unclear whether specific individual medications may have had an effect. Medications are often heterogeneous, and polypharmacy is common, therefore, controlling the effects of medications through statistical techniques such as stratification may not always be feasible. Likewise, studying unmedicated individuals BD may also be inadequate because such individuals are typically not representative (Phillips, Travis, Fagiolini, & Kupfer, 2008). Therefore, it is important for future research to carefully consider strategies for assessing and controlling medication effects. Potential strategies to assess the effects of medications in future work may include, for example, limiting samples to specific types of medications or adapting within-subject longitudinal designs (Phillips et al., 2008).

Finally, more work is needed to differentiate MI and SD process that are universal from those that are disorder-specific. Since the current study did not have a control group (such as individuals with an alternative diagnosis or healthy controls), it is unclear to what extent the current results are generaliseable. Previous research has found some differences between disorders in associations between sleep and mood. For example, Carr and colleagues found clear differences between BPD, BD, and healthy controls in their study of correlations between diurnal rhythms and MI (Carr et al., 2018). Specifically, BPD showed the greatest variability in mood and diurnal rhythms and several positive correlations between MI and variability in HR, activity, and sleep, whereas BD showed intermediate variability in mood and sleep and weak correlations between MI and diurnal rhythms except for a strong positive correlation between MI and variability in sleep phase. Talbot and colleagues also found differences between patients with BD, insomnia, and healthy controls in their study of the temporal relationship between SD and mood changes. While negative mood was heightened in both interepisode BD and insomnia, there were no apparent differences between the three groups in positive mood. Also, only total wake time was associated with next morning negative mood in BD, while both negative mood and positive mood were associated with total wake time in insomnia (Talbot et al., 2012). Enhanced knowledge of similarities and differences in MI and SD between disorders may serve to further understanding of underlying mechanisms and facilitate development of targeted or transdiagnostic treatment strategies.

6.5 Conclusion

MI and SD are each clinically important because of their negative impacts on disease course, quality of life, and functioning. Although important transdiagnostically, MI and SD are highly prevalent in BD, therefore providing a strong signal to permit in-depth study of their association. The current study extends evidence that SD is closely related to alterations in intensity of positive and negative affect in BD, with the strongest evidence for changes occurring during the same week. This study also provides further support that sleep duration is positively associated with more negative mood, and inversely associated with more positive mood, typically occurring with a 1-day latency (Bauer et al., 2006; Talbot et al., 2012). However, little evidence was found to clarify the direction of a relationship between sleep duration and MI. The current study was limited by the relative infrequency of symptom assessments and the inability to account for medication effects. It will be critical for future research to clarify the nature and measurement of MI, employ standardised and objective measurements sleep and circadian rhythm disturbances to establish their relative significance, and isolate the effects of medications. All of these will promote advancements of knowledge about the associations between MI and SD, which showed promise for providing a framework for developing new treatment strategies to prevent complications and improve outcomes in BD, and other psychiatric disorders.

Chapter Seven: Discussion and Conclusion

7.1 Thesis Summary

This thesis investigated the epidemiological relationship between MI and SD as transdiagnostic features on the pathway to ill-health. Chapter 2 examined prevalence data for MI available in the literature. The systematic review showed extensive heterogeneity in prevalence data stemming largely from an absence of clear and consistent operational definitions of MI, with prevalence estimates ranging hugely between 6% and 68%. Chapters 3 and 4 used data from the APMS 2007 to investigate the epidemiology of MI and SD in a representative sample of adults in England. It was observed that MI and SD are common and strongly related, irrespective of mental illness. MI and SD were related independently to a wide range of social and health outcomes, and the co-occurrence of the two features was particularly devastating. Chapter 5 examined the clinical features and incidence rates of clinical outcomes in patients presenting to secondary mental health care. This study showed that MI and SD are common transdiagnostically and predict higher service utilisation even when compared with other clinical features of mental disorder. The results also support and extend evidence from Chapter 3 showing that the co-occurrence of MI and SD is more strongly related to clinical features than either symptom alone. Finally, Chapter 6 aimed to examine the temporality between MI and SD in a cohort of patients with BD. While there was a clear relationship between MI and SD occurring during the same week, the temporality of the relationship remains unclear.

7.2 Challenges and Limitations

The major limitations of this thesis stemmed principally from three interrelated challenges. Foremost, it remains difficult to obtain high quality, deeply phenotyped MI and SD on an epidemiological scale. Limitations in the measurement of MI and SD within existing epidemiological samples have hindered progress, despite widespread advancements in measurement technologies. Furthermore, secondary data analysis of existing datasets presents challenges in the design of good quality research that answer pre-specified questions.

7.2.1 Secondary Data Analysis

Epidemiological research often requires the use of existing data because the time and financial costs often makes primary data collection unfeasible. This presents a major challenge in study design because the data are often collected for purposes other than the objective of the study. The above weakness in measurement reflect a broader challenge of analysing data originally collected for purposes other than the specific objectives of this thesis. Secondary data analysis often requires compromise that may otherwise be addressed if primary data collection was undertaken.

7.2.2 Weaknesses in Measurement

The major challenges and limitations throughout this thesis stemmed principally from weaknesses in measurement of MI and SD. In the broader literature, there exists very little information about the validity of different MI assessments. For example, no

information is available for the validity of the single item used to examine MI in the APMS 2007. While the QIDS and ASRM have been validated, little is known about the differences between various techniques for quantifying MI from time series data. Nevertheless, this thesis used several methods to assess MI and all showed similar trends in terms of a strong relationship with SD.

Furthermore, assessments of SD used in this thesis were often crude and retrospective. It would have been beneficial to combine different methods, such as self-report questionnaire or sleep diary, with other objective measures, like actigraphy. This would enable more detailed assessment of sleep problems and permit the collection of physiological markers of diurnal rhythms or rest-activity cycles, which are very closely linked with sleep and likely to be equally important.

A related limitation, present throughout this thesis, was the inability to examine severity and chronicity of symptoms. Dimensional assessments are important in order to distinguish clinically important symptoms from normal variations in experience, and to establish the presence of a 'dose-response' relationship–a core component for establishing causality. This will be a key area to improve in future research.

Inadequate temporal information limited the ability to examine the directionality between MI and SD, and between these features and social and health outcomes. For example, in Chapter 3 it was unclear whether SD caused suicidal ideation and behavior attempt or if suicidality led to SD. These are essential pieces of knowledge before mechanisms can be fully understood. It is hypothesized that MI and SD are mutually

maintaining, and therefore it is likely that he temporality between the two will be very difficult to disentangle.

Advances in technology and the emergence of digital health are providing improved measurement techniques and bringing new opportunities to conduct this type of research on an epidemiological scale. For example, the implementation of wrist-worn actigraphy in the UK Biobank has offered an unparalleled opportunity to study sleep and circadian rhythms in over 70,000 participants (Ferguson et al., 2018). Still, few epidemiological studies have the infrastructure required to study these factors prospectively with the accuracy of deep phenotyping, and while these opportunities are exciting, difficulties of getting high quality data to scale remain.

Missing data are an important consideration when designing future studies of this type because increasing the resolution of information is also likely to increase the risk and impact of missing data. Surveys, such as the APMS 2007, are often capable of capturing large amounts of data while minimising non-responses, however, this is often done at the expense of information. Passive data collection is one increasingly preferred option for minimising both participant burden and missing responses when collecting high frequency data within large studies.

While passive data collection through wearable devices lends well to the collection of objective markers of sleep and circadian rhythms, current methods for collecting mood responses still relies heavily on active participation and sustained engagement. Although the use of EMA procedures is promising, maintaining adherence remains a major

challenge in their implementation. As a result, one alternative for future research may be to move away from subjective mood reports, towards more objective assessments of other highly correlated parameters. For example, physiological markers of stress may be appropriate proxies for mood.

7.3 Future Directions

7.3.1 Standardised Nomenclature, Assessment, and Reporting

In all research fields, standardised nomenclature, assessment, and reporting are key to propelling knowledge growth, and ensuring quality, comparability, and accurate interpretation of research findings. As evidenced by the systematic review of MI prevalence (Chapter 2), the absence of such standards can lead to highly inconsistent results, and perhaps ultimately, hinder advancement in research and its translation into empirically founded clinical and public health practice. Therefore, the production and widespread adoption of principles for studying and reporting MI and SD are key steps in progressing this field of research.

In 2006, Buysse and colleagues released recommendations for research assessment of insomnia (D. J. Buysse et al., 2006). While these standards have been largely adopted in clinical and laboratory research settings, they are less frequently followed in population surveys. In the case of the APMS, sleep assessments were derived for secondary analysis from the sleep section of the CIS-R. This may be largely because the assessment of sleep is not typically a core objective for these surveys, and therefore, sleep measures are not selected specifically for the survey. One primary use of epidemiological surveys, like the

APMS, is surveillance of health states within the nation. Given the importance of good sleep for optimizing health, and the potential disease burden associated with poor sleep, the addition of a sleep (and circadian rhythm) module within national surveys is warranted.

Similarly, future research should aim to identify and implement standards within the measurement of MI. Like the guidelines put forward for insomnia, specific recommendations should consider the objective of the research (for example, to evaluate biological mechanisms or treatment effectiveness) and the study design (for example, randomised-controlled trial, cross-sectional, or prospective designs). Importantly, recommendations for reporting electronically-collected mood data have been recently produced, and will likely help to advance the field of MI research (Faurholt-Jepsen et al., 2019). Still, more work is required to better understand and improve MI measurement techniques. To date, there has been no study directly comparing methods for assessing MI, and few have used multiple methods within the same study. In order to identify the best methods for assessment, more knowledge is needed with regards to the suitability of measures under different conditions or objectives, and their theoretical and clinical implications. Furthermore, additional research is needed to clarify the relative contributions of different aspects of MI and to develop measures of MI that capture the construct in its entirety.

7.3.2 Clarification of Transdiagnostic Models

Future research should seek to clarify transdiagnostic models involving SD, MI, and mental illness. A useful transdiagnostic model should consider both *multifinity* (how a single transdiagnostic factors can lead to multiple different disorders) and *divergent trajectories* (how a transdiagnostic factor may be associated with one set of symptoms in one individual, and yet a different set of symptoms in another individual; Nolen-Hoeksema & Watkins, 2011). Therefore, in order to clarify the process by which SD and MI may lead to mental illness, future research should aim to answer these two questions.

While empirically driven theory suggests disruptions in biological pathways involved in both mood disturbance and sleep and circadian timings, particularly neural circuitry and neurotransmitter release, are at the core of mental illness (Wulff et al., 2010), the mechanisms have not been fully elucidated. Foremost, the directionality between MI and SD remains unclear. Chapter 6 showed a strong and consistent cross-sectional relationship between mood and sleep during the same week, but an attempt to distinguish temporal patterns provided little clear evidence. Synthesis of existing literature suggests that MI and SD may be related bi-directionally such that SD may disrupt subsequent mood and disturbances in daytime mood may lead to poor nighttime sleep.

Additionally, future research should aim to understand the factors that influence trajectories from SD and MI to different mental illness. Future work may aim to identify possible factors that determine whether transdiagnostic factors predict different sets of

symptoms or outcomes. For example, SD takes many different forms within the population and it is possible that the interaction of these different forms with distinctive sets of factors (like MI) may produce characteristic symptoms of different mental illness.

7.4 Clinical and Public Health Implications

7.4.1 Routine Assessment and Higher Treatment Priority

Findings showed that MI and SD were consistently, cross-sectionally, associated with poor health and social outcomes (Chapter 4), and patients with MI and SD showed significantly increased rates of hospitalization, prescribed medication, and contacts with mental health professionals (Chapter 6).

The poor prognosis associated with MI and SD may be, in part, explained by their poor recognition and inadequate treatment. For example, SD is traditional viewed as secondary to the 'primary dysfunction' that will resolve upon treatment of the underlying condition. Complaints of SD are typically not seen as serious and, consequently, often given a low priority in care planning. However, given that mechanisms involved in SD may be at the origins of many psychiatric disturbances, the effects of improving sleep on mental health are likely to be extensive. Therapies to address SD are effective, and often produce significant in improvements psychosocial functioning in addition to sleep (Freeman et al., 2017). Likewise, stabilizing sleep in patients admitted to hospital for acute psychiatric care has been shown to decrease length of hospital stays by, on average, approximately 8 days (Sheaves et al., 2017).

In contrast to sleep, mood disturbances, are typically given a higher priority during treatment, however, there appears to be inadequate recognition and understanding of MI by clinicians. Training for clinicians in the recognition and implications of MI should be implemented more widely. Furthermore, it needs better recognised that MI is present in a wider range of disorders than just those for which it is officially recognised according to current diagnostic systems.

Disrupted social rhythms and MI may contribute a cumulative effect on mental illness. There appears to be a bi-directional relationship between mood and sleep such that poor sleep negatively affects daytime mood, and, in turn, mood disturbances further disrupt subsequent nighttime sleep. Furthermore, SCRD may lead to atypical behavioural patterns such as eating, social activity, and light exposure, which may further destabilize sleep and circadian physiology, thereby exacerbating existing abnormalities in physiological diurnal rhythms such as neurotransmitter release (Wulff et al., 2010). Abnormal social rhythms are exemplified in patients with BD. For instance, measured using geolocation data obtained from smartphones, depressed BD patients show considerably less diurnal movement as compared with non-depressed BD patients and healthy controls (Palmius et al., 2018). Behavioural interventions may be particularly effective for long-term treatment through stabilizing rhythms. While social rhythm therapies are typically confined to a small set of disorders, they may be effective in a wider range of illnesses given a potential common underlying causal pathway involving SCRD. The frequent co-occurrence of MI and SD and their potential interaction presents a unique challenge for treatment. For example, pharmacotherapy used to address MI

often produces contradictory effects on sleep, and treatment for one may provoke or exacerbate the other. On the other hand, treatments to stabilize rhythms and improve sleep may be less likely to produce negative effects on mood.

7.4.2 Mind-Body Connection

The findings of this thesis also highlight a critical need for health care professionals to further recognise and emphasise the connection between mental and physical well-being. While comorbidity of physical illnesses is often viewed as requiring simultaneous treatment of both disorders, comorbidity of psychiatric and somatic illnesses are not as often viewed the same way (Sartorius, 2018). The connections between psychiatric and other medical fields tend to be relatively weak compared with linkages between departments specialised in somatic conditions. However, many biological systems work across multiple organs, including the brain. Furthermore, the co-occurrence of mental and somatic conditions is an important issue. For example, approximately 78% of excess deaths in persons with mental illness are attributable to physical illness (Lawrence, Hancock, & Kisely, 2013), and the cost of treating comorbid disease is much higher than if the diseases appeared alone (McDaid & Park, 2015).

In keeping with this evidence, Chapter 4 observed significantly increased associations between MI, SD and a range of physical health conditions such as cardiovascular and digestive problems, and arthritis. Both mood and sleep disturbances are associated with a wide range of illnesses. Many physiological functions, such as blood pressure, metabolism, heart rate, and immunity, follow cyclic patterns and their dysfunctions are

linked with disruptions in pathways involving sleep and circadian rhythms. As a result, treatment of dysfunctions underlying these cyclical processes, such as sleep problems, may be advantageous not only for mental health, but also physical well-being. Together these highlight the advantage of more holistic approaches. While improving, there is still need for better communication between mental health professionals and other medical practitioners and more emphasis on the interconnection of multiple organ systems in order to prevent or reduce complications.

7.4.3 Treatment and Prevention Strategies

The findings presented in this thesis are consistent with growing evidence in favour of MI and SD as transdiagnostic processes, involved in both the origins and maintenance of mental illness (Aldao, 2016; A. G. Harvey, 2008a; Howes et al., 2011; Jackson et al., 2003). In this thesis, MI and SD were strongly related (Chapter 3), and observed to occur in a range of individuals, including patients from all diagnostic classifications (Chapter 6). Transdiagnostic processes involved in mental illness are important and worthwhile targets for clinical assessment and interventions and public health policy and initiatives. If SD and MI are true transdiagnostic features and contribute to the cause of mental illness, then clinical and public health efforts should emphasise preventing and alleviating these symptoms present in a wide range of disorders. There are several advantages of identifying and understanding transdiagnostic processes. For example, mental disorders are often comorbid and clarifying processes involved in several disorders may help to further understand their underlying mechanisms. Second,

knowledge and treatment in one disorder may propel similar progression in other disorders. Third, interventions targeted at transdiagnostic processes may support more parsimonious training for clinicians and efficient treatment of symptoms or conditions (A. G. Harvey et al., 2011a).

The development of psychosocial therapies targeted at transdiagnostic processes have become more prominent in recent years (Mansell, Harvey, Watkins, & Shafran, 2009; Nolen-Hoeksema & Watkins, 2011), including, for example, treatment intended to address deficits in emotion regulation (Mennin & Fresco, 2010), and cognitive-behavioural interventions for SD (A. G. Harvey, 2009). Transdiagnostic treatments may be particularly effective if scalable to larger populations as they can be implemented in a wide range of individuals. Perhaps more importantly, if MI and SD are underlying processes involved in the origins of disease, then their treatment may be effective preventing or delaying the onset of disease and reducing related complications.

A challenge for all transdiagnostic treatments is to adequately address the range of presentations that exist across individuals. For example, the range of possible sleep problems and their differential associations with mental disorders implies that some degree of disorder-specific or symptom-specific tailoring is required (Harvey et al., 2011). BD, for example, tends to show hypersomnia during depressive periods, whereas manic episodes are associated with significant symptoms of insomnia. Importantly, treatments for one may exacerbate the other; while sleep deprivation has been shown to temporarily relieve symptoms of depression in persons with unipolar depression, it may

induce mania among persons with bipolar depression (Barbini et al., 1996; Benedetti & Colombo, 2011; Giedke & Schwärzler, 2002). Therefore, a 'one size fits all' approach may inadequately address symptoms within everyone, and at worst, may exacerbate one's illness. As suggested by Harvey *et al.*, a useful approach may be modular, such that all individuals are delivered core modules, while additional optional modules are available based on the individuals' specific sleep problems.

Digitally-delivered therapies are potentially cost-effective treatments that can be tailored to individuals' specific needs. For example, Sleepio (www.sleepio.com), a digitally-delivered cognitive behavioural therapy for insomnia, offers personalised sessions based on the participant's baseline assessment, adherence, and progression. A secondary analysis of routinely collected secondary health care data from the Greater Manchester area showed that eTherapies for mental health, such as Sleepio, significantly improve sleep and mental health outcomes in patients with a range of mental health difficulties (Elison et al., 2017). Crucially, internet-based therapies may help to reduce wait times, which represent a significant barrier to mental health services in the UK (Frith, 2017; Mind, 2014).

Treatments for MI may be slightly more difficult to scale-up, although remote monitoring is becoming increasingly available in clinical settings and may offer lower cost solutions for surveilling mood changes in patients with MI. These may be most effectively targeted at patients for whom MI presents a high risk for relapse. For example, a high degree of MI and mood changes are a salient indicator of impending

relapse in patients with BD. In the long-term, effective implementation of remote mood monitoring may decrease health care costs through preventing complications, such as hospitalisation.

Given the potential causal role of SD in mental and physical health and the modifiable nature of sleep, SD may be a particularly worthwhile target for public health intervention. Internet-based communication allows sleep education to be delivered to a significant portion of the population at relatively low cost and are likely to benefit individuals even without clinical illness. A potentially effective programme aimed at primary prevention may include implementation of curriculum to teach sleep hygiene to children in schools. Despite extensive evidence for the benefits of improving sleep, such as improved academic performance (Roberts, Roberts, & Duong, 2009), formal education on good sleep hygiene is not provided in UK schools. Within adults, similar educational programmes may be implemented in the workplace. A major challenge still exists in creating optimal sleep conditions for individuals in professions with continuous work hours, particularly among shift workers. Some evidence suggests that interventions delivered in the workplace may be worthwhile. For example, a brief correspondence-delivered therapy for poor sleepers in a Japanese workplace was shown to improve sleep habits, duration, and quality (Adachi et al., 2003). These interventions may be mutually beneficial for employers, given the links between sleep and alertness, performance, absenteeism, and safety (Cappuccio, Miller, & Lockley, 2010).

Later school start times are regularly discussed as potential options for combatting sleep deprivation and 'social jetlag' in adolescents by allowing pupils to awaken more naturally and be more alert during school. Evaluations of such programmes implemented in the US have demonstrated associations between delayed school start times and increased sleep duration, decreased daytime sleepiness and improved mood (Chan, Poon, Leung, Lau, & Lau, 2018; Owens, Dearth-Wesley, Herman, Oakes, & Whitaker, 2017). Unfortunately, evaluations of these types of programmes appear to be less feasible in the UK (Illingworth et al., 2018).

7.5 Conclusion

Mental disorders contribute substantially to disease burden. The origins of mental illness are complex and multifactorial. Identifying and understanding factors common to mental illness will provide important advances in assessment, treatment and prevention both at the clinical and population levels. SD and MI are common, closely linked, and may represent transdiagnostic factors on the pathway to mental illness. While independently associated with poor health and social outcomes, the co-occurrence of MI and SD is particularly detrimental. Given these associations, MI and SD need to be better recognised and receive a higher priority in clinical settings. SD may be a particularly modifiable feature. Given its association with a wide range of physical and mental health, SD should be viewed as a public health issue, and is a suitable target for public health policy and initiatives. To advance our understanding of this issue, future research is needed in order to better understand MI as a construct, and to clarify the mechanisms

that underpin the relationship between MI and SD, and poor outcomes such as mental illness.

Appendix A: Chapter 2 Supplementary Materials

Table A.1 Data extraction sheet.

	Publication Details		Study Characteristics						
Study #	**Author**	**Year**	**Study Design**	**Location**	**Source population**	**Sampling Method**	**Inclusion Criteria**	**Exclusion Criteria**	**Time of Data Collection**
1	Angst, J. *et al.*	2003	Cohort	Zurich, Switzerland	All residents	Stratified random sampling	Age 19 (M) & 20 (F)	Not available	1979-1993
2	Berenson, A., *et al.*	2008	Cross-sectional	n/a	Women aged 16-33 years	Stratified random sampling	None	Current or planned pregnancy/breastfeeding, current use or contraindication of hormonal contraception, current amenorrhea, specified medical disorders & dietary restrictions	2001-2004
3	Marwaha, S., *et. al.*	2013	Cross-sectional	England	Adults (16+) from private households in England	Multi-stage stratified probability	n/a	n/a	2006-2007
4	Milutinovic, D., *et al.*	2012	Cross-sectional	Serbia	ICU Nurses in secondary and tertiary care services	Opinion Poll	n/a	n/a	n/a
5	Peters, E.M., *et al.*	2016	Cross-sectional	England, Scotland, Wales	Adults (16-74) from private households in England Scotland and Wales	Multi-stage stratified probability	Common mental disorder, CIS-R score of 12+	n/a	2006-2007
6	Ward, J., *et al.*	2017	Cohort	UK	UK residents 40-69 years	Random	White UK ancestry	None	2006-2010

	Sample Characteristics					Measurement of MI	
Study #	**Response Rate (%)**	**Sample size**	**Age**		**Gender**		
			Range	**Mean (SD)**	**% Female**	**Scale/ tool**	**Item**
1	Baseline: 90% 15-year follow-up: 69%	A: 591 (261 controls) B: 499 (173 controls)	A: 19-34 (M) 20-35 (F) B: 26-49 (M) 27-50 (F)		A: 50.6 B: 50.1	Professional interviews at home	"Would you say you are one of those people who have frequent ups and downs?"
2	75.5	608	16-33		100.0	n/a	'mood swings'
3	57.0	403	16+	46.4 (0.3)	51.4	SCID-II	''Do you have a lot of sudden mood changes?'
4	86.9	1000	20+	33.2 (4.3)	95.1	n/a	'frequent mood swings'
5	79.0	2344	16-74	43.4 (0.5)	57.5	SCID-II	''Do you have a lot of sudden mood changes?'
6	5.5	113,968	40-69	56.8 (8.0)	52.3	EPQ-R-S	"Does your mood often go up and down?"

	Prevalence/Frequency Estimates							
	If proportion is reported:				If frequencies are reported:			
Study #	**Prevalence**	**Prevalence type**	**Error estimate**	**Error type**	**Number with MI (*n*)**	**Total sample size (*N*)**	**Calculated Prevalence[a]**	**Calculated SE[b]**
1	A: 5.8 B: 6.1	Lifetime	A: 1.4 B: 0.8	SE				
2		3 months			171	253	0.676	0.036
3	14.7	Several years	0.5	SE				
4		6 months			280	1000	0.280	0.027
5	13.9	Several years	0.9	SE				
6	35.3	Lifetime	0.03	SE				

M = Male, F = Female; CIS-R = Clinical Interview Schedule-Revised; SE = Standard error; [a]P = n/N; [b]SE = sqrt[p*((1-p)/n].

Table A.2 Adapted risk of bias tool.

Risk of Bias Tool
Adapted from Hoy et al. (2012)

For each study, please select the appropriate response option and provide a reason for your selection. Please record these responses on the data extraction sheet.
Note: If there is insufficient information in the article to permit a judgement for a particular item, please answer HIGH RISK for that particular item.

	Item	Risk of Bias	Notes & Examples
	Selection Bias		
1.	Was the sampling frame a true or close representation of the target population?	**LOW**	• The sampling frame was a list of almost every individual within the target population. • The cluster sampling method was used and the sample of clusters/villages was drawn from a list of all villages in the target population.
		HIGH	• The sampling frame was NOT a true or close representation of the target population. • The sampling frame was a list of just one particular ethnic group within the overall target population, which comprised many groups.
2.	Was some form of random selection used to select the sample, OR, was a census undertaken?	**LOW**	• Some form of random sampling was used (e.g. simple random sampling, stratified random sampling, etc.) • A census was undertaken; The target population was the village and every person in the village was sampled.
		HIGH	• A census was NOT undertaken, AND some form of random selection was NOT used to select the sample. • The nearest villages to the capital city were selected in order to save on the cost of fuel.
3.	Was the likelihood of non-response bias minimal?	**LOW**	• The response rate was >= 75% or the analysis showed no significant difference in relevant demographic characteristics between responders and non-responders. • The response rate was 68%; however, the researchers did an analysis and found no significant difference between responders and non-responders in terms of age, sex, occupation and socioeconomic status.
		HIGH	• The response rate was 69% and the researchers did an analysis and found a significant difference in age, sex and socio-economic status between responders and non-responders. • The response rate was 65% and the researchers did NOT carry out an analysis to compare relevant demographic characteristics between responders and non-responders
	Measurement Bias		
4.	Was an acceptable case definition used in the study?	**LOW**	• Mood instability can be a definition that includes some aspect of sudden, frequent and/or intense mood changes, regardless of the label.
		HIGH	• There was no description or an inadequate description of mood instability.
5.	Was the study instrument that	**LOW**	• The used a standardised scale that has been previously validated.

	measured the parameter of interest (mood instability) shown to have reliability and validity?		
		HIGH	• The authors used a measure with poor reliability and validity. • The authors developed their own questionnaire and did not test this for validity or reliability.
6.	Was the same mode of data collection used for all subjects?	**LOW**	• The mode of data collection is the method used for collecting information from the subjects. • All eligible subjects had a face-to face interview.
		HIGH	• The same mode of data collection was NOT used for all subjects • Some subjects were interviewed over the telephone and some filled in postal questionnaires.
7.	Was the length of the shortest prevalence period for the parameter of interest appropriate?	**LOW**	• The prevalence period is the period that the subject is asked about e.g. “Have you experienced mood instability during the past month. • The longer the prevalence period, the greater the likelihood of the subject forgetting if they experienced the symptom of interest.
		HIGH	• The prevalence period was several months or longer.
8.	Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	**LOW**	• The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of mood instability). • There were no errors in the reporting of the numerator(s) AND denominator(s) for the prevalence of mood instability.
		HIGH	• The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate. • E.g. In reporting the overall prevalence of mood instability (in both men and women), the authors accidentally used the population of women as the denominator rather than the combined population.
	Overall risk of study bias		
9.	Summary	**LOW**	• Further research is very unlikely to change our confidence in the estimate. Select if none of items 1-8 are labelled high risk.
		HIGH	• Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate. Select if items, 1, 2, 3 or 8 are labelled high risk. • Insufficient information is available to make an informed judgment about the risk of bias. Select if any of items 1-8 are labelled unclear risk and none are labelled high risk.

Table A.3 Summary of risk of bias assessment.

	Publication Details		Criteria								
Study #	**Author**	**Year**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Overall**
1	Angst, J. *et al.*	2003	Low	Low	Low	High	High	Low	High	Low	High
2	Berenson, A., *et al.*	2008	High	Low	Low	High	High	High	High	Low	High
3	Marwaha, S., *et. al.*	2013	Low	Low	High	High	High	Low	High	Low	High
4	Milutinovic, D., *et al.*	2012	High	High	Low	High	High	Low	High	Low	High
5	Peters, E.M., *et al.*	2016	Low	Low	Low	High	High	Low	High	Low	High
6	Ward, J., *et al.*	2017	Low	Low	High	High	High	High	High	Low	High

Appendix B: Chapter 3 Supplementary Materials

Table B.1 Classification of psychotropic medications based on high and low risk of sedating effects.

	High Risk	Low Risk
1st generation antipsychotics	trifluoperazine haloperidol flupentixol decanoate zuclopenthixol decanoate fluphenazine decanoate	
2nd generation antipsychotics	risperidone olanzapine clozapine quetiapine	aripiprazole sulpiride
Antidepressants	paroxetine phenelzine moclobemide amitriptyline clomipramine hydrochloride dosulepin hydrochloride doxepin mirtazapine	fluoxetine sertraline venlafaxine citalopram imipramine
Anxiolytics	diazepam lorazepam chlordiazepoxide hydrochloride temazepam nitrazepam buspirone	
Other		lithium

Table B.2 Estimated odds ratios and 95% confidence intervals for sleep disturbance in subjects taking medications with high risk of sedation and subjects not taking sedating medication.

	Female					**Male**				
	Sedating Medication		**No Sedating Medication**			**Sedating Medication**		**No Sedating Medication**		
	OR	**95% CI**	**OR**	**95% CI**	***p***	**OR**	**95% CI**	**OR**	**95% CI**	***p***
Any sleep problem	1.39	0.68–2.84	2.93	2.36–3.64	0.051	10.13	2.66–38.62	4.70	3.58–6.17	0.269
Insomnia	1.73	0.86–3.45	2.62	2.13–3.22	0.259	3.81	1.17–12.39	3.95	3.05–5.12	0.953
Hypersomnia	–	–	3.60	2.17–5.95	–	12.52	1.37–114.11	5.82	3.25–10.42	0.505

[a] All females with MI taking sedating medications also reported hypersomnia, therefore, odds ratio estimate for females taking sedating medications not available. Wald test for effect modification by sedating medication could not be computed.

Appendix C: Chapter 5 Supplementary Materials

This appendix describes the development of NLP applications used to identify MI, SD, and psychotropic medications for the study presented in Chapter 5. Some of the information presented here has been published previously (Patel et al., 2015; Perera et al., 2016). The outputs of each application require post-processing in order to derive the variables used in the analysis. Post-processing is also described below.

C.1. Phrases and terms identified by the NLP applications

C.1.1. Mood Instability

Three NLP applications were developed using the SLaM BRC Case Register in order to ascertain the concept of MI. Keywords were mood, affect and emotion. An initial search was conducted for each keyword (and variations such as affective or emotional) to identify the most commonly used modifier words indicating variability or instability (up to two words either side of the keyword). Table A.1 shows the list of modifier words for each keyword—*mood*, *affect*, and *emotion*—identified during the initial search of the BRC Case Register and the literature. These 'bags of words' were used in the development of the NLP applications. Outputs from the three NLP applications were combined to form the single construct of MI.

Table C.1 ‘Bag of words’ included during the development of the mood, affective, and emotional instability NLP application.

Mood	Affect	Emotion
change	change	changes
changeable	changes	difficulties regulating
changeable*	dysfunction	displays of
changes	instability	dysfunction
chaotic	irregular	dysregulation
dysfunction	labile	extremes
extremes	lability	instability
fluctuate	range	irregular
fluctuated	variable	lability
fluctuates		levels
fluctuating		outbursts of
fluctuation		range
fluctuations		regulation difficulties
instability		unstable
irregular		waves of
labile		
lability		
liability*		
liable*		
rapid cycling		
swings		
unpredictable		
unsettled		
unstable		
variable		
variation		
variations		
volatile		

*common misspelling. From Patel et al. (2015).

C.1.2. Disturbed Sleep

The disturbed sleep NLP application was designed identify the broad construct of problems with sleep from within free text. The application identified mentions of *sleep* (keyword) with modifier words within 0 to 5 words either side of the keyword. The modifier words included *poor**, *interrupt**, **disturb**, *disorder**, *prevent**, *stop**, and *problem**. Any side-by-side occurrence of *sleep* and *not* was also included.

C.1.3. Insomnia

The insomnia NLP application was designed to identify a narrower construct of insomnia. The insomnia application identified instances of *insom**, where * indicates any suffix (for example, insomnia or insomniac).

C.1.4. Prescribed Medication

The medication application was intended to identify names of medications prescribed to the patient and the dose. The application is intended to distinguish between medications that are currently prescribed, medications that have been prescribed in the past, and to ignore medications that are being considered for future prescription. Terms used in the development of the medication applications included generic and brand names of medications, both psychotropic and non-psychotropic. Dosage information was not considered in this study.

C.2. Post-processing of the NLP Outputs

During application development, key contextual information was annotated in addition to the phrases and terms directly referencing the feature. The contextual information considered in each application included: Contextual information considered in the all applications included:

> *Observation*. The feature was present (e.g. ‘has problems sleeping’), absent (‘has other problems, but sleeping is fine’), or uncertain (e.g. ‘possible insomnia’).
>
> *Temporality/Tense*. The feature was referenced in the past tense (e.g. ‘he used to have sleep problems’).

Experiencer. The mention was in reference to a person other than the patient (e.g. 'her mother's mood is unstable').

Directionality. The phrase in reference to the feature was negated (e.g. 'mood was not unstable').

Additionally, the medication application included:

Status. The medication was to be started (e.g. 'start on 75 mg venlafaxine'), stopped (e.g. 'change from 75mg venlafaxine to citalopram') or continued (e.g. 'to continue 75 mg venlafaxine').

Table C.2 shows how this contextual information was applied to determine the presence or absence of MI, disturbed sleep, insomnia, and medication.

Table C.2 Derivation of the presence or absence of mood instability, disturbed sleep, insomnia, and medication using the contextual information.

Application	**Attribute**	**Present**	**Absent**
Mood instability Disturbed sleep Insomnia	observation	positive	negative form unknown
	temporality	-	historical not particular
	directionality	-	negated
	experiencer	-	other
Medication	status	continuing	stop start
	temporality	-	historical not particular
	experiencer	-	other
	tense	present	past

Additional processing was required for outputs from the medication application. The medication application was designed to identify all classes of medications, including both brand names and generic names. Where applicable, medication brand names were converted to their generic name and classified according to the British National Formulary (BNF; https://bnf.nice.org.uk/). Given the specific interest in psychotropic medications and sleep-altering medications within Chapter 5, only specific medications were included. Table C.3 shows the classification of medications included in the study.

Table C.3 Classification of medications from the medications NLP application.

Antidepressants	**Antipsychotics**	**Mood stabilising antiepileptics**	**Sedative-hypnotics**	**Amfetamines**	**Sympathomimmetics**	**Antihistamines**
Agomelatine Amoxapine Bupropion Citalopram Clomipramine Dosulepin Doxepin Duloxetine Escitalopram Fluoxetine Fluvoxamine Isocarboxazid Lofepramine Mianserin Mirtazapine Moclobemide Nefazodone Nortriptyline Reboxetine Sertraline Tranylcypromine Trazodone Trimipramine Venlafaxine	Amisulpride Amitriptyline Aripiprazole Asenapine Chlorpromazine Clozapine Droperidol Flupentixol Fluphenazine Haloperidol Imipramine Lurasidone Olanzapine Paliperidone Periciazine Perphenazine Pimozide Pipotiazine Prochlorperazine Promazine Quetiapine Risperidone Sertindole Sulpiride Thioridazine Ziprasidone Zuclopenthixol	Carbamazepine Lamotrigine Sodium valproate Valproic acid	Alprazolam Bromazepam Buspirone Chloral hydrate Chlordiazepoxide Clobazam Clomethiazole Clonazepam Diazepam Flunitrazepam Flurazepam Loprazolam Lorazepam Lormetazepam Melatonin Midazolam Nitrazepam Oxazepam Zolpidem Zopiclone	Dexamfetamine Lisdexamfetamine	Atomoxetine Methylphenidate Modafinil	Promethazine

C.3. Validation Metrics

The formulae used to calculate sensitivity, specificity, and positive and negative predictive values are shown below. The manual annotations were treated as the gold standard for the purpose of these calculations.

		Manual Annotation		
		Present	**Absent**	
NLP Classifier	**Present**	TP	FP	*PPV = TP / (TP + FP)*
	Absent	FN	TN	*NPV = TN / (TN + FN)*
		SE = TP / (TP + FN)	*SP = TN / (TN + FP)*	

Abbreviations
TP = true positive
TN = true negative
FP = false positive
FN = false negative
PPV = positive predictive value
NPV = negative predictive value
SE = sensitivity
SP = specificity

References

Adachi, Y., Tanaka, H., Kunitsuka, K., Takahashi, M., Doi, Y., Kawakami, N., & Minowa, M. (2003). Brief behavior therapy for sleep-habit improvement in a work place by correspondence. *Sleep and Biological Rhythms, 1*(2), 133-135. doi:10.1046/j.1446-9235.2003.00022.x

Akiskal, H. S., Maser, J. D., Zeller, P. J., Endicott, J., Coryell, W., Keller, M., . . . Goodwin, F. (1995). Switching from unipolar to bipolar-II – an 11-year prospective-study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry, 52*, 114-123.

Akiskal, H. S., Mendlowicz, M. V., Jean-Louis, G., Rapaport, M. H., Kelsoe, J. R., Gillin, J. C., & Smith, T. L. (2005). TEMPS-A: validation of a short version of a self-rated instrument designed to measure variations in temperament. *J Affect Disord, 85*(1-2), 45-52. doi:10.1016/j.jad.2003.10.012

Al-Karawi, D., & Jubair, L. (2016). Bright light therapy for nonseasonal depression: Meta-analysis of clinical trials. *J Affect Disord, 198*, 64-71. doi:10.1016/j.jad.2016.03.016

Aldao, A. (2016). Introduction to the Special Issue: Emotion Regulation as a Transdiagnostic Process. *Cognitive Therapy and Research, 40*(3), 257-261. doi:10.1007/s10608-016-9764-2

Altman, E. G., Hedeker, D., Peterson, J. L., & Davis, J. M. (1997). The Altman Self-Rating Mania Scale. *Biol Psychiatry, 42*(10), 948-955. doi:10.1016/S0006-3223(96)00548-3

Altman, E. G., Hedeker, D. R., Janicak, P. G., Peterson, J. L., & Davis, J. M. (1994). The Clinician-Administered Rating Scale for Mania (CARS-M): development, reliability, and validity. *Biol Psychiatry, 36*(2), 124-134. doi:10.1016/0006-3223(94)91193-2

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders : DSM-III-Revised*. Washington, D.C: Washington, D.C : American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, DC: American Psychiatric Publishing.

Angst, J., Gamma, A., & Endrass, J. (2003). Risk factors for the bipolar and depression spectra. *Acta Psychiatr Scand Suppl, 108*(418), 15-19.

Arber, S., Bote, M., & Meadows, R. (2009). Gender and socio-economic patterning of self-reported sleep problems in Britain. *Soc Sci Med, 68*(2), 281-289. doi:10.1016/j.socscimed.2008.10.016

Argyropoulos, S. V., Hicks, J. A., Nash, J. R., Bell, C. J., Rich, A. S., Nutt, D. J., & Wilson, S. J. (2003). Correlation of subjective and objective sleep measurements at different stages of the treatment of depression. *Psychiatry Res, 120*(2), 179-190. doi:10.1016/S0165-1781(03)00187-2

Barbini, B., Benedetti, F., Colombo, C., Dotoli, D., Bernasconi, A., Cigala-Fulgosi, M., . . . Smeraldi, E. (2005). Dark therapy for mania: a pilot study. *Bipolar Disord, 7*(1), 98-101. doi:10.1111/j.1399-5618.2004.00166.x

Barbini, B., Bertelli, S., Colombo, C., & Smeraldi, E. (1996). Sleep loss, a possible factor in augmenting manic episode. *Psychiatry Res, 65*(2), 121-125. doi:10.1016/s0165-1781(96)02909-5

Bauer, M., Grof, P., Rasgon, N., Bschor, T., Glenn, T., & Whybrow, P. C. (2006). Temporal relation between sleep and mood in patients with bipolar disorder. *Bipolar Disord, 8*(2), 160-167. doi:10.1111/j.1399-5618.2006.00294.x

Beedie, C. J., Terry, P. C., & Lane, A. M. (2005). Distinctions between emotion and mood. *Cogn Emot, 19*(6), 847-878. doi:10.1080/02699930541000057

Benedetti, F., & Colombo, C. (2011). Sleep deprivation in mood disorders. *Neuropsychobiology, 64*(3), 141-151. doi:10.1159/000328947

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society, Series B, Methodological, 57*(1), 289.

Berenson, A. B., Odom, S. D., Breitkopf, C. R., & Rahman, M. (2008). Physiologic and psychologic symptoms associated with use of injectable contraception and 20 microg oral contraceptive pills. *Am J Obst Gynecol, 199*(4), 351.e351-312. doi:https://dx.doi.org/10.1016/j.ajog.2008.04.048

Bernert, R. A., Kim, J. S., Iwata, N. G., & Perlis, M. L. (2015). Sleep disturbances as an evidence-based suicide risk factor. *Curr Psychiatry Rep, 17*(3), 554. doi:10.1007/s11920-015-0554-4

Bernstein, G. A., & Garfinkel, B. D. (1992). The Visual Analog Scale for Anxiety - Revised - Psychometric Properties. *J Anx Disord, 6*(3), 223-239. doi:Doi 10.1016/0887-6185(92)90035-6

Bilderbeck, A. C., Atkinson, L. Z., McMahon, H. C., Voysey, M., Simon, J., Price, J., . . . Goodwin, G. M. (2016). Psychoeducation and online mood tracking for patients with bipolar disorder: A randomised controlled trial. *J Affect Disord, 205*, 245-251. doi:10.1016/j.jad.2016.06.064

Bilderbeck, A. C., Reed, Z. E., McMahon, H. C., Atkinson, L. Z., Price, J., Geddes, J. R., . . . Harmer, C. J. (2016). Associations between mood instability and emotional processing in a large cohort of bipolar patients. *Psychol Med, 46*(15), 3151-3160. doi:10.1017/S003329171600180X

Bin, Y. S., Marshall, N. S., & Glozier, N. (2013). Sleeping at the limits: the changing prevalence of short and long sleep durations in 10 countries. *Am J Epidemiol, 177*(8), 826-833. doi:10.1093/aje/kws308

Black, D. W., Blum, N., Letuchy, E., Carney Doebbeling, C., Forman-Hoffman, V. L., & Doebbeling, B. N. (2006). Borderline personality disorder and traits in veterans: psychiatric comorbidity, healthcare utilization, and quality of life along a continuum of severity. *CNS Spectr, 11*(9), 680-689; quiz 719. doi:10.1017/S1092852900014772

Blot, W.J., Day, N.E., 1979. Synergism and interaction: are they equivalent? *Am J Epidemiol, 110*, 99.

Boivin, D. B., Czeisler, C. A., Dijk, D. J., Duffy, J. F., Folkard, S., Minors, D. S., . . . Waterhouse, J. M. (1997). Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. *Arch Gen Psychiatry, 54*(2), 145-152. doi:10.1001/archpsyc.1997.01830140055010

Boland, E. M., Stange, J. P., Molz Adams, A., LaBelle, D. R., Ong, M. L., Hamilton, J. L., . . . Alloy, L. B. (2015). Associations between sleep disturbance, cognitive functioning and work disability in Bipolar Disorder. *Psychiatry Res, 230*(2), 567-574. doi:10.1016/j.psychres.2015.09.051

Bopp, J. M., Miklowitz, D. J., Goodwin, G. M., Stevens, W., Rendell, J. M., & Geddes, J. R. (2010). The longitudinal course of bipolar disorder as revealed through weekly text messaging: a feasibility study. *Bipolar Disord, 12*(3), 327-334. doi:10.1111/j.1399-5618.2010.00807.x

Borbely, A. A. (1982). A two process model of sleep regulation. *Hum Neurobiol, 1*(3), 195-204.

Bowen, R., Balbuena, L., Leuschen, C., & Baetz, M. (2012). Mood instability is the distinctive feature of neuroticism. Results from the British Health and Lifestyle Study (HALS). *Personality and Individual Differences, 53*(7), 896-900. doi:10.1016/j.paid.2012.07.003

Broome, M. R., He, Z., Iftikhar, M., Eyden, J., & Marwaha, S. (2015). Neurobiological and behavioural studies of affective instability in clinical populations: a systematic review. *Neurosci Biobehav Rev, 51,* 243-254. doi:10.1016/j.neubiorev.2015.01.021

Brown, R. E., Basheer, R., McKenna, J. T., Strecker, R. E., & McCarley, R. W. (2012). Control of sleep and wakefulness. *Physiol Rev, 92*(3), 1087-1187. doi:10.1152/physrev.00032.2011

Buysse, D. J. (2014). Sleep health: can we define it? Does it matter? *Sleep, 37*(1), 9-17. doi:10.5665/sleep.3298

Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Lichstein, K. L., & Morin, C. M. (2006). Recommendations for a standard research assessment of insomnia. *Sleep, 29*(9), 1155-1173. doi:10.1093/sleep/29.9.1155

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. *Psychiatry Res, 28*(2), 193-213.

Campbell-Sills, L., Barlow, D. H., Brown, T. A., & Hofmann, S. G. (2006). Acceptability and suppression of negative emotion in anxiety and mood disorders. *Emotion, 6*(4), 587-595. doi:10.1037/1528-3542.6.4.587

Cappuccio, F. P., D'Elia, L., Strazzullo, P., & Miller, M. A. (2010). Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. Sleep, 33(5), 585-592.

Cappuccio, F. P., Miller, M. A., & Lockley, S. W. (2010). *Sleep, health and society: from aetiology to public health*. Oxford: Oxford University Press.

Carr, O., Saunders, K. E. A., Tsanas, A., Bilderbeck, A. C., Palmius, N., Geddes, J. R., . . . De Vos, M. (2018). Variability in phase and amplitude of diurnal rhythms is related to variation of mood in bipolar and borderline personality disorder. *Sci Rep, 8*(1), 1649. doi:10.1038/s41598-018-19888-9

Chan, C. S., Poon, C. Y. S., Leung, J. C. Y., Lau, K. N. T., & Lau, E. Y. Y. (2018). Delayed school start time is associated with better sleep, daytime functioning, and life satisfaction in residential high-school students. *J Adolesc, 66*, 49-54. doi:10.1016/j.adolescence.2018.05.002

Cirelli, C., & Tononi, G. (2008). Is sleep essential? *PLoS Biol, 6*(8), e216. doi:10.1371/journal.pbio.0060216

Clark, L. A. (1993). *Schedule for Nonadaptive and Adaptive Personality.* In V. Zeigler-Hill & T. K. Shackelford (Eds.). Minneapolis, MN: University of Minnesota Press.

Conners, C. K., Erhardt, D., & Sparrow, E. (1999). *Conners' Adult ADHD Rating Scales (CAARS) Technical Manual.* North Tonawanda: Multi-Health Systems, Inc.

Crowell, S. E., Beauchaine, T. P., & Linehan, M. M. (2009). A biosocial developmental model of borderline personality: Elaborating and extending Linehan's theory. *Psychol Bull, 135*(3), 495-510. doi:10.1037/a0015616

Croy, I., Smith, M. G., Gidlof-Gunnarsson, A., & Persson-Waye, K. (2017). Optimal Questions for Sleep in Epidemiological Studies: Comparisons of Subjective and Objective Measures in Laboratory and Field Studies. *Behav Sleep Med, 15*(6), 466-482. doi:10.1080/15402002.2016.1163700

de Graaf, R., Bijl, R. V., Smit, F., Ravelli, A., & Vollebergh, W. A. (2000). Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Am J Epidemiol, 152*(11), 1039-1047. doi:10.1093/aje/152.11.1039

De Vos, M., Goodwin, G., Clifford, G., Osipov, M., Palmius, N., Saunders, K., . . . Tsanas, A. (2016). Daily longitudinal self-monitoring of mood variability in bipolar disorder and borderline personality disorder. *Journal of Affective Disorders, 205*, 225-233.

Dean, R. T., & Dunsmuir, W. T. (2016). Dangers and uses of cross-correlation in analyzing time series in perception, performance, movement, and neuroscience: The importance of constructing transfer function autoregressive models. *Behav Res Methods, 48*(2), 783-802. doi:10.3758/s13428-015-0611-2

Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., . . . Pack, A. I. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep, 20*(4), 267-277. doi:10.1093/sleep/20.4.267

Ebner-Priemer, U. W., Kuo, J., Kleindienst, N., Welch, S. S., Reisch, T., Reinhard, I., . . . Bohus, M. (2007). State affective instability in borderline personality disorder assessed by ambulatory monitoring. *Psychol Med, 37*(7), 961-970. doi:10.1017/S0033291706009706

Ebner-Priemer, U. W., & Sawitzki, G. (2007). Ambulatory assessment of affective instability in borderline personality disorder - The effect of the sampling frequency. *Eur J Psychol Assess, 23*(4), 238-247. doi:10.1027/1015-5759.23.4.238

Eidelman, P., Gershon, A., McGlinchey, E. L., & Harvey, A. G. (2012). Sleep and psychopathology. In C. M. Morin & C. A. Espie (Eds.), *The Oxford handbook of sleep and sleep disorders*. (pp. 172-189). New York, NY, US: Oxford University Press, US.

Elison, S., Ward, J., Williams, C., Espie, C., Davies, G., Dugdale, S., . . . Smith, K. (2017). Feasibility of a UK community-based, eTherapy mental health service in Greater Manchester: repeated-measures and between-groups study of 'Living Life to the Full Interactive', 'Sleepio' and 'Breaking Free Online' at 'Self Help Services'. *BMJ Open, 7*(7). doi:10.1136/bmjopen-2017-016392

Espie, C. A. (2002). Insomnia: conceptual issues in the development, persistence, and treatment of sleep disorder in adults. *Annu Rev Psychol, 53*(1), 215-243. doi:10.1146/annurev.psych.53.100901.135243

Espie, C. A., Kyle, S. D., Williams, C., Ong, J. C., Douglas, N. J., Hames, P., & Brown, J. S. (2012). A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep, 35*(6), 769-781. doi:10.5665/sleep.1872

Eysenck, S. B. G., Eysenck, H. J., & Barrett, P. (1985). A revised version of the psychoticism scale. *Pers Individ Dif, 6*(1), 21-29. doi:10.1016/0191-8869(85)90026-1

Faurholt-Jepsen, M., Geddes, J. R., Goodwin, G. M., Bauer, M., Duffy, A., Kessing, L., & Saunders, K. (2019). Reporting guidelines on remotely collected electronic mood data in mood disorder (eMOOD) - Recommendations. *Transl Psychiatry, 9*(1), 162. doi:10.1038/s41398-019-0484-8

Faurholt-Jepsen, M., Ritz, C., Frost, M., Mikkelsen, R. L., Margrethe Christensen, E., Bardram, J., . . . Kessing, L. V. (2015). Mood instability in bipolar disorder type I versus type II-continuous daily electronic self-monitoring of illness activity using smartphones. *J Affect Disord*(C), 342-349. doi:10.1016/j.jad.2015.06.026

Ferguson, A., Lyall, L. M., Ward, J., Strawbridge, R. J., Cullen, B., Graham, N., . . . Smith, D. J. (2018). Genome-Wide Association Study of Circadian Rhythmicity in 71,500 UK Biobank Participants and Polygenic Association with Mood Instability. *EBioMedicine, 35*, 279-287. doi:10.1016/j.ebiom.2018.08.004

Ferrie, J. E., Shipley, M. J., Cappuccio, F. P., Brunner, E., Miller, M. A., Kumari, M., & Marmot, M. G. (2007). A prospective study of change in sleep duration: associations with mortality in the Whitehall II cohort. *Sleep, 30*(12), 1659-1666.

First, M. B., Gibbon, M., Spitzer, R. L., Williams, J. B. W., & Benjamin, L. S. (1997). *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II).* Washington, D.C.: American Psychiatric Press, Inc.,

Foster, R. G., & Wulff, K. (2005). The rhythm of rest and excess. *Nat Rev Neurosci, 6*(5), 407-414. doi:10.1038/nrn1670

Freeman, D., Sheaves, B., Goodwin, G. M., Yu, L. M., Nickless, A., Harrison, P. J., . . . Espie, C. A. (2017). The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. *Lancet Psychiatry, 4*(10), 749-758. doi:10.1016/S2215-0366(17)30328-0

Frith, E. (2017). *Access and waiting times in children and young people's mental health services.* Education Policy Institute. Retrieved from https://epi.org.uk/publications-and-research/access-waiting-times-children-young-peoples-mental-health-services/

Geddes, J. R., & Miklowitz, D. J. (2013). Treatment of bipolar disorder. *Lancet, 381*(9878), 1672-1682. doi:10.1016/S0140-6736(13)60857-0

Geoffroy, P. A., Scott, J., Boudebesse, C., Lajnef, M., Henry, C., Leboyer, M., . . . Etain, B. (2015). Sleep in patients with remitted bipolar disorders: a meta-analysis of actigraphy studies. *Acta Psychiatr Scand, 131*(2), 89-99. doi:10.1111/acps.12367

Gershon, A., Do, D., Satyanarayana, S., Shah, S., Yuen, L. D., Hooshmand, F., . . . Ketter, T. A. (2017). Abnormal sleep duration associated with hastened depressive recurrence in bipolar disorder. *J Affect Disord, 218*, 374-379. doi:10.1016/j.jad.2017.05.015

Gershon, A., & Eidelman, P. (2015). Inter-episode affective intensity and instability: predictors of depression and functional impairment in bipolar disorder. *J Behav Ther Exp Psychiatry, 46*, 14-18. doi:10.1016/j.jbtep.2014.07.005

Gershon, A., Thompson, W. K., Eidelman, P., McGlinchey, E. L., Kaplan, K. A., & Harvey, A. G. (2012). Restless pillow, ruffled mind: sleep and affect coupling in interepisode bipolar disorder. *J Abnorm Psychol, 121*(4), 863-873. doi:10.1037/a0028233

Giedke, H., & Schwärzler, F. (2002). Therapeutic use of sleep deprivation in depression. *Sleep Med Rev, 6*(5), 361-377. doi:10.1053/smrv.2002.0235

Giglio, L. M., Andreazza, A. C., Andersen, M., Cereser, K. M., Walz, J. C., Sterz, L., & Kapczinski, F. (2009). Sleep in bipolar patients. *Sleep Breath, 13*(2), 169-173. doi:10.1007/s11325-008-0215-5

Gilbert, P. (2001). Depression and stress: a biopsychosocial exploration of evolved functions and mechanisms. *Stress, 4*(2), 121-135.

Gilbert, P., Allan, S., Nicholls, W., & Olsen, K. (2005). The assessment of psychological symptoms of patients referred to community mental health teams: distress, chronicity and life interference. *Clin Psychol Psychother, 12*(1), 10-27. doi:10.1002/cpp.426

Global Burden of Disease Study 2013 Collaborators. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet, 386*(9995), 743-800. doi:10.1016/s0140-6736(15)60692-4

Glod, C. (2017). Seasonal affective disorder (SAD) and light therapy: State of the science. *Eur Psychiatry, 41*(sS), S528-S528. doi:10.1016/j.eurpsy.2017.01.713

Gonzalez, R., Tamminga, C., Tohen, M., & Suppes, T. (2013). Comparison of objective and subjective assessments of sleep time in subjects with bipolar disorder. *J Affect Disord, 149*(1-3), 363-366. doi:10.1016/j.jad.2013.02.013

Gratz, K. L., & Roemer, L. (2008). Multidimensional Assessment of Emotion Regulation and Dysregulation: Development, Factor Structure, and Initial Validation of the Difficulties in Emotion Regulation Scale. *J Psychopathol Behav Assess, 30*(4), 315-315. doi:10.1007/s10862-008-9102-4

Green, M. J., Espie, C. A., Hunt, K., & Benzeval, M. (2012). The longitudinal course of insomnia symptoms: inequalities by sex and occupational class among two different age cohorts followed for 20 years in the west of Scotland. *Sleep, 35*(6), 815-823. doi:10.5665/sleep.1882

Gross, J. J. (1998). The Emerging Field of Emotion Regulation: An Integrative Review. *Rev Gen Psychol, 2*(3), 271-299. doi:10.1037/1089-2680.2.3.271

Gruber, J., Harvey, A. G., Wang, P. W., Brooks, J. O., 3rd, Thase, M. E., Sachs, G. S., & Ketter, T. A. (2009a). Sleep functioning in relation to mood, function, and quality of life at entry to the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *J Affect Disord, 114*(1-3), 41-49. doi:10.1016/j.jad.2008.06.028

Gruber, J., Harvey, A. G., Wang, P. W., Brooks, J. O., Thase, M. E., Sachs, G. S., & Ketter, T. A. (2009b). Sleep functioning in relation to mood, function, and quality of life at entry to the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *J Affect Disord, 114*(1-3), 41-49. doi:10.1016/j.jad.2008.06.028

Gruber, J., Miklowitz, D. J., Harvey, A. G., Frank, E., Kupfer, D., Thase, M. E., . . . Ketter, T. A. (2011). Sleep matters: sleep functioning and course of illness in bipolar disorder. *J Affect Disord, 134*(1-3), 416-420. doi:10.1016/j.jad.2011.05.016

Hamilton, M. (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry, 23*(1), 56-62. doi:10.1136/jnnp.23.1.56

Hamilton, M. (1967). Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol, 6*(4), 278-296. doi:10.1111/j.2044-8260.1967.tb00530.x

Harvey, A. G. (2008a). Insomnia, psychiatric disorders, and the transdiagnostic perspective. *Current Directions in Psychological Science, 17*(5), 299–303. doi:10.1111/j.1467-8721.2008.00594.x

Harvey, A. G. (2008b). Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *Am J Psychiatry, 165*(7), 820-829. doi:10.1176/appi.ajp.2008.08010098

Harvey, A. G. (2009). A transdiagnostic approach to treating sleep disturbance in psychiatric disorders. *Cogn Behav Ther, 38 Suppl 1*, 35-42. doi:10.1080/16506070903033825

Harvey, A. G., Murray, G., Chandler, R. A., & Soehner, A. (2011a). Sleep disturbance as transdiagnostic: consideration of neurobiological mechanisms. *Clin Psychol Rev, 31*(2), 225-235. doi:10.1016/j.cpr.2010.04.003

Harvey, A. G., Murray, G., Chandler, R. A., & Soehner, A. (2011b). Sleep disturbance as transdiagnostic: consideration of neurobiological mechanisms. *Clinical Psychology Review, 31*(2), 225–235. doi:10.1016/j.cpr.2010.04.003

Harvey, A. G., Schmidt, D. A., Scarna, A., Semler, C. N., & Goodwin, G. M. (2005). Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *Am J Psychiatry, 162*(1), 50-57. doi:10.1176/appi.ajp.162.1.50

Harvey, A. G., Soehner, A. M., Kaplan, K. A., Hein, K., Lee, J., Kanady, J., . . . Buysse, D. J. (2015). Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: a pilot randomized controlled trial. *J Consult Clin Psychol, 83*(3), 564-577. doi:10.1037/a0038655

Harvey, P. D., Greenberg, B. R., & Serper, M. R. (1989). The affective lability scales: development, reliability, and validity. *J Clin Psychol, 45*(5), 786-793. doi: 10.1002/1097-4679(198909)45:5<786::aid-jclp2270450515>3.0.co;2-p

Henry, C., Mitropoulou, V., New, A. S., Koenigsberg, H. W., Silverman, J., & Siever, L. J. (2001). Affective instability and impulsivity in borderline personality and bipolar II disorders: similarities and differences. *J Psychiatr Res, 35*(6), 307-312. doi:10.1016/S0022-3956(01)00038-3

Henry, C., Van den Bulke, D., Bellivier, F., Roy, I., Swendsen, J., M'Bailara, K., . . . Leboyer, M. (2008). Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period. *Psychiatry Res, 159*(1-2), 1-6. doi:10.1016/j.psychres.2005.11.016

Holm, S. (1979). A Simple Sequentially Rejective Multiple Test Procedure. *Scand J Stat, 6*(2), 65-70.

Horne, J. A., & Ostberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol, 4*(2), 97-110.

Hotopf, M., Churchill, R., & Lewis, G. (1999). Pragmatic randomised controlled trials in psychiatry. *Br J Psychiatry, 175*, 217-223. doi:10.1192/bjp.175.3.217

Howes, O. D., Lim, S., Theologos, G., Yung, A. R., Goodwin, G. M., & McGuire, P. (2011). A comprehensive review and model of putative prodromal features of bipolar affective disorder. *Psychol Med, 41*(8), 1567-1577. doi:10.1017/S0033291710001790

Hoy, D., Brooks, P., Woolf, A., Blyth, F., March, L., Bain, C., . . . Buchbinder, R. (2012). Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol, 65*(9), 934-939. doi:10.1016/j.jclinepi.2011.11.014

Hyndman, R., Athanasopoulos, G., Bergmeir, C., Caceres, G., Chhay, L., O'Hara-Wild, M., . . . Yasmeen, F. (2018). forecast: Forecasting functions for time series and linear models.

Illingworth, G., Sharman, R., Jowett, A., Harvey, C. J., Foster, R. G., & Espie, C. A. (2018). Challenges in implementing and assessing outcomes of school start time change in the UK: experience of the Oxford Teensleep study. *Sleep Med*. doi:10.1016/j.sleep.2018.10.021

Jackson, A., Cavanagh, J., & Scott, J. (2003). A systematic review of manic and depressive prodromes. *J Affect Disord, 74*(3), 209-217. doi:https://doi.org/10.1016/S0165-0327(02)00266-5

Jackson, R. G., Ball, M., Patel, R., Hayes, R. D., Dobson, R. J. B., & Stewart, R. (2014). TextHunter--A User Friendly Tool for Extracting Generic Concepts from Free

Text in Clinical Research. *Proc Am Med Informatics Assoc*(1), 729-738. doi:10.13140/2.1.3722.9121

Joint Formulary Committee. (2018). British National Formulary. Retrieved 01/09/2018 https://bnf.nice.org.uk/

Kaiser, J. F. (1990). On a simple algorithm to calculate the 'energy' of a signal. 381-384. doi:10.1109/ICASSP.1990.115702

Kaiser, J. F. (1993). Some useful properties of Teager's energy operators. *3*, 149-152. doi:10.1109/ICASSP.1993.319457

Kerkhof, G. A. (2017). Epidemiology of sleep and sleep disorders in The Netherlands. *Sleep Med, 30*, 229-239. doi:10.1016/j.sleep.2016.09.015

Knutson, K. L., Van Cauter, E., Rathouz, P. J., DeLeire, T., & Lauderdale, D. S. (2010). Trends in the prevalence of short sleepers in the USA: 1975-2006. *Sleep, 33*(1), 37-45.

Koenigsberg, H. W., Harvey, P. D., Mitropoulou, V., Schmeidler, J., New, A. S., Goodman, M., . . . Siever, L. J. (2002). Characterizing affective instability in borderline personality disorder. *Am J Psychiatry, 159*(5), 784-788. doi:10.1176/appi.ajp.159.5.784

Kraemer, H. C., Noda, A., & O'Hara, R. (2004). Categorical versus dimensional approaches to diagnosis: methodological challenges. *Journal of Psychiatric Research, 38*(1), 17-25. doi:10.1016/s0022-3956(03)00097-9

Kripke, D. F., Garfinkel, L., Wingard, D. L., Klauber, M. R., & Marler, M. R. (2002). Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry, 59*(2), 131-136. doi:10.1001/archpsyc.59.2.131

Krishnamurthy, V., Mukherjee, D., Reider, A., Seaman, S., Singh, G., Fernandez-Mendoza, J., & Saunders, E. (2018). Subjective and objective sleep discrepancy in symptomatic bipolar disorder compared to healthy controls. *J Affect Disord, 229*, 247-253. doi:10.1016/j.jad.2017.12.100

Kröger, C., Theysohn, S., Hartung, D., Vonau, M., Lammers, C.-H., & Kosfelder, J. (2010). Die Skala zur Erfassung der Impulsivitat der Borderliine-Personlichkeitsstorung (IS-27) – ein Beitrag zur Qualitatssicherung in der Psychotherapy [The scale measuring impulsiveness of Borderline Personality Disorder (IS-27) – A contribution to quality assurance in psychotherapy]. *Diagnostica, 56*, 178-189.

Kushida, C. A., Chang, A., Gadkary, C., Guilleminault, C., Carrillo, O., & Dement, W. C. (2001). Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. *Sleep Med, 2*(5), 389-396. doi:https://doi.org/10.1016/S1389-9457(00)00098-8

Kyle, S. D., Sexton, C. E., Feige, B., Luik, A. I., Lane, J., Saxena, R., . . . Spiegelhalder, K. (2017). Sleep and cognitive performance: cross-sectional associations in the UK Biobank. *Sleep Med, 38*, 85-91. doi:10.1016/j.sleep.2017.07.001

Landgraf, D., McCarthy, M. J., & Welsh, D. K. (2014a). Circadian clock and stress interactions in the molecular biology of psychiatric disorders. *Curr Psychiatry Rep, 16*(10), 483. doi:10.1007/s11920-014-0483-7

Landgraf, D., McCarthy, M. J., & Welsh, D. K. (2014b). The role of the circadian clock in animal models of mood disorders. *Behavioral Neuroscience, 128*(3), 344-359. doi:10.1037/a0036029

Larsen, R. J., Diener, E., & Emmons, R. A. (1986). Affect Intensity and Reactions to Daily Life Events. *J Pers Soc Psychol, 51*(4), 803-814. doi:Doi 10.1037/0022-3514.51.4.803

Lawrence, D., Hancock, K. J., & Kisely, S. (2013). The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. *BMJ, 346*(7909), f2539. doi:10.1136/bmj.f2539

Leng, Y., Cappuccio, F. P., Surtees, P. G., Luben, R., Brayne, C., & Khaw, K. T. (2016). Daytime napping, sleep duration and increased 8-year risk of type 2 diabetes in a British population. *Nutr Metab Cardiovasc Dis, 26*(11), 996-1003. doi:10.1016/j.numecd.2016.06.006

Leon, D. A., & McCambridge, J. (2006). Liver cirrhosis mortality rates in Britain, 1950 to 2002. *Lancet, 367*(9511), 645-645. doi:10.1016/s0140-6736(06)68250-0

Lewis, G., Pelosi, A. J., Araya, R., & Dunn, G. (2009). Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychol Med, 22*(02), 465. doi:10.1017/s0033291700030415

Li, X., Zhou, P., & Aruin, A. S. (2007). Teager-Kaiser energy operation of surface EMG improves muscle activity onset detection. *Ann Biomed Eng, 35*(9), 1532-1538. doi:10.1007/s10439-007-9320-z

Linehan, M. (1993). *Cognitive-behavioral treatment of borderline personality disorder*. Guildford Press, New York

Liu, H., Bielinski, S. J., Sohn, S., Murphy, S., Wagholikar, K. B., Jonnalagadda, S. R., . . . Chute, C. G. (2013). An Information Extraction Framework for Cohort Identification Using Electronic Health Records. *AMIA Jt Summits Transl Sci Proc, 2013*, 149-153.

Liverant, G. I., Brown, T. A., Barlow, D. H., & Roemer, L. (2008). Emotion regulation in unipolar depression: the effects of acceptance and suppression of subjective emotional experience on the intensity and duration of sadness and negative affect. *Behav Res Ther, 46*(11), 1201-1209. doi:10.1016/j.brat.2008.08.001

Lockley, S. W., Skene, D. J., & Arendt, J. (2002). Comparison between subjective and actigraphic measurement of sleep and sleep rhythms. *J Sleep Res, 8*(3), 175-183. doi:10.1046/j.1365-2869.1999.00155.x

Luik, A. I., Bostock, S., Chisnall, L., Kyle, S. D., Lidbetter, N., Baldwin, N., & Espie, C. A. (2017). Treating Depression and Anxiety with Digital Cognitive Behavioural Therapy for Insomnia: A Real World NHS Evaluation Using Standardized Outcome Measures. *Behav Cogn Psychother, 45*(1), 91-96. doi:10.1017/S1352465816000369

Lunsford-Avery, J. R., Judd, C. M., Axelson, D. A., & Miklowitz, D. J. (2012). Sleep impairment, mood symptoms, and psychosocial functioning in adolescent bipolar disorder. *Psychiatry Res, 200*(2-3), 265-271. doi:10.1016/j.psychres.2012.07.037

Mackinnon, D. F., & Pies, R. (2006). Affective instability as rapid cycling: theoretical and clinical implications for borderline personality and bipolar spectrum disorders. *Bipolar Disord, 8*(1), 1.

Malhotra, R. K., & Avidan, A. (2017). Scoring of Normal Sleep and Arousals. In S. Chokroverty (Ed.), *Sleep Disorders Medicine: Basic Science, Technical Considerations and Clinical Aspects: Fourth Edition* (4 ed., pp. 405-430). New York, NY: Springer-Verlag New York.

Manolio, T. A., & Collins, R. (2010). Enhancing the feasibility of large cohort studies. *JAMA, 304*(20), 2290-2291. doi:10.1001/jama.2010.1686

Mansell, W., Harvey, A., Watkins, E., & Shafran, R. (2009). Conceptual Foundations of the Transdiagnostic Approach to CBT. *Journal of Cognitive Psychotherapy, 23*(1), 6-19. doi:10.1891/0889-8391.23.1.6

Maragos, P., Kaiser, J. F., & Quatieri, T. F. (1993). On Amplitude and Frequency Demodulation Using Energy Operators. *IEEE Transactions on Signal Processing, 41*(4), 1532-1550. doi:Doi 10.1109/78.212729

Marron, S. E., Tomas-Aragones, L., Navarro-Lopez, J., Gieler, U., Kupfer, J., Dalgard, F. J., . . . Marijuan, P. C. (2018). The psychosocial burden of hand eczema: Data from a European dermatological multicentre study. *Contact Dermatitis, 78*(6), 406-412. doi:10.1111/cod.12973

Marwaha, S., Balbuena, L., Winsper, C., & Bowen, R. (2015). Mood instability as a precursor to depressive illness: A prospective and mediational analysis. *Aust N Z J Psychiatry, 49*(6), 557-565. doi:10.1177/0004867415579920

Marwaha, S., Broome, M. R., Bebbington, P. E., Kuipers, E., & Freeman, D. (2014). Mood instability and psychosis: analyses of British national survey data. *Schizophr Bull, 40*(2), 269-277. doi:10.1093/schbul/sbt149

Marwaha, S., He, Z., Broome, M., Singh, S. P., Scott, J., Eyden, J., & Wolke, D. (2014). How is affective instability defined and measured? A systematic review. *Psychol Med, 44*(9), 1793-1808. doi:10.1017/S0033291713002407

Marwaha, S., Parsons, N., & Broome, M. (2013). Mood instability, mental illness and suicidal ideas: results from a household survey. *Soc Psychiatry Psychiatr Epidemiol, 48*(9), 1431-1437. doi:10.1007/s00127-013-0653-7

Marwaha, S., Parsons, N., Flanagan, S., & Broome, M. (2013a). The prevalence and clinical associations of mood instability in adults living in England: results from the Adult Psychiatric Morbidity Survey 2007. *Psychiatry Res, 205*(3), 262-268. doi:https://dx.doi.org/10.1016/j.psychres.2012.09.036

McDaid, D., & Park, A. L. (2015). Counting all the costs: the economic impact of comorbidity. In N. Sartorius, R. I. G. Holt, & M. Maj (Eds.), *Comorbidity of mental and physical disorders.* (pp. 23-32). Basel: Karger.

Mennin, D. S., & Fresco, D. M. (2010). Emotion regulation as an integrative framework for understanding and treating psychopathology. In A. M. Kring & D. M. Sloan (Eds.), *Emotion regulation and psychopathology* (pp. 356-379). New York, NY: Guildford Press.

Michal, M., Wiltink, J., Kirschner, Y., Schneider, A., Wild, P. S., Munzel, T., . . . Beutel, M. E. (2014). Complaints of sleep disturbances are associated with cardiovascular disease: results from the Gutenberg Health Study. *PLoS ONE, 9*(8), e104324. doi:10.1371/journal.pone.0104324

Miklowitz, D. J., Price, J., Holmes, E. A., Rendell, J., Bell, S., Budge, K., . . . Geddes, J. R. (2012). Facilitated Integrated Mood Management for adults with bipolar disorder. *Bipolar Disord, 14*(2), 185-197. doi:10.1111/j.1399-5618.2012.00998.x

Miller, C. B., Kyle, S. D., Marshall, N. S., & Espie, C. A. (2013). Ecological momentary assessment of daytime symptoms during sleep restriction therapy for insomnia. *J Sleep Res, 22*(3), 266-272. doi:10.1111/jsr.12024

Miller, J. D., & Pilkonis, P. A. (2006). Neuroticism and affective instability: the same or different? *Am J Psychiatry, 163*(5), 839-845. doi:10.1176/ajp.2006.163.5.839

Milutinovic, D., Golubovic, B., Brkic, N., & Prokes, B. (2012). Professional stress and health among critical care nurses in Serbia. *Arh Hig Rada Toksikol, 63*(2), 171-180. doi:10.2478/10004-1254-63-2012-2140

Mind. (2014). We need to talk: getting the right therapy at the right time. London, UK.

Moore, S. R., Gresham, L. S., Bromberg, M. B., Kasarkis, E. J., & Smith, R. A. (1997). A self report measure of affective lability. *J Neurol Neurosurg Psychiatry, 63*(1), 89-93. doi:10.1136/jnnp.63.1.89

Morey, L. C. (1991). *Personality Assessment Inventory: Professional Manual.* Odessa, FL.: Psychological Assessment Resources.

Morin, C. M. (1993). *Insomnia: Psychological Assessment and Management.* New York, NY: Guilford Press.

Moritz, S., & Bartz-Beielstein, T. (2017). imputeTS: Time Series Missing Value Imputation in R. *R Journal, 9*(1), 207-218.

Murray, G., & Harvey, A. (2010). Circadian rhythms and sleep in bipolar disorder. *Bipolar Disord, 12*(5), 459-472. doi:10.1111/j.1399-5618.2010.00843.x

National Centre for Social Research and University of Leicester. (January 2011). *Adult Psychiatric Morbidity Survey, 2007 [computer file]*.

National Centre for Social Research, U. o. L. (2017). Adult Psychiatric Morbidity Survey, 2007. [data collection]. from UK Data Service. http://doi.org/10.5255/UKDA-SN-6379-2

Newhill, C. E., Mulvey, E. P., & Pilkonis, P. A. (2004). Initial development of a measure of emotional dysregulation for individuals with cluster B personality disorders. *Res Soc Work Pract, 14*(6), 443-449. doi:10.1177/1049731504267332

NHS England. (2016). Mental Health Clustering Booklet (v5.0).

Nolen-Hoeksema, S., & Watkins, E. R. (2011). A Heuristic for Developing Transdiagnostic Models of Psychopathology: Explaining Multifinality and Divergent Trajectories. *Perspect Psychol Sci, 6*(6), 589-609. doi:10.1177/1745691611419672

O'Donnell, L. A., Ellis, A. J., Van de Loo, M. M., Stange, J. P., Axelson, D. A., Kowatch, R. A., . . . Miklowitz, D. J. (2018). Mood instability as a predictor of clinical and functional outcomes in adolescents with bipolar I and bipolar II disorder. *J Affect Disord, 236*, 199-206. doi:10.1016/j.jad.2018.04.021

Ohayon, M. M. (2002). Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev, 6*(2), 97-111. doi:10.1053/smrv.2002.0186

Ohayon, M. M. (2008). From wakefulness to excessive sleepiness: what we know and still need to know. *Sleep Med Rev, 12*(2), 129-141. doi:10.1016/j.smrv.2008.01.001

Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep, 27*(7), 1255-1273. doi:10.1093/sleep/27.7.1255

Ohayon, M. M., Caulet, M., & Lemoine, P. (1998). Comorbidity of mental and insomnia disorders in the general population. *Compr Psychiatry, 39*(4), 185-197. doi:https://doi.org/10.1016/S0010-440X(98)90059-1

Oliver, M. N. I., & Simons, J. S. (2004). The affective lability scales: Development of a short-form measure. *Pers Indiv Differ, 37*(6), 1279-1288. doi:10.1016/j.paid.2003.12.013

Owens, J. A., Dearth-Wesley, T., Herman, A. N., Oakes, J. M., & Whitaker, R. C. (2017). A quasi-experimental study of the impact of school start time changes on adolescent sleep. *Sleep Health, 3*(6), 437-443. doi:10.1016/j.sleh.2017.09.001

Palmius, N., Saunders, K. E. A., Carr, O., Geddes, J. R., Goodwin, G. M., & De Vos, M. (2018). Group-Personalized Regression Models for Predicting Mental Health Scores From Objective Mobile Phone Data Streams: Observational Study. *J Med Internet Res, 20*(10), e10194. doi:10.2196/10194

Panchal, P., Scholl, J., Nelissen, N., Saunders, K., Darby, D., Rushworth, M., . . . Harmer, C. (2018). Mood instability and reward processing: daily remote monitoring as a modern phenotyping tool for bipolar disorder. *European Neuropsychopharmacology, 28*, S88-S89. doi:10.1016/j.euroneuro.2017.12.121

Paris, J. (2004). Borderline or bipolar? Distinguishing borderline personality disorder from bipolar spectrum disorders. *Harv Rev Psychiatry, 12*(3), 140-145. doi:10.1080/10673220490472373

Patel, R., Lloyd, T., Jackson, R., Ball, M., Shetty, H., Broadbent, M., . . . Taylor, M. (2015). Mood instability is a common feature of mental health disorders and is

associated with poor clinical outcomes. *BMJ Open, 5*(5). doi:10.1136/bmjopen-2014-007504

Perera, G., Broadbent, M., Callard, F., Chang, C.-K., Downs, J., Dutta, R., . . . Stewart, R. (2016). Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record-derived data resource. *BMJ Open, 6*(3). doi:10.1136/bmjopen-2015-008721

Peters, E. M., Baetz, M., Marwaha, S., Balbuena, L., & Bowen, R. (2016). Affective instability and impulsivity predict nonsuicidal self-injury in the general population: a longitudinal analysis. *Borderline Personal Disord Emot Dysregul, 3*, 17. doi:10.1186/s40479-016-0051-3

Peters, E. M., Balbuena, L., Baetz, M., Marwaha, S., & Bowen, R. (2015). Mood instability underlies the relationship between impulsivity and internalizing psychopathology. *Med Hypotheses, 85*(4), 447-454.

Phillips, M. L., Travis, M. J., Fagiolini, A., & Kupfer, D. J. (2008). Medication effects in neuroimaging studies of bipolar disorder. *Am J Psychiatry, 165*(3), 313-320. doi:10.1176/appi.ajp.2007.07071066

Pigeon, W. R., Pinquart, M., & Conner, K. (2012). Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatry, 73*(9), e1160-1167. doi:10.4088/JCP.11r07586

Plante, D. T., & Winkelman, J. W. (2008). Sleep disturbance in bipolar disorder: therapeutic implications. *Am J Psychiatry, 165*(7), 830-843. doi:10.1176/appi.ajp.2008.08010077

R Development Core Team. (2017). R: A Language and Environment for Statistical Computing,. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from http://www.R-project.org

Reeve, S., Nickless, A., Sheaves, B., Stewart, S. L. K., Gumley, A., Fowler, D., . . . Freeman, D. (2018). Sleep duration and psychotic experiences in patients at risk of psychosis: A secondary analysis of the EDIE-2 trial. *Schizophr Res, 204*, 326-333. doi: 10.1016/j.schres.2018.08.006

Reich, D. B., Zanarini, M. C., & Fitzmaurice, G. (2012). Affective lability in bipolar disorder and borderline personality disorder. *Compr Psychiatry, 53*(3), 230-237. doi:10.1016/j.comppsych.2011.04.003

Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., & Nissen, C. (2010). The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev, 14*(1), 19-31. doi:10.1016/j.smrv.2009.04.002

Ritter, P. S., Marx, C., Lewtschenko, N., Pfeiffer, S., Leopold, K., Bauer, M., & Pfennig, A. (2012). The characteristics of sleep in patients with manifest bipolar disorder, subjects at high risk of developing the disease and healthy controls. *J Neural Transm (Vienna), 119*(10), 1173-1184. doi:10.1007/s00702-012-0883-y

Roberts, R. E., Roberts, C. R., & Duong, H. T. (2009). Sleepless in adolescence: prospective data on sleep deprivation, health and functioning. *J Adolesc, 32*(5), 1045-1057. doi:10.1016/j.adolescence.2009.03.007

Rosekind, M. R., Gregory, K. B., Mallis, M. M., Brandt, S. L., Seal, B., & Lerner, D. (2010). The cost of poor sleep: workplace productivity loss and associated costs. *J Occup Environ Med, 52*(1), 91-98. doi:10.1097/JOM.0b013e3181c78c30

Roth, T., Jaeger, S., Jin, R., Kalsekar, A., Stang, P. E., & Kessler, R. C. (2006). Sleep problems, comorbid mental disorders, and role functioning in the national comorbidity survey replication. *Biol Psychiatry, 60*(12), 1364-1371. doi:10.1016/j.biopsych.2006.05.039

Rothman, K. J., Greenland, S., & Walker, A. M. (1980). Concepts of interaction. *Am J Epidemiol, 112*(4), 467-470. doi:10.1093/oxfordjournals.aje.a113015

Rush, A. J., Giles, D. E., Schlesser, M. A., Fulton, C. L., Weissenburger, J., & Burns, C. (1986). The Inventory for Depressive Symptomatology (IDS): preliminary findings. *Psychiatry Res, 18*(1), 65-87. doi:10.1016/0165-1781(86)90060-0

Rush, A. J., Gullion, C. M., Basco, M. R., Jarrett, R. B., & Trivedi, M. H. (1996). The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med, 26*(3), 477-486. doi:10.1017/S0033291700035558

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., . . . Keller, M. B. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry, 54*(5), 573-583. doi:10.1016/s0006-3223(02)01866-8

Saper, C. B., Cano, G., & Scammell, T. E. (2005). Homeostatic, circadian, and emotional regulation of sleep. *J Comp Neurol, 493*(1), 92-98. doi:10.1002/cne.20770

Saper, C. B., Chou, T. C., & Scammell, T. E. (2001). The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci, 24*(12), 726-731. doi:10.1016/S0166-2236(00)02002-6

Saracci, R. (1980). Interaction and synergism. *Am J Epidemiol, 112*(4), 465-466. doi:10.1093/oxfordjournals.aje.a113014

Sartorius, N. (2018). Comorbidity of mental and physical disorders: a key problem for medicine in the 21st century. *Acta Psychiatr Scand, 137*(5), 369-370. doi:10.1111/acps.12888

Schernhammer, E. S., Laden, F., Speizer, F. E., Willett, W. C., Hunter, D. J., Kawachi, I., & Colditz, G. A. (2001). Rotating Night Shifts and Risk of Breast Cancer in Women Participating in the Nurses' Health Study. *JNCI Journal of the National Cancer Institute, 93*(20), 1563-1568. doi:10.1093/jnci/93.20.1563

Sheaves, B. C., Freeman, D., Isham, L., McInerney, J., Nickless, A., Yu, L., . . . Barrera, A. (2018). Stabilising sleep for patients admitted at acute crisis to a psychiatric hospital (OWLS): an assessor-blind pilot randomised controlled trial. *Psychol Med, 48*(10), 1694-1704. doi:10.1017/S0033291717003191

Siegel, J. M. (2005). Clues to the functions of mammalian sleep. *Nature, 437*(7063), 1264-1271. doi:10.1038/nature04285

Simon, J., Budge, K., Price, J., Goodwin, G. M., & Geddes, J. R. (2017). Remote mood monitoring for adults with bipolar disorder: An explorative study of compliance and impact on mental health service use and costs. *Eur Psychiatry, 45*, 14-19. doi:10.1016/j.eurpsy.2017.06.007

Smith, D. J., Muir, W. J., & Blackwood, D. H. (2004). Is borderline personality disorder part of the bipolar spectrum? *Harv Rev Psychiatry, 12*(3), 133-139. doi:10.1080/10673220490472346

StataCorp. (2009). Stata Statistical Software: Release 11 College Station, TX: StataCorp LP.

StataCorp. (2017). Stata Statistical Software: Release 15 College Station, TX: StataCorp LLC.

Stein, M. B., Belik, S. L., Jacobi, F., & Sareen, J. (2008). Impairment associated with sleep problems in the community: relationship to physical and mental health comorbidity. *Psychosom Med, 70*(8), 913-919. doi:10.1097/PSY.0b013e3181871405

Steinan, M. K., Scott, J., Lagerberg, T. V., Melle, I., Andreassen, O. A., Vaaler, A. E., & Morken, G. (2016). Sleep problems in bipolar disorders: more than just insomnia. *Acta Psychiatr Scand, 133*(5), 368-377. doi:10.1111/acps.12523

Stone, A. A., Broderick, J. E., Kaell, A. T., DelesPaul, P. A., & Porter, L. E. (2000). Does the peak-end phenomenon observed in laboratory pain studies apply to real-world pain in rheumatoid arthritics? *J Pain, 1*(3), 212-217. doi:10.1054/jpai.2000.7568

Stone, A. A., & Shiffman, S. (1994). Ecological momentary assessment in behavioral medicine. *Ann Behav Med, 16*, 199-202.

Stone, A. A., Shiffman, S., Schwartz, J. E., Broderick, J. E., & Hufford, M. R. (2003). Patient compliance with paper and electronic diaries. *Control Clin Trials, 24*(2), 182-199. doi:10.1016/S0197-2456(02)00320-3

Srejilevich, S. A., Martino, D. J., Murru, A., Teitelbaum, J., Fassi, G., Marengo, E., . . . Colom, F. (2013). Mood instability and functional recovery in bipolar disorders. *Acta Psychiatr Scand, 128*(3), 194-202. doi:10.1111/acps.12065

Sylvia, L. G., Dupuy, J. M., Ostacher, M. J., Cowperthwait, C. M., Hay, A. C., Sachs, G. S., . . . Perlis, R. H. (2012). Sleep disturbance in euthymic bipolar patients. *Journal of Psychopharmacology, 26*(8), 1108–1112. doi:10.1177/0269881111421973

Talbot, L. S., Hairston, I. S., Eidelman, P., Gruber, J., & Harvey, A. G. (2009). The effect of mood on sleep onset latency and REM sleep in interepisode bipolar disorder. *J Abnorm Psychol, 118*(3), 448-458. doi:10.1037/a0016605

Talbot, L. S., Stone, S., Gruber, J., Hairston, I. S., Eidelman, P., & Harvey, A. G. (2012). A test of the bidirectional association between sleep and mood in bipolar disorder and insomnia. *J Abnorm Psychol, 121*(1), 39–50. doi:10.1037/a0024946

Taquet, M., Quoidbach, J., de Montjoye, Y.-A., Desseilles, M., & Gross, J. J. (2016). Hedonism and the choice of everyday activities. *Proc Natl Acad Sci, 113*(35), 9769.

Thompson, R. J., Berenbaum, H., & Bredemeier, K. (2011). Cross-sectional and longitudinal relations between affective instability and depression. *J Affect Disord, 130*(1-2), 53-59. doi:10.1016/j.jad.2010.09.021

Trull, T. J., Solhan, M. B., Tragesser, S. L., Jahng, S., Wood, P. K., Piasecki, T. M., & Watson, D. (2008). Affective instability: measuring a core feature of borderline personality disorder with ecological momentary assessment. *J Abnorm Psychol, 117*(3), 647-661. doi:10.1037/a0012532

Tsanas, A., Saunders, K., Bilderbeck, A., Palmius, N., Goodwin, G., & De Vos, M. (2017). Clinical Insight Into Latent Variables of Psychiatric Questionnaires for Mood Symptom Self-Assessment. *JMIR Ment Health, 4*(2), e15. doi:10.2196/mental.6917

Tsanas, A., Saunders, K. E., Bilderbeck, A. C., Palmius, N., Osipov, M., Clifford, G. D., . . . De Vos, M. (2016). Daily longitudinal self-monitoring of mood variability in bipolar disorder and borderline personality disorder. *J Affect Disord, 205*, 225-233. doi:10.1016/j.jad.2016.06.065

VanderWeele, T. J. (2015). *Explanation in causal inference: methods for mediation and interaction*. New York: Oxford University Press.

Vigo, D., Thornicroft, G., & Atun, R. (2016). Estimating the true global burden of mental illness. *Lancet Psychiatry, 3*(2), 171-178. doi:10.1016/S2215-0366(15)00505-2

Ward, J., Strawbridge, R. J., Bailey, M. E. S., Graham, N., Ferguson, A., Lyall, D. M., . . . Smith, D. J. (2017). Genome-wide analysis in UK Biobank identifies four loci associated with mood instability and genetic correlation with major depressive disorder, anxiety disorder and schizophrenia. *Transl Psychiatry, 7*(11), 1264. doi:10.1038/s41398-017-0012-7

Waters, F. A., Sinclair, C., Rock, D., Jablensky, A., Wulff, K., & Foster, R. (2010). Daily Variations in Sleep-Wake Patterns and Severity of Psychosis. *Schizophr Res, 117*(2-3), 531. doi:10.1016/j.schres.2010.02.1025

Wehr, T. A., Goodwin, F. K., Wirz-Justice, A., Breitmaier, J., & Craig, C. (1982). 48-hour sleep-wake cycles in manic-depressive illness: naturalistic observations and sleep deprivation experiments. *Arch Gen Psychiatry, 39*(5), 559-565.

Wender, P. H. (1995). *Attention-Deficit Hyperactivity Disorder in Adults.* New York: Oxford University Press.

Westen, D., Muderrisoglu, S., Fowler, C., Shedler, J., & Koren, D. (1997). Affect regulation and affective experience: Individual differences, group differences, and measurement using a Q-sort procedure. *J Consult Clin Psychol, 65*(3), 429-439. doi:Doi 10.1037/0022-006x.65.3.429

Widiger, T. A., Mangine, S., Corbitt, E. M., Ellis, C. G., & Thomas, G. V. (1995). *Personality Disorder Interview-IV: A Semistructured Interview for the Assessment of Personality Disorders*. Odessa, FL.: Psychological Assessment Resources.

Williams, K. E., Chambless, D. L., & Ahrens, A. (1997). Are emotions frightening? An extension of the fear of fear construct. *Behav Res Ther, 35*(3), 239-248. doi:10.1016/S0005-7967(96)00098-8

Wilsnack, R. W., Vogeltanz, N. D., Wilsnack, S. C., Harris, T. R., Ahlstrom, S., Bondy, S., . . . Weiss, S. (2000). Gender differences in alcohol consumption and adverse drinking consequences: cross-cultural patterns. *Addiction, 95*(2), 251-265.

Wing, J. K., Beevor, A. S., Curtis, R. H., Park, S. B., Hadden, S., & Burns, A. (1998). Health of the Nation Outcome Scales (HoNOS). Research and development. *Br J Psychiatry, 172*(1), 11-18. doi:10.1192/bjp.172.1.11

Winkelman, J. W., & Plante, D. T. (2010). *Foundations of psychiatric sleep medicine*. Cambridge: Cambridge : Cambridge University Press.

World Health Organization. (1992). International Statistical Classification of Diseases and Related Health Problems (ICD-10). Geneva: World Health Organization.

Wulff, K., Gatti, S., Wettstein, J. G., & Foster, R. G. (2010). Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nat Rev Neurosci, 11*(8), 589-599. doi:10.1038/nrn2868

Wulff, K., Porcheret, K., Cussans, E., & Foster, R. G. (2009). Sleep and circadian rhythm disturbances: multiple genes and multiple phenotypes. *Curr Opin Genet Dev, 19*(3), 237-246. doi:10.1016/j.gde.2009.03.007

Wynchank, D., Ten Have, M., Bijlenga, D., Penninx, B. W., Beekman, A. T., Lamers, F., . . . Kooij, J. J. S. (2018). The Association Between Insomnia and Sleep Duration in Adults With Attention-Deficit Hyperactivity Disorder: Results From a General Population Study. *J Clin Sleep Med, 14*(3), 349-357. doi:10.5664/jcsm.6976

Yen, S., Shea, M. T., Sanislow, C. A., Grilo, C. M., Skodol, A. E., Gunderson, J. G., . . . Morey, L. C. (2004). Borderline personality disorder criteria associated with prospectively observed suicidal behavior. *Am J Psychiatry, 161*(7), 1296-1298. doi:10.1176/appi.ajp.161.7.1296

Zanini, M. A., Castro, J., Cunha, G. R., Asevedo, E., Pan, P. M., Bittencourt, L., . . . Brietzke, E. (2015). Abnormalities in sleep patterns in individuals at risk for psychosis and bipolar disorder. *Schizophr Res, 169*(1-3), 262-267. doi:10.1016/j.schres.2015.08.023

Zhang, B., & Wing, Y. K. (2006). Sex differences in insomnia: a meta-analysis. *Sleep, 29*(1), 85-93. doi:10.1093/sleep/29.1.85