

Sleep Disruption as a Pathway to Mania in Bipolar Disorder

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Summary

Sleep loss may act as a trigger or early warning sign of manic episodes in individuals with bipolar disorder (BD) but the nature of this relationship remains unclear. The aim of this thesis was to explore the relationship between sleep disruption and mania in individuals with BD.

The datasets used in this thesis were obtained from the Bipolar Disorder Research Network (BDRN), an ongoing research programme of over 6000 individuals with mood disorders recruited from across the UK. Psychiatric diagnoses were determined using a semi-structured diagnostic research interview and case notes.

First, in 3140 BDRN participants with bipolar-I disorder (BD-I) or bipolar-II disorder (BD-II), I found that 20% of participants reported that sleep loss had triggered episodes of high mood. This was more commonly reported by individuals with BD-I than those with BD-II, and more commonly reported by women than men.

Second, I found that women were more likely to have experienced episodes of mania or psychosis after childbirth (termed postpartum psychosis, PP) if sleep loss had triggered episodes of high mood. This effect suggested that a tendency for sleep loss to trigger episodes of high mood might be associated with vulnerability to PP.

Third, in BDRN participants who had used an online mood monitoring system to track symptoms of mania and depression, I found that participants could be grouped into three classes based on their trajectories in symptoms of insomnia prior to episodes of high mood.

Finally, I designed and conducted a pilot study using actigraphy to measure perinatal sleep in pregnant women at high risk of developing PP. I found that this methodology was challenging to implement in this population but can produce detailed information on sleep during the perinatal period.

The findings of this thesis could help inform clinical practice by expanding current knowledge on how sleep loss affects individuals with BD.

Publications

The work in this thesis is reproduced in whole or in part in the following publications:

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

1	INTRODUCTION	1
1.1	BACKGROUND	3
1.2	BIPOLAR DISORDER	4
1.2.1	MODERN DIAGNOSIS OF BIPOLAR DISORDER	4
1.2.2	DIFFERENCES BETWEEN DSM-5 AND DSM-IV CRITERIA FOR MANIC AND HYPOMANIC EPISODES	7
1.2.3	BIPOLAR DISORDER SUBTYPES	7
1.2.4	EPIDEMIOLOGY AND IMPORTANCE OF UNDERSTANDING AETIOLOGY	9
1.2.5	BIPOLAR DISORDER AND THE PERINATAL PERIOD	11
1.2.6	AETIOLOGY: CURRENT KNOWLEDGE	13
1.3	SLEEP AND BIPOLAR DISORDER	16
1.3.1	REGULATION OF THE SLEEP-WAKE CYCLE	17
1.3.2	THE PHYSIOLOGICAL EFFECTS OF SLEEP DISRUPTION	19
1.3.3	THE EFFECTS OF SLEEP DISRUPTION ON MENTAL HEALTH	20
1.3.4	THE ROLE OF SLEEP DISRUPTION IN THE AETIOLOGY OF BIPOLAR DISORDER	23
1.4	SLEEP DISTURBANCE AS A PATHWAY TO MANIA	29
1.4.1	THE SLEEP-REDUCTION MODEL OF MANIA	30
1.4.2	SUPPORTING EVIDENCE	33
1.4.3	POTENTIAL MECHANISMS	45
1.4.4	IMPLICATIONS FOR CLINICAL PRACTICE	47
1.5	SLEEP DISTURBANCE AS A PATHWAY TO MANIA: IMPLICATIONS FOR POSTPARTUM PSYCHOSIS	48

1.6	LIMITATIONS IN CURRENT KNOWLEDGE OF THE SLEEP REDUCTION MODEL	51
1.6.1	SLEEP DISRUPTION AND DEPRESSIVE SYMPTOMS	52
1.6.2	NON-MANIC RESPONSES TO SLEEP DEPRIVATION PROTOCOLS	53
1.6.3	HOW MUCH SLEEP LOSS TRIGGERS EPISODES?	54
1.6.4	INDIVIDUAL DIFFERENCES IN RESPONSE TO SLEEP DISRUPTION	54
1.6.5	SUMMARY	55
1.7	AIMS AND STRUCTURE OF THESIS	56
2	<u>GENERAL METHOD</u>	<u>58</u>
2.1	BACKGROUND	59
2.2	SAMPLE RECRUITMENT	59
2.3	INCLUSION AND EXCLUSION CRITERIA	60
2.4	ASSESSMENT PROCEDURE	60
2.5	BDRN DATA AND SAMPLES USED IN THIS THESIS	61
2.5.1	SLEEP LOSS AS A TRIGGER OF MOOD EPISODES	62
2.5.2	TRUE COLOURS ONLINE PROSPECTIVE MOOD MONITORING	63
2.5.3	PROSPECTIVE SLEEP MONITORING IN PREGNANCY STUDY	63
2.5.4	SUMMARY OF SAMPLES	64
2.6	STATISTICAL ANALYSIS	65
3	<u>SLEEP LOSS AS A TRIGGER OF MOOD EPISODES IN BIPOLAR DISORDER: INDIVIDUAL DIFFERENCES BASED ON DIAGNOSTIC SUBTYPE AND GENDER</u>	<u>66</u>
3.1	INTRODUCTION	67
3.2	METHOD	70
3.2.1	SAMPLE	70
3.2.2	ASSESSMENTS	70
3.2.3	STATISTICAL ANALYSIS	70
3.3	RESULTS	72

3.3.1	PREVALENCE OF SLEEP LOSS TRIGGERING MOOD EPISODES IN BIPOLAR DISORDER	73
3.3.2	DIFFERENCES BETWEEN BIPOLAR SUBTYPES	73
3.3.3	GENDER DIFFERENCES	76
3.3.4	MULTIVARIATE BINARY LOGISTIC REGRESSION MODELS	78
3.4	DISCUSSION	79
3.4.1	BIPOLAR SUBTYPE	80
3.4.2	GENDER	81
3.4.3	EPISODES OF DEPRESSION TRIGGERED BY SLEEP LOSS	82
3.4.4	STRENGTHS AND LIMITATIONS	83
3.4.5	FUTURE RESEARCH	85
3.4.6	IMPLICATIONS FOR CLINICAL PRACTICE	86
3.4.7	SUMMARY	87
4	<u>SLEEP LOSS AS A TRIGGER OF MANIA AND SUSCEPTIBILITY TO POSTPARTUM PSYCHOSIS</u>	89
4.1	INTRODUCTION	90
4.2	METHOD	92
4.2.1	RECRUITMENT AND INCLUSION CRITERIA	92
4.2.2	ASSESSMENTS AND DEFINITION OF POSTPARTUM EPISODES	92
4.2.3	STATISTICAL ANALYSIS	93
4.3	RESULTS	94
4.3.1	SAMPLE CHARACTERISTICS AND PERINATAL EPISODES	94
4.3.2	MANIA TRIGGERED BY SLEEP LOSS AND POSTPARTUM PSYCHOSIS	95
4.3.3	SPECIFICITY OF FINDINGS	98
4.3.4	ANALYSES TO ADDRESS POTENTIAL RECALL BIAS	100
4.4	DISCUSSION	101
4.4.1	STRENGTHS AND LIMITATIONS	102

4.4.2	VULNERABILITY TO THE MANIA-INDUCING QUALITIES OF SLEEP LOSS	103
4.4.3	CLINICAL IMPLICATIONS	104
4.4.4	FUTURE STUDIES	105
4.4.5	SUMMARY	106
5	<u>TRAJECTORIES IN INSOMNIA PRIOR TO EPISODES OF HIGH MOOD: RESULTS</u>	
	<u>FROM AN ONLINE MOOD MONITORING SYSTEM</u>	107
5.1	INTRODUCTION	108
5.2	METHOD	113
5.2.1	THE TRUE COLOURS ONLINE MOOD MONITORING SYSTEM	113
5.2.2	SAMPLE	115
5.2.3	DATA PREPARATION	116
5.2.4	IDENTIFYING MOOD EPISODES	117
5.2.5	EXTRACTING DATA PRIOR TO EPISODE RELAPSE	117
5.2.6	MEASURING INSOMNIA	118
5.2.7	STATISTICAL ANALYSIS: LATENT GROWTH MIXTURE MODELLING	120
5.3	RESULTS	122
5.3.1	INSOMNIA TRAJECTORIES PRIOR TO EPISODES OF HIGH MOOD	122
5.3.2	PREDICTORS OF INSOMNIA CLASS MEMBERSHIP PRIOR TO EPISODES OF HIGH MOOD	124
5.3.3	INSOMNIA TRAJECTORIES PRIOR TO EPISODES OF LOW MOOD	130
5.4	DISCUSSION	132
5.4.1	STRENGTHS AND LIMITATIONS	135
5.4.2	FUTURE RESEARCH	137
5.4.3	CONCLUSIONS	138
6	<u>USING ACTIGRAPHY TO MEASURE SLEEP DISTURBANCE IN PREGNANT WOMEN</u>	
	<u>AT HIGH-RISK OF POSTPARTUM PSYCHOSIS</u>	139
6.1	INTRODUCTION	140

6.1.1	PROSPECTIVE STUDIES OF SLEEP AND RISK OF POSTPARTUM PSYCHOSIS	140
6.1.2	ACTIGRAPHY AND SLEEP	142
6.1.3	AIMS	144
6.2	METHOD	146
6.2.1	RECRUITMENT	146
6.2.2	INCLUSION AND EXCLUSION CRITERIA	147
6.2.3	ANTENATAL INTERVIEW	147
6.2.4	SLEEP MONITORING	147
6.2.5	POSTNATAL INTERVIEW	150
6.2.6	LIFETIME DIAGNOSES AND POSTPARTUM EPISODES	151
6.2.7	PREPARATION OF ACTIGRAPHY DATA	152
6.2.8	ANALYSIS	153
6.3	RESULTS	155
6.3.1	RECRUITMENT AND RETENTION	155
6.3.2	RETENTION AND ACCEPTABILITY	156
6.3.3	WOMEN WHO COMPLETED SLEEP MONITORING	156
6.3.4	ACTIGRAPHY	158
6.3.5	PSYCHIATRIC SEQUELAE AND SLEEP DURATION	162
6.4	DISCUSSION	166
6.4.1	SLEEP DEPRIVATION IN THE PERINATAL PERIOD	166
6.4.2	BARRIERS TO USING ACTIGRAPHY IN WOMEN AT HIGH RISK OF POSTPARTUM PSYCHOSIS	168
6.4.3	STRENGTHS	170
6.4.4	LIMITATIONS	170
6.4.5	FUTURE RESEARCH	171
6.4.6	CLINICAL IMPLICATIONS	174
6.4.7	CONCLUSIONS	174

7	<u>GENERAL DISCUSSION</u>	176
7.1	INTRODUCTION	177
7.2	THESIS AIMS	179
7.2.1	AIM 1	179
7.2.2	AIM 2	181
7.2.3	AIM 3	182
7.2.4	AIM 4	183
7.3	STRENGTHS AND LIMITATIONS	185
7.4	THE ROLE OF SLEEP LOSS IN THE GENESIS OF MANIA: TRIGGER, PRODROME OR SYMPTOM?	186
7.5	SUBJECTIVE VS. OBJECTIVE MEASURES OF SLEEP DISRUPTION	188
7.6	ADDITIONAL INFLUENCES ON SLEEP AND MOOD	190
7.7	FUTURE RESEARCH	191
7.8	CLINICAL IMPLICATIONS	192
7.8.1	THE RELATIONSHIP BETWEEN SLEEP AND MOOD IN BD	192
7.8.2	INDIVIDUAL DIFFERENCES IN WHETHER SLEEP LOSS ACTS AS A PATHWAY TO MANIA	194
7.9	FINAL CONCLUSIONS	195
8	<u>REFERENCES</u>	196
9	<u>APPENDICES</u>	220
	APPENDIX A – TRIGGERS OF MOOD EPISODES INTERVIEW QUESTIONS	221
	APPENDIX B - QUICK INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY (SELF-REPORT)	223
	APPENDIX C - ALTMAN SELF-RATING MANIA SCALE	225
	APPENDIX D – COMPARISON OF TRIGGERS OF MOOD EPISODES BY GENDER	226
	APPENDIX E – TRUE COLOURS EXAMPLE PARTICIPANT SUMMARY GRAPH	227
	APPENDIX F – SAMPLE SIZE CALCULATIONS FOR CHAPTER 5	228
	APPENDIX G – SLEEP DISORDER SCREENING QUESTIONS	229

APPENDIX H – SLEEP DIARY AND ACTIGRAPHY INSTRUCTIONS	230
APPENDIX I – GP AND PSYCHIATRIST QUESTIONNAIRES	236
APPENDIX J – ACTIGRAPHY DATA PROCESSING PROTOCOL	242
APPENDIX K – PARTICIPANT CORRESPONDENCE	243
APPENDIX L – PARTICIPANT SLEEP CHARTS DERIVED FROM ACTIGRAPHY DATA	244

List of Tables

Table 1-1. DSM-5 criteria for manic and hypomanic episodes (American Psychiatric Association 2013).....	6
Table 1-2. Summary of DSM-5 diagnostic criteria for bipolar disorder (American Psychiatric Association 2013).....	8
Table 1-3. DSM-5 criteria for major depressive episodes (American Psychiatric Association 2013).....	9
Table 1-4. Rates of mania and hypomania in BD patients following total sleep deprivation therapy for depression.....	37
Table 1-5. Prospective studies between sleep and mania in participants with bipolar disorder.	43
Table 3-1. Clinical and demographic information of participants with BD-I or BD-II who were asked about triggers of mood episodes.	72
Table 3-2. Response frequencies of triggers of mood episodes of participants with bipolar disorder.....	73
Table 4-1. Sample clinical and demographic information for 870 parous women with bipolar-I disorder.....	95
Table 5-1. Number of days between participant entries on the True Colours system.....	116
Table 5-2. Descriptives of participants enrolled in True Colours who met symptom and duration criteria for likely episodes of high mood or low mood.	118

Table 5-3. QIDS insomnia items and responses.	119
Table 5-4. Correlations between QIDS insomnia items.....	119
Table 5-5. Model selection criteria to determine trajectory classes of insomnia prior to episodes of high mood.	123
Table 5-6. Descriptives of age split by insomnia trajectory class.	126
Table 5-7. Model selection criteria to determine trajectory classes of insomnia prior to episodes of low mood.	131
Table 6-1. Demographic and clinical characteristics of women who expressed interest in sleep monitoring.	157
Table 6-2. Additional information on medication, delivery and psychiatric sequelae of women who completed sleep monitoring.	165
Table 7-1. Summary of main findings of studies described within this thesis.....	178
Table 9-1. Comparison between men and women in likelihood of reporting different triggers of mood episodes.....	226
Table 9-2. Sample sizes per group for class comparisons (alpha = 0.05, power = 0.80)	228

List of Figures

Figure 1-1. Interaction between the circadian drive for arousal (Process C) and the homeostatic sleep drive (Process S) (Borbély 1982).	18
Figure 1-2. Hypothesised relationship between sleep and circadian disruption and psychiatric illness (Wulff et al. 2010).....	22
Figure 1-3. Proposed model of the relationship between sleep disruption and mania (Wehr et al. 1987).	32
Figure 1-4. Longitudinal 16-week record of sleep duration and mood in 59 year old woman with bipolar illness (Wehr 1991).	33
Figure 2-1. Diagram to illustrate the derivation of the samples used for each chapter of this thesis.....	65
Figure 3-1. Percentage of individuals with bipolar disorder who report that sleep loss has triggered episodes of (hypo)mania (Panel A) or depression (Panel B) split by bipolar subtype. Error bars represent 95% confidence intervals.	75
Figure 3-2. Percentage of individuals with bipolar disorder who report that sleep loss has triggered episodes of (hypo)mania (Panel A) or depression (Panel B) split by gender. Error bars represent 95% confidence intervals.	77
Figure 4-1. Proportion of women with perinatal episodes split by manic response to sleep loss. Abbreviations: PP, Postpartum Psychosis; PD, Postpartum Depression; no PD/PP, includes: no perinatal episode, any other psychiatric illness occurring in the perinatal	

period up to 6 months postpartum, or onset of PP or PD outside of 6 weeks of delivery.
..... 97

Figure 4-2. Proportion of women with perinatal episodes split by depressive response to sleep loss. Abbreviations: PP, Postpartum Psychosis; PD, Postpartum Depression; no PD/PP, includes: no perinatal episode, any other psychiatric illness occurring in the perinatal period up to 6 months postpartum, or onset of PP or PD outside of 6 weeks of delivery.
..... 99

Figure 5-1. The sleep reduction model of mania (Wehr et al. 1987). 108

Figure 5-2. Welcome screen and example question from the Quick Inventory for Depression Symptomatology (QIDS) used in the True Colours online mood monitoring system. ... 114

Figure 5-3. Welcome screen and example question from the Altman Mania Scale used in the True Colours online mood monitoring system. 115

Figure 5-4. Mean insomnia score in weeks prior to episode of high mood. Error bars represent 95% confidence intervals. 122

Figure 5-5. Mean insomnia scores prior to episodes of high mood, split by class. Error bars represent 95% confidence intervals. 124

Figure 5-6. Insomnia trajectory class split by bipolar diagnostic subtype (BD-I, bipolar-I disorder, BD-II, bipolar-II disorder). 125

Figure 5-7. Insomnia trajectory class split by gender. 125

Figure 5-8. Mean Altman Mania Scale (AMS) scores prior to episodes of high mood. Error bars represent 95% confidence intervals..... 127

Figure 5-9. Average scores on the ‘reduced need for sleep’ item of the AMS. Error bars indicate 95% confidence intervals..... 128

Figure 5-10. Average QIDS summary scores (minus insomnia items) by class during 4 weeks prior to an episode of high mood. Error bars indicate 95% confidence intervals. 129

Figure 5-11. Average trajectory in insomnia severity over 4 weeks preceding episodes of low mood. Error bars represent 95% confidence intervals..... 130

Figure 6-1. Actiwatch Spectrum Plus Actigraph (Philips Respironics). 149

Figure 6-2. Example sleep diary. Shaded regions indicate sleep, vertical lines indicate bed times and rise times. 150

Figure 6-3. Brief summary of assessments used in the prospective pregnancy study..... 152

Figure 6-4. Recruitment chart for actigraphy study. 155

Figure 6-5. Example actogram of one participant during the postpartum period. Day numbers indicate days of monitoring..... 159

Figure 6-6. Example sleep parameters derived from actigraphy for one participant during pregnancy and the postpartum period. The yellow shaded region indicates the week prior to delivery, the blue shaded region indicates the week following delivery. 160

Figure 6-7. Total number of hours slept per night two weeks before and after delivery date in 7 women, measured using actigraphy. Onset of DSM-5 psychiatric episodes is labelled if women became unwell. 161

Abbreviations

AMS (Altman Mania Scale)

BD (Bipolar Disorder)

BD-I (Bipolar-I Disorder)

BD-II (Bipolar-II Disorder)

BIC (Bayesian Information Criterion)

BLRT (Bootstrap Likelihood Ratio Test)

CBT-I (Cognitive Behavioural Therapy for Insomnia)

CBTI-BP (Cognitive Behavioural Therapy for Insomnia modified for use in Bipolar disorder)

EEG (Electroencephalography)

GMM (Growth Mixture Modelling)

GWAS (Genome Wide Association Studies)

HPA axis (Hypothalamic-Pituitary-Adrenocortical axis)

IPSRT (Interpersonal and Social Rhythm Therapy)

NHS (National Health Service)

NREM (Non-Rapid Eye Movement)

PD (Postpartum Depression)

PP (Postpartum Psychosis)

PSG (Polysomnography)

QIDS (Quick Inventory of Depressive Symptomatology)

RCT (Randomised Controlled Trial)

REM (Rapid Eye Movement)

SCAN (Schedules for Clinical Assessment in Neuropsychiatry)

SCN (Suprachiasmatic Nuclei)

TSD (Total Sleep Deprivation)

VLMR-LRT (Vuong-Lo-Mendell-Rubin Likelihood Ratio Test)

Contributions

The work in this thesis is primarily based on analysis of existing data for which I was not directly involved in collecting. I was directly involved in data collection for Chapter 6. The following is a list of my contributions to the work described in this thesis.

Work presented in Chapter 3, Chapter 4 and Chapter 5:

I designed the analytic plan for analysis of the data used in these chapters and cleaned the datasets prior to analysis. I conducted the statistical analyses and interpreted the results for each of these chapters. In addition, I performed data wrangling prior to cleaning the dataset for Chapter 5.

Work presented in Chapter 6: Using actigraphy to measure sleep disturbance in pregnant women at high-risk of postpartum psychosis:

I designed all aspects of the prospective pregnancy study relating to the measurement of sleep, which included researching and selecting the most suitable actigraph models, as well as researching which sleep diary would be most appropriate for use in this sample. I also helped prepare the application for ethical approval for this study. I interviewed all women who expressed interest in the sleep study, and scored all resulting actigraphy, questionnaire and interview data. I designed the analytic plan, performed data wrangling for actigraphy data, and interpreted the results.

1 INTRODUCTION

Reported in part by (Lewis et al. 2016)

For doe but consider what an excellent thing sléepe is: It is so inestimable a Jewell, that if a Tyrant would give his crowne for an houres slumber, it cannot be bought... yea so greatly indebted are we to this kinseman of death, that we owe the better tributary, halfe of our life to him: and thers good cause why we should do so: for sleepe is that golden chaine that ties health and our bodies together. Who complaines of want? of woundes? of cares? of great mens oppressions? of captivity? whilst hée sléepeth? Beggars in their beds take as much pleasure as Kings: can we therefore surfet on this delicate Ambrosia? can we drink too much of that whereof to tast too little, tumbles us into a Church-yard, and to use it but indifferently, throwes us into Bedlam? (Dekker 1609 p.10)

1.1 Background

Bipolar disorder (BD) is a psychiatric condition characterised by severe episodes of mood instability that range from depression to mania (extreme elation or irritability). Mania is the defining feature of BD that distinguishes it from other mood disorders such as major depressive disorder, and can include psychotic symptoms such as hallucinations and delusions. These recurrent episodes of mood instability result in significant impairment to personal, social and occupational functioning (Simon 2003), with associated costs to health services and the economy (Kleinman et al. 2003; Young et al. 2011). The primary goal for health care professionals, therefore, is to ensure prompt and effective treatment of mood episodes and, if possible, to prevent episodes from occurring (Leboyer and Kupfer 2010; National Institute for Health and Care Excellence, NICE, 2017). To inform these efforts, we must better understand what factors cause or signal the onset of mood episodes in individuals with BD.

Current evidence suggests that a myriad of environmental and genetic factors may increase risk of BD (Craddock and Sklar 2013), and mood episodes may be precipitated by a variety of bio-psycho-social factors (Alloy et al. 2005). However, increasing evidence suggests that sleep disturbance, itself a symptom of both depression and mania, could provide valuable insight into the causes and early signs of mood episodes. If so, sleep patterns could be an easily monitored, non-pharmacologic target for intervention.

In this chapter, I will first outline the characteristics of BD and current knowledge of its aetiology. Second, I will describe the systems governing the sleep-wake system and the physical and psychological consequences of disrupting these systems. Third, I will discuss evidence that research on sleep disturbance can provide valuable insight into the aetiology of

BD. Fourth, I will expound on the sleep-reduction model of mania, which informs the central focus of this thesis, that measuring sleep reduction could provide a valuable means for predicting episodes of mania in BD. The chapter will conclude with limitations in current knowledge of how sleep is involved in the pathway to mania, followed by a description of the aims for this thesis.

1.2 Bipolar Disorder

The modern concept of BD as a distinct entity derives from 19th and early 20th century psychiatry (Angst and Sellaro 2000; Angst and Marneros 2001). In 1851, the French psychiatrist Jean-Pierre Falret described an illness characterised by episodes of mania, depression and euthymia, which he termed ‘folie circulaire’ (Pichot 1995; Angst and Marneros 2001). Subsequently, in the 1890s, Emil Kraepelin built upon the concept of ‘folie circulaire’ to devise the concept of ‘manic-depressive insanity’, which encompassed both bipolar and unipolar mood disorders and distinguished them from dementia praecox (i.e. schizophrenia) (Kraepelin 1893; Kraepelin 1896; Kraepelin 1899; Angst and Sellaro 2000). This categorisation prevailed until the 1950s, when Karl Leonhard distinguished between unipolar and bipolar affective disorders (Leonhard 1957), a distinction which is now used in modern diagnostic systems (Grande et al. 2015). As will be described in the following section, the defining feature of BD is mania.

1.2.1 Modern Diagnosis of Bipolar Disorder

At present, the two most widely acknowledged diagnostic classification systems are the International Classification of Diseases (ICD) (World Health Organisation, WHO, 1992) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association 2013), currently in their 10th and 5th editions, respectively.

This thesis uses the DSM criteria for BD diagnosis, which is centred on a set of operationalized criteria for mania. The fifth edition of the DSM (American Psychiatric Association 2013) defines manic episodes as distinct periods of (i) high mood or irritability and (ii) increased goal-directed activity or energy, which are accompanied by symptoms such as inflated self-esteem or pressurised speech (see Table 1-1 for full list of symptoms). The episodes must cause marked impairment in important areas of functioning, such as occupational or social activities and persist for at least one week. Manic episodes are also diagnosed if the duration criterion is not met but there are psychotic symptoms (hallucinations and delusions) or the symptom severity warrants hospitalisation.

Episodes that do not meet the duration or severity criteria but last for at least 4 days are termed 'hypomanic'. Hypomanic episodes are not of sufficient severity to result in hospitalisation and do not cause marked impairment in social or occupational functioning. However, the symptoms must be observable by others and represent a marked change from typically functioning mood. Table 1-1 outlines DSM-5 criteria for manic and hypomanic episodes.

Table 1-1. DSM-5 criteria for manic and hypomanic episodes (American Psychiatric Association 2013).

Symptoms	Duration criteria	Impairment criteria
<p>A distinct period of abnormally and persistently elevated, expansive, or irritable mood and persistently increased goal-directed activity or energy*, that is accompanied by at least three (if the mood is high) or four (if the mood is irritable) of the following symptoms:</p> <ol style="list-style-type: none"> 1. Inflated self-esteem or grandiosity 2. Decreased need for sleep (e.g. feeling rested after only 3 hours of sleep) 3. More talkative than usual or pressure to keep talking 4. Flight of ideas/subjective experience that thoughts are racing 5. Distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli) 6. Increase in goal-directed activity (socially, at work/school, sexually) or psychomotor agitation 7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments) 	<p><u>Mania:</u></p> <p>At least 1 week (or any duration if hospitalization necessary).</p>	<p><u>Mania:</u></p> <p>Any of the following:</p> <ul style="list-style-type: none"> • Marked impairment in occupational or social functioning. • Necessitates hospitalisation to prevent harm to self or others. • Includes psychotic features.
	<p><u>Hypomania:</u></p> <p>At least 4 days (mood change must also be clearly different from the usual non-depressed mood).</p>	<p><u>Hypomania:</u></p> <ul style="list-style-type: none"> • Unequivocal change in functioning that is uncharacteristic of the person when not symptomatic. • Disturbances in mood and change in functioning are observable by others. <p>The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features.</p>

*Goal-directed activity was added as a core symptom of mania in the 5th edition of the DSM. All other criteria are consistent with DSM-IV (American Psychiatric Association 2000).

1.2.2 Differences Between DSM-5 and DSM-IV Criteria for Manic and Hypomanic Episodes

Most of the data available for this thesis were collected prior to the release of the DSM-5 in 2013, therefore Chapters 3-5 in this thesis rely on DSM-IV criteria for BD (American Psychiatric Association 2000). As shown in Table 1-1, DSM-IV and DSM-5 criteria for (hypo)manic episodes are consistent except for the addition of increased goal-directed activity or energy as a core symptom of mood change. A recent analysis on the dataset used in this thesis (described in Chapter 2) suggests that this new criterion does not result in substantial changes to existing DSM-IV diagnoses, with 94% of 3993 cases with a lifetime DSM-IV diagnosis of BD meeting DSM-5 criteria for BD (Gordon-Smith et al. 2017).

1.2.3 Bipolar Disorder Subtypes

There are a number of subtypes of bipolar disorder, which are summarised in Table 1-2. Bipolar-I disorder (BD-I) is diagnosed when individuals meet criteria for experiencing at least one manic episode. In contrast, bipolar-II disorder (BD-II) is diagnosed where individuals have experienced hypomanic (rather than ‘manic’) episodes and requires a history of at least one major depressive episode (criteria shown in Table 1-3). Although traditionally considered a milder form of bipolar disorder, BD-II is actually associated with high rates of recurrence, high rates of psychiatric comorbidities, and recurrent suicidal behaviours that impair quality of life (Vieta and Suppes 2008).

Additional variations in diagnosis (summarised in Table 1-2) include cyclothymic disorder and bipolar disorder ‘not otherwise specified’. These categories are part of the ‘bipolar

spectrum' (Ghaemi et al. 2002) whereby an individual does not meet full criteria for BD but presents with a condition that appears to be related to BD.

Table 1-2. Summary of DSM-5 diagnostic criteria for bipolar disorder (American Psychiatric Association 2013).

Disorder	Manic Symptom Criteria	Depressive Symptom Criteria
Bipolar-I disorder	<ul style="list-style-type: none"> • Manic episodes 	<ul style="list-style-type: none"> • Not required for diagnosis
Bipolar-II disorder	<ul style="list-style-type: none"> • One or more episodes of hypomania • No manic episodes 	<ul style="list-style-type: none"> • Major depressive episodes
Cyclothymic disorder	<ul style="list-style-type: none"> • Hypomanic symptoms present for at least 2 years 	<ul style="list-style-type: none"> • Periods of depressive symptoms that do not meet criteria for a major depressive episode
Bipolar disorder not otherwise specified	<ul style="list-style-type: none"> • Presence of manic symptoms that do not meet criteria for bipolar-I, bipolar-II or cyclothymic disorder 	<ul style="list-style-type: none"> • Not required for diagnosis

Both BD-I and BD-II can exhibit a 'rapid-cycling' course of illness, where at least four (hypo)manic or depressive episodes occur within a year (each episode separated by either partial or full remission or by switching to an opposite polarity episode) (American Psychiatric Association 2013). The lifetime prevalence of rapid-cycling BD has been estimated at 25-43% and is associated with an earlier age at illness onset, more illegal drug and alcohol abuse, and increased suicidality (Carvalho et al. 2014). In addition, DSM-5 criteria state that mood episodes in BD-I and BD-II can present with 'mixed features', whereby episodes of (hypo)mania or depression occur simultaneously with at least three symptoms of the opposite polarity (American Psychiatric Association 2013). This is in contrast to DSM-IV criteria, which instead describes 'mixed episodes'. These are only present in BD-I and occur when an episode of mania simultaneously presents with full symptom criteria for a major depressive episode (American Psychiatric Association 2000).

Table 1-3. DSM-5 criteria for major depressive episodes (American Psychiatric Association 2013).

Symptom criteria	Duration and Impairment criteria
<p>Five or more of the following symptoms (<i>at least one symptom must be either depressed mood or anhedonia</i>).</p> <ul style="list-style-type: none"> • Depressed mood • Anhedonia • Weight change (>5% increase or decrease in body weight) or change in appetite • Insomnia/hypersomnia • Psychomotor agitation/retardation • Fatigue/loss of energy • Feelings of worthlessness/excessive guilt • Poor concentration/ability to make decisions • Recurrent thoughts of death, suicidal ideation, attempts or plans for committing suicide 	<p>Duration: Symptoms must be present nearly every day (except suicidal thoughts) for a 2-week period</p> <p>Impairment: Clinically significant distress/impairment in social, occupational or other important areas of functioning that represents a change from previous functioning.</p>

1.2.4 Epidemiology and Importance of Understanding Aetiology

The onset of BD is usually in late adolescence or early adulthood, with the median age of onset estimated at 17.5 years (Kupfer et al. 2002) and symptom onset most common between the ages of 15 and 19 years of age (Weissman et al. 1996).

Estimates of the lifetime prevalence of BD vary across studies, ranging from 0.3 to 2.4% for BD-I, and 0.3 to 4.8% for BD-II (Weissman et al. 1996; Kleinman et al. 2003; Waraich et al. 2004; Pini et al. 2005; Benazzi 2007; Merikangas et al. 2011). The estimates of lifetime prevalence for broader definitions of BD (e.g. that include cyclothymia) range from 0.8 to 13.5% (Benazzi 2007). Variation in estimates may reflect different assessment methods and criteria for generating diagnoses. However, evidence suggests that, due to under-identification and misdiagnosis (Goldberg et al. 2001; Hirschfeld et al. 2003; Baca-Garcia et al. 2007; Berk et al. 2007), true prevalence is

underestimated. Such factors may contribute to the 5-10 year intervals between initial onset of illness and first treatment (Suppes et al. 2001; Baldessarini et al. 2003).

With respect to sex differences, BD is equally prevalent among men and women (Lloyd et al. 2005; Wells et al. 2006) but analysis of bipolar subtypes suggests that although BD-I is equally prevalent between genders, BD-II is actually more common in women than men (Di Florio and Jones 2010; Nivoli et al. 2011).

In addition to the impairment caused directly by mood episodes, BD has a chronic course of illness that is associated with high rates of physical and psychiatric comorbidities (Angst 1998; Fiedorowicz 2008), substance misuse (Angst 1998), and higher rates of mortality compared to the general population (Angst et al. 2002). In addition, BD has been associated with neurocognitive deficits during mood episodes and periods of remission (Martínez-Arán et al. 2004; Martínez-Arán and Vieta 2015) as well as enduring psychosocial impairment that worsens with increasing number of episodes experienced (Rosa et al. 2012).

BD also has a considerable economic impact. When examining the effect of common physical and mental health disorders on productivity in 24 countries, Alonso et al. (2011) found that BD was associated with the most days completely out of role in the workplace. Furthermore, Das Gupta and Guest (2002) estimated the total annual cost of BD on UK society at £2 billion in 1999/2000 prices. A more recent study estimated that the direct annual costs of BD to the UK healthcare system are £342 million at 2009/2010 prices, with hospitalizations accounting for 60% of this cost (Young et al. 2011).

The debilitating effects of BD on psychological, physical and occupational functioning, combined with substantial delays between the first manifestations of illness and diagnosis, mean that a primary goal of research is to inform efforts to improve early identification and intervention strategies (Bauer et al. 2008). One method of achieving this is to understand risk factors for BD (Correll et al. 2007). Before discussing the aetiology of BD in general I am going to discuss the role of childbirth – another area in which the effects of BD can have a significant impact on individuals and their families.

1.2.5 Bipolar Disorder and the Perinatal Period

Women with BD are at high risk of affective psychoses (i.e. mania, mixed¹ episodes and psychotic depression) in the postpartum period (Jones et al. 2014). These episodes have traditionally been labelled as ‘postpartum psychosis’ (PP). The nosology of PP remains under debate (Chaudron and Pies 2003; Robertson et al. 2005) but evidence suggests that the majority of episodes have a sudden onset, typically occurring within the first two postpartum weeks (Brockington et al. 1981; Heron et al. 2007). In addition to the main symptoms of mania described previously in Table 1-1, PP is characterised by symptoms such as hallucinations, delusions and lability of mood (Jones et al. 2010).

There is substantial evidence to suggest a relationship between PP and BD. In the general population, PP affects approximately 1 in 1000 parous women (Kendell et al. 1987). In contrast, PP affects 20-30% of parous women with a history of bipolar disorder (Jones and Craddock 2001;

¹ In DSM-IV, a ‘mixed’ episode refers to an episode of mania or hypomania that simultaneously presents with full symptom criteria for a major depressive episode (American Psychiatric Association 2000). DSM-5 replaced ‘mixed episodes’ with ‘manic/hypomanic episode with mixed features’ in which subsyndromal depressive symptoms are present in (hypo)manic episodes (American Psychiatric Association 2013).

Di Florio et al. 2013; Wesseloo et al. 2016). This, combined with evidence that episodes of PP typically have a manic presentation (Brockington et al. 1981) and evidence that PP can be a marker for a more familial form of BD (Jones and Craddock 2002) suggests that PP may be best conceptualised as a bipolar diathesis combined with a vulnerability to a puerperal (i.e. childbirth-related) trigger.

Women with BD are also at high risk of experiencing major affective episodes in general during the postpartum period (Brockington, 1996), with estimates of relapse as high as 52% (Viguera et al. 2011). These findings persist even when accounting for potential changes or interruptions in medication around this time (Viguera et al. 2000). This suggests that specific aspects of childbirth trigger bipolar illness and that identifying these factors could provide useful information on the aetiology of BD in general.

Due to the temporal proximity of mood episodes to childbirth, usually within two weeks of birth (Heron et al. 2007), researchers have endeavoured to identify which aspects of childbirth are responsible for triggering such episodes. To date, researchers have examined a variety of variables, which include delivery complications, gender of the baby, changes in medication, hormonal changes, psychosocial risk factors, immunological abnormalities, genetic vulnerabilities, and neurological factors (Robertson Blackmore et al. 2006; Spinelli 2009; Jones et al. 2014). To date, the most promising factors implicated in the aetiology of PP include primiparity, dysregulation of immune system function, and genetic factors (Jones et al. 2014; Bergink et al. 2016). One under-researched area within this line of research is the role of sleep loss in triggering PP. This will be discussed in further detail in section 1.5.

1.2.6 *Aetiology: Current Knowledge*

The aetiology of BD is currently not clearly established but evidence to date suggests that the cause is multifactorial, involving a complex interaction between genetic and environmental factors (Craddock and Sklar 2013). A number of research avenues have examined biological, psychological and social factors that could be involved in the aetiology of BD. The following subsections provide a brief overview of this research.

Genetics

A detailed discussion of the genetic findings for BD is beyond the scope of this thesis and what follows is a brief summary (for more comprehensive reviews, see Craddock and Sklar, 2013, Maletic and Raison, 2014, Heyes et al. 2015).

A wealth of evidence implicates a genetic component to BD. An individual's likelihood of developing BD is greater if they have an identical twin or first-degree relative who also has the disorder (Goodwin and Jamison 1990; Lichtenstein et al. 2009), with an estimated heritability of 60-90% (Smoller and Finn 2003; Craddock and Sklar 2013).

Genome wide association studies (GWAS), which aim to identify single nucleotide polymorphisms (SNPs) within the genes of people with BD have suggested that genetic factors that increase risk for BD overlap largely with those associated with other psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013), particularly schizophrenia (Lee et al. 2013; Stahl et al. 2017). GWAS using large samples with well-defined bipolar phenotypes (e.g. only patients with bipolar-I diagnoses) have replicated results for genes such as *CACNA1C*, *ODZ4*, and *ANK3*, which are involved in brain-specific functions such as neuronal signalling (Psychiatric GWAS

Consortium Bipolar Disorder Working Group 2011; Mühleisen et al. 2014; Stahl et al. 2017).

However, these studies also unveil that the pattern of inheritance is complex, involving multiple genes which each confer only a small increase in risk for the disorder (Craddock and Jones 1999).

The influence of genes on BD is further complicated by the fact that the environment may exert changes on gene expression via epigenetic changes (Machado-Vieira et al. 2011).

Neurochemistry and Neuroendocrinology

Research investigating the role of neurotransmitter functioning suggests that neurotransmitter imbalances or abnormal neurotransmitter receptors may be involved in the genesis of manic or depressive states. These include dopamine, noradrenaline and serotonin (Vawter et al. 2000; Shastry 2005; van Enkhuizen et al. 2014; Lin et al. 2014). Neuroendocrine abnormalities have also been implicated, such as hyperactivity in the hypothalamic-pituitary-adrenocortical (HPA) axis (Duffy et al. 2012) and abnormalities in indices of immune system functioning, such as pro-inflammatory cytokines (Kauer-Sant'Anna et al. 2009).

Brain Structure and Function

Some studies suggest that individuals with BD have abnormalities in brain areas involved in emotion regulation (Houenou et al. 2007; Phillips et al. 2008). Imaging studies report structural abnormalities in individuals with BD compared to healthy controls, such as enlarged amygdala (Altshuler et al. 1998; Strakowski et al. 1999), and abnormalities in white matter structure in prefrontal-limbic-cortical areas (Strakowski et al. 2005; Maletic and Raison 2014). BD has also been associated with abnormal processing of emotional information and abnormal activation in areas of the brain involved in emotion regulation during emotion-processing tasks (Yurgelun-Todd et al. 2000; Foland et al. 2008; Phillips et al. 2008; Pan et al. 2009; Townsend and Altshuler

2012). However, the cross-sectional nature of these studies means it is difficult to determine whether abnormalities in cortical and subcortical areas are precursors or merely a result of deterioration due to the illness and/or medication use (Drevets 2000).

Psychosocial Factors

Genetic predispositions cannot fully explain the onset and ongoing presentation of BD – evidenced by the fact that heritability estimates are less than 100% – and must therefore interact with environmental factors to produce the bipolar phenotype. Environmental and psychosocial factors proposed to trigger initial onset and recurrence of BD include stressful life events, alcohol or substance abuse, parenting styles and history of maltreatment (Johnson and Miller 1997; Frank and Thase 1999; Strakowski and Delbello 2000; Leverich et al. 2002). However, the evidence for parenting styles and maltreatment history is less conclusive than that for life events and alcohol or substance misuse (Alloy et al. 2005).

Further research has explored the potential mechanisms by which environmental factors may trigger manic or depressive episodes. One theory is that individuals with BD have cognitive styles that result in overly high affect following positive life events (e.g. goal attainment) and overly negative affect following negative life events (Depue and Iacono 1989; Leboyer and Kupfer 2010; Hamlat et al. 2016). This ‘emotional reactivity’ has been supported by evidence from functional and structural brain imaging studies, in which BD patients show abnormal processing of emotional information and (as mentioned above) abnormalities in brain areas involved in emotion regulation (Houenou et al. 2007; Phillips et al. 2008).

Another mechanism, proposed by Ehlers et al. (1988), is that life events which disrupt social rhythms subsequently disturb sleep and circadian rhythms, with the resultant biological

consequences culminating in relapse. This explanation is discussed in further detail in section 1.3.4.

Summary

In summary, a number of bio-psycho-social factors could be involved in the aetiology of BD, and the likelihood is that such factors interact to contribute to illness onset and recurrence. The relationship between sleep disruption and BD has primarily been considered only insofar as sleep disruption is a symptom of mania. However, there is compelling evidence that disruption to the sleep-wake cycle also plays a role in the aetiology of BD. This will be explored in the following section in which I will outline how sleep disruption could be an additional paradigm through which we can understand more about the aetiology of BD.

1.3 Sleep and Bipolar Disorder

Emil Kraepelin was one of the first psychiatrists to document an association between abnormal sleep patterns and poor mental health (Kraepelin 1883), and in modern diagnostic systems (e.g. DSM-IV, DSM-5 and ICD-10) sleep disruption is a symptom of mania (a reduced need for sleep) and depression (hypersomnia and/or insomnia) (WHO 1992; American Psychiatric Association 2000; American Psychiatric Association 2013).

Disrupted sleep, although not a mandatory symptom for diagnosing manic or depressive episodes, is commonly reported by individuals with BD during episodes of depression and mania (Harvey 2008b), which has been verified using objective measures of sleep (de Maertelaer et al. 1987; Hudson et al. 1988; Hudson et al. 1992).

Before discussing the role of sleep disruption in the aetiology of BD, the following section will outline the systems governing the sleep-wake cycle in humans.

1.3.1 Regulation of the Sleep-Wake Cycle

At a behavioural level, sleep is characterised by reduced movement and poor responsiveness to external stimuli (Bonnett 2011). This is accompanied by distinctive patterns in brain activation as a result of differential patterns in neurotransmitter release (Pace-Schott and Hobson 2002). A brief summary of these processes is as follows. Throughout wakefulness, a pressure to sleep develops due to the accumulation of adenosine in brain areas such as the basal forebrain. This results in the production of GABA (γ -aminobutyric acid) and galanin, which in turn inhibit arousal-promoting systems within the brainstem, midbrain and basal forebrain, resulting in the onset of sleep. Once sleep is initiated, further variations in neurotransmitters serve to divide sleep into REM (rapid eye moment) and non-REM (NREM) sleep, which can be distinguished according to variations in electroencephalographic (EEG) oscillations (Wulff et al. 2010). NREM is characterised by inhibition of all aminergic and cholinergic neurotransmitters, as well as inhibition of the neuropeptide orexin. In contrast, in REM sleep orexin is released in addition to acetylcholine from the brainstem, midbrain and basal forebrain neurons (Peplow 2013).

The alternating periods of sleep and wakefulness are known as the sleep-wake cycle, which in humans lasts approximately 24-hours. Patterns of behaviour or physiology that conform to a 24-hour period are collectively termed circadian rhythms, from the Latin 'circa diem' meaning 'about a day'. An individual's propensity to sleep is thought to be an interaction of circadian rhythms in arousal (also known as Process C) and a homeostatic 'sleep pressure' (i.e. Process S) which increases the longer that someone is awake and then dissipates upon sleeping (Borbély 1982).

The interaction between Process S and Process C is demonstrated in Figure 1-1. This figure demonstrates that sleep onset is most likely at the time in the day when there is the largest difference between Process S and Process C.

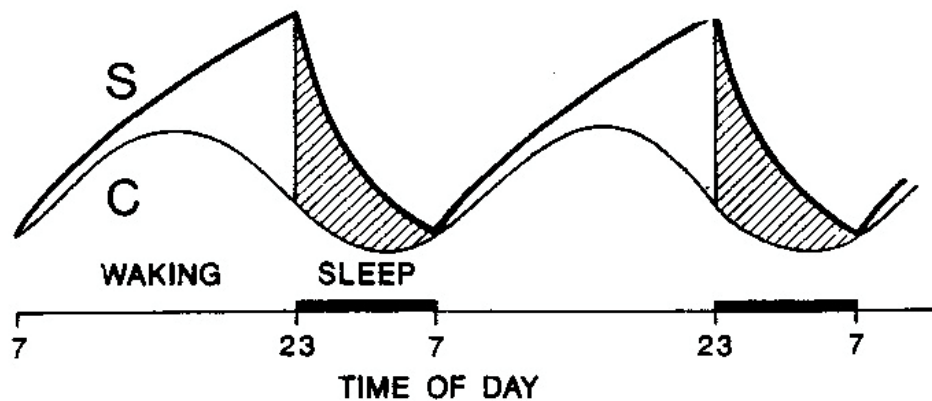


Figure 1-1. Interaction between the circadian drive for arousal (Process C) and the homeostatic sleep drive (Process S) (Borbély 1982).

Aside from theories regarding adenosine accumulation in the brain, little is known about the physiology of Process S. In contrast, more research has been conducted on the generation and control of circadian rhythms. Multiple physiological processes throughout the body (such as hormone secretion, body temperature and blood pressure) display circadian rhythms (Foster and Kreitzman 2014) and serve to align various aspects of human behaviour (e.g. eating, sleeping, activity) to the changing requirements of the day. For example, in anticipation of sleep, body temperature and blood pressure decrease and levels of melatonin increase (Foster and Wulff 2005).

Circadian rhythms are generated by a collection of neurons in the anterior hypothalamus called the suprachiasmatic nuclei (SCN), also referred to as the 'master clock' (Foster and Kreitzman 2014). Under constant conditions, the human sleep-wake cycle runs at approximately, but not

exactly, 24 hours (Harvey et al. 2011), therefore the SCN acts as a pacemaker to align the sleep-wake cycle with the 24-hour day. This process is known as 'entrainment', which is achieved through zeitgebers (a German term meaning 'time-giver'). The primary zeitgeber is the external light-dark cycle of the earth. Light levels detected by the eyes are relayed via a retinohypothalamic tract to the SCN, which then signals via multi-synaptic pathways to other areas of the brain. Activation of these brain areas then serves to coordinate the 'peripheral clocks' present within cells and tissues throughout the body. In turn, emerging evidence shows that peripheral clocks are able to entrain the SCN via non-photic information such as temperature, social cues, feeding or physical activity (Mistlberger et al. 2000). Therefore the circadian system is complex and constantly adapting to environmental factors that may or may not be due to human volition (e.g. staying awake due to long-haul travel or shift-work).

1.3.2 The Physiological Effects of Sleep Disruption

The processes governing the onset, maintenance and control of sleep interact with numerous processes in the body such as hormone release, metabolism, digestion, immune system functioning, and cognition. Thus, disruptions to sleep and circadian regulatory systems have widespread effects throughout the body.

There is a burgeoning literature examining the associations between sleep disruption and poor health. For example, epidemiological studies find that individuals who are exposed to sleep and circadian disruption through shift work are at an increased risk of obesity (Gangwisch et al. 2005), cardiovascular mortality (Harrington 2001), cancer (Schernhammer et al. 2003), and poor reproductive health (Nurminen 1998; Zhu et al. 2004). Proposed mechanisms include disrupted metabolic processes (Knutson et al. 2007) and effects on immune system functioning (Irwin

2002). The physiological effects of sleep disruption have been further confirmed in studies of gene expression following mistimed sleep, with a study by Archer and colleagues finding that the function of genes involved in inflammation and immunity were affected when human subjects slept at times at odds with their circadian clock (Archer et al. 2014).

1.3.3 The Effects of Sleep Disruption on Mental Health

The physiological effects of sleep disruption also have implications for mental health, and emerging research suggests that the neural mechanisms underlying sleep and mental health overlap, therefore disruption to one pathway results in dysfunction in the other (Wulff et al. 2010; Harvey et al. 2011; Foster and Kreitzman 2014). Numerous observational studies indicate that disrupted sleep precedes the onset of poor mental health (Kahn-Greene et al. 2007; Morphy et al. 2007; Ritter et al. 2011) and abnormalities in sleep architecture (e.g. increased REM density) have been identified as risk factors for developing affective disorders (Modell et al. 2003). In addition, sleep disorders are highly comorbid with the majority of psychiatric disorders (Harvey 2011).

However, the relationship between sleep disruption and mental health can be difficult to disentangle as disrupted sleep is often a core symptom of psychiatric disorders (Harvey 2008a; American Psychiatric Association 2013), with 80% of patients with depression or schizophrenia experiencing sleep problems (Wulff et al. 2010). As shown in Figure 1-2, the consequences of psychiatric illness, such as medication use, may also increase the risk of sleep disruption. This

makes it difficult for researchers to determine whether sleep disruption is a trigger, prodrome², or an early symptom of impending illness. More convincing evidence that disrupted sleep could have a causal role in the development of mental illness are provided by sleep deprivation protocols, in which healthy subjects are kept awake under experimental conditions. These studies find that sleep deprivation results in impaired cognition and mood (Scott et al. 2006; Acheson et al. 2007; Banks and Dinges 2007; McKenna and Eyer 2012). In addition, animal studies find that disrupting the function of circadian genes disrupts mood regulation, increases anxiety, and moderates responses to reward (McClung 2011).

Currently, the exact mechanisms by which sleep disruption results in poor mental health are unclear. However, the theory that has received the most attention proposes that disruptions to sleep (and the circadian rhythms underlying it) are associated with psychiatric illness via common overlapping mechanisms (Figure 1-2).

² Changes in behaviour, affect and cognition that precede illness onset or relapse (Bustillo et al. 1995; Jackson et al. 2003).

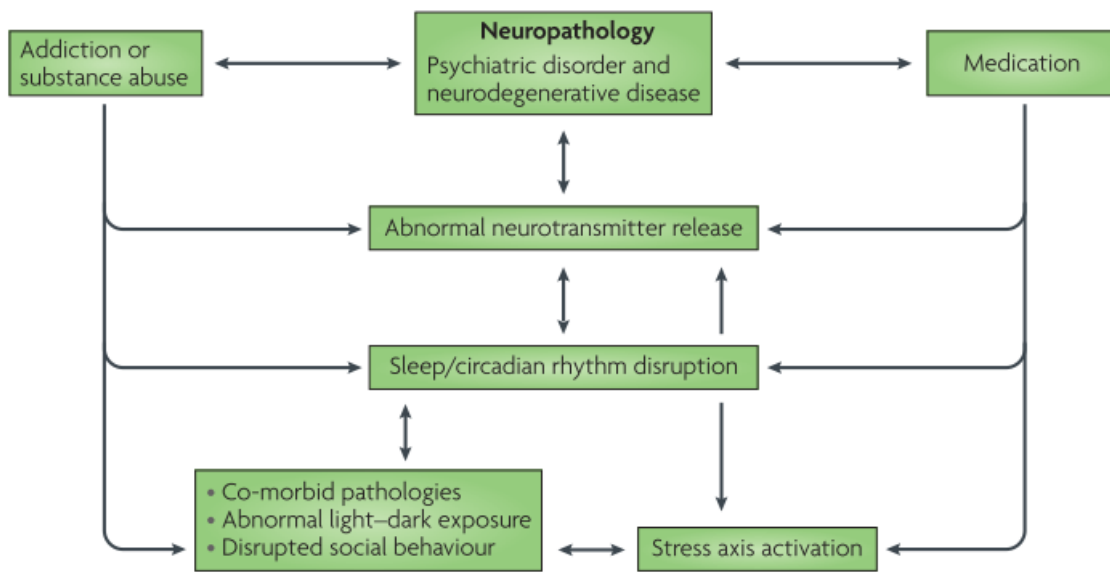


Figure 1-2. Hypothesised relationship between sleep and circadian disruption and psychiatric illness (Wulff et al. 2010).

The main common overlapping mechanism proposed is that, as sleep and circadian systems affect numerous neurotransmitter systems throughout the brain, perturbations in these systems due to sleep disruption results in widespread effects on other processes that rely on these systems for healthy functioning, such as mental and physical health (Wulff et al. 2010). More specifically, sleep disruption may affect mood via a mismatch between sleep and circadian systems. An example of how this may occur is in jet lag, whereby travelling across multiple time zones results in major variations in light exposure, activity and eating patterns. This information results in the peripheral clocks of the body becoming misaligned with the master clock, as the SCN, although entrained by light, takes multiple days to completely entrain to external light patterns.

The abnormal phase relationship between the sleep and circadian systems is thought to produce the aberrations in neurotransmitter and neuroendocrine functions (e.g. stress axis activation) that lead to dysregulated mood and poor cognition (Murray and Harvey 2010; Wulff et al. 2010).

This theory has been supported by the effectiveness of therapies involving a combination of sleep deprivation, light therapy and imposed sleep schedules, which are thought to work by resetting the mismatched sleep and circadian systems (Wirz-Justice and Van den Hoofdakker 1999; Benedetti et al. 2007). Further evidence for an overlap between circadian systems and psychiatric disorders is derived from studies finding that genes that govern the generation and regulation of circadian systems have been associated with mood disorders, anxiety disorders, and schizophrenia (Serretti et al. 2003; Lamont et al. 2007; Partonen et al. 2007; Partonen 2012; Pritchett et al. 2012).

However, Figure 1-2 also highlights that there are other factors associated with psychiatric disorders, abnormal neurotransmitter release, and sleep/circadian rhythm disruption. These include addiction or substance abuse and medication. This can make it difficult to determine whether sleep and circadian rhythm disruption is a cause or a result of psychiatric illness.

In summary, there is considerable evidence that sleep disturbance could play a role in psychiatric illness beyond being merely a symptom. However, like the aetiology of psychiatric disorders in general, the relationship is complex and involves multiple interacting bio-psycho-social factors. In the next section, I will discuss the role of sleep disruption in the aetiology of BD in particular.

1.3.4 The Role of Sleep Disruption in the Aetiology of Bipolar Disorder

The evidence I have described so far suggests that sleep disruption could play an important role in the aetiology of mood disorders. As previously discussed, sleep disturbance is a symptom of episodes of depression and mania. However, in this section I will focus on the evidence that sleep

disruption plays a role in the aetiology of BD. There are four main lines of evidence supporting this theory:

1. **Sleep disruption is a trait marker for BD** – sleep disruption is evident in individuals with BD during periods of euthymia and prior to illness onset.
2. There are plausible **biological mechanisms** through which sleep disruption could affect mood in BD, specifically mania.
3. **Treating sleep disruption** in individuals with BD appears to **improve illness outcomes**.
4. Sleep deprivation imposed under experimental settings **triggers mania** (e.g. total sleep deprivation therapy)

In this section, I will outline the evidence for each of these statements. Following this, in section 1.4 I will focus on the specific role of sleep as a pathway to mania in BD. This is the primary manner in which sleep has a different relationship with BD compared to other psychiatric disorders, and it is this which forms the central theme of this thesis.

1. Sleep Disruption as a Trait Marker for BD

Disrupted sleep precedes the onset of BD (Ritter et al. 2011) and persists during periods of euthymia. For example, numerous studies using objective indices of sleep, such as actigraphy (a method of measuring sleep using activity monitors), have found that individuals with BD show disrupted sleep-wake schedules when euthymic (Jones et al. 2005; Salvatore et al. 2008; Gershon et al. 2012; Kaplan et al. 2012). There is also evidence that euthymic BD individuals show abnormalities in the architecture of sleep, such as increased REM density (Eidelman et al. 2010). Furthermore, children of individuals with BD show more disturbed sleep than those whose

parents have no history of mood disorders (Duffy et al. 2010), suggesting that sleep disruption could be an endophenotype of the disorder.

Sleep disorders during euthymia are also common in BD. For example, compared to the general population, individuals with BD are more likely (during euthymic periods) to experience sleep disorders such as obstructive sleep apnoea, insomnia, hypersomnia, and circadian rhythm sleep phase disorders (Plante and Winkelman 2008; Soehner et al. 2013; Kanady et al. 2015; Bradley et al. 2017).

In addition to perturbed sleep-wake cycles, there is evidence that a variety of circadian rhythms (which, as discussed in section 1.3.1, are pivotal to the regulation of the sleep-wake cycle) such as general activity and temperature rhythms, are disrupted in BD (Kripke et al. 1978; Pflug et al. 1982; Jones et al. 2005)). This evidence suggests that BD is associated with an underlying instability in circadian rhythms. This has been supported by studies showing that greater instability in circadian rhythms is associated with symptom severity (Gonzalez et al. 2014) and risk of relapse (Jones 2001) in BD.

Further evidence for a role of circadian influence in BD derives from research on chronotype. Chronotype refers to the time of day at which individuals prefer to do particular activities (including but not limited to sleep), and has been correlated with a number of physiological parameters implicated in BD, such as catecholamine and hormone secretion, temperature rhythms, and arousal (Akerstedt and Fröberg 1976; Liu et al. 2000; Duffy et al. 2001; Kudielka et al. 2006). Preliminary data suggest that BD patients are more likely to show an evening chronotype (i.e. a preference for performing activities during the evening) than healthy

participants (Mansour et al. 2005; Ahn et al. 2008; Wood et al. 2009). However, it is unclear whether such studies are confounded by other factors such as medication and social schedules.

2. Biological Mechanisms

There are plausible biological mechanisms that could account for the association between BD and sleep disruption. Of note is that many of these mechanisms have been independently implicated in the aetiology of BD. Therefore sleep disruption may be a unifying mechanism through which these biological effects are involved in the pathogenesis of BD.

One proposed mechanism for these findings is that circadian rhythm abnormalities in BD are due to abnormalities in the genes governing circadian rhythms, otherwise referred to as 'clock genes' (Shi et al. 2008). The literature on this is still in its early stages, however a number of candidate gene studies have found associations between polymorphisms in clock genes and BD (Mansour et al. 2006; Lamont et al. 2007; M. Ha et al. 2009; Kripke et al. 2009; McGrath et al. 2009; Wulff et al. 2010; Benedetti and Terman 2013; Gonzalez 2014; Geoffroy et al. 2015). Other studies have found that clock genes are associated with course of illness, such as early onset and response to lithium treatment (Benedetti et al. 2004; Rybakowski et al. 2014). Finally, there is evidence that pharmacological treatments for BD, such as lithium and valproic acid, restore rhythmicity in clock genes (Johansson et al. 2011; Osland et al. 2011; McCarthy et al. 2013).

Monoamines implicated in BD, such as serotonin and dopamine, have also been found to display circadian rhythms in their release, suggesting that they are under circadian control (McClung 2007). In addition, some theories propose that the pathology of BD might be due, in part, to abnormal circadian rhythms in the production of melatonin (Pacchierotti et al. 2001). To date, findings are mixed, however there is preliminary evidence that BD patients show blunted

circadian rhythms in melatonin (Nurnberger et al. 2000) and overactive melatonin secretion in response to light (Lewy et al. 1985). Additional evidence for the involvement of the melatonergic system comes from research on the melatonin receptor agonist agomelatine which is reported to affect sleep architecture and circadian rhythms (Zupancic and Guilleminault 2006), as well as preliminary evidence that it could be an effective treatment for BD patients (De Berardis et al. 2015).

Sleep disruption may also perturb neuroendocrine functions that have been implicated in BD, for example via the abnormal activation of the HPA axis (Morris et al. 2012) and increases in proinflammatory cytokines (Imeri and Opp 2009). Of interest is that alterations in peptides involved in feeding and metabolism have been shown to be arrhythmic in *Clock* knockout mice, who also show increased weight gain and symptoms similar to those seen in metabolic syndrome (Turek et al. 2005). This may provide a potential mechanism to explain why individuals with BD have an increased risk of obesity and metabolic syndrome (Fiedorowicz 2008).

Mood episodes display a seasonal pattern in some individuals with BD, with depressive episodes more common in winter months and manic episodes more common in summer months (Hardin et al. 1991; Silverstone et al. 1995; Cassidy and Carroll 2002; Hakkarainen et al. 2003). The DSM-5 includes a seasonal specifier for course of mood variation to reflect this (American Psychiatric Association 2013). It has been hypothesised that this seasonal variation is due to the effects of varying light-exposure on the circadian system, which will, in turn, disrupt mood regulation (McClung 2007; Gonzalez 2014). This theory is further supported by results that light therapy can be used as an effective treatment for bipolar depression (Colombo et al. 2000; Benedetti et al. 2005), and dark therapy for mania (Wirz-Justice et al. 2009).

3. Treating Sleep Disruption Improves Illness Outcomes

If sleep disruption is involved in the aetiology or pathology of BD, then improvements in sleep should lead to improvements in symptoms of the illness as well as functioning and prognosis. Preliminary evidence supports this theory, as interventions that aim to restore regularity in circadian rhythms in BD have been associated with positive outcomes. For example, the central tenet of interpersonal and social therapy (IPSRT) (Frank et al. 2000) is that bipolar episodes result from disruption to circadian rhythms (Ehlers et al. 1988). IPSRT aims to stabilise circadian rhythms through maintaining schedules in social interaction, eating patterns, work patterns as well as sleep patterns. To date there is preliminary evidence that this form of therapy may be a beneficial complement to pharmacotherapy, and may be associated with a reduced rate of relapse (Frank et al. 2005), however there is still currently a lack of randomised-controlled trials to corroborate its efficacy (Haynes et al. 2016).

An emerging treatment for insomnia, CBT-I (cognitive behavioural therapy for insomnia) has been adapted for use in psychiatric populations, with preliminary results suggesting that it could be effective for reducing psychotic symptoms in patients with schizophrenia (Freeman et al. 2013; Freeman et al. 2015). To date, there has been one randomised controlled trial (RCT) assessing the efficacy of CBT-I as a treatment in BD; in a pilot RCT, Harvey and colleagues compared psychoeducation to CBTI-BP (CBT-I adapted for use in patients with BD) and found that CBTI-BP was associated with a reduced risk of relapse over a 6 month follow-up period (Harvey et al. 2015).

4. Sleep Deprivation Imposed Under Experimental Settings Triggers Mania

The final line of evidence that sleep plays a role in the aetiology of BD stems from findings that experimentally-imposed sleep deprivation (i.e. when individuals are intentionally deprived of sleep for research or therapeutic purposes) is associated with mania (Colombo et al. 1999). The theory of sleep disturbance acting as a trigger or pathway to mania, and its implications for our understanding of BD, are discussed fully in the next section.

1.4 Sleep Disturbance as a Pathway to Mania

In this section, I will focus on the role of sleep disruption as a pathway in the aetiology of BD, specifically manic episodes. This will be followed by a discussion of current limitations in this area of research, concluding with the aims of the thesis. This literature review was conducted using online databases (e.g. MEDLINE, EMBASE, Web of Science, Scopus) using the terms “prodrome”, “trigger”, “early warning sign”, “precipitant”, “precedent”, “predictor”, “mania”, “hypomania”, “high mood”, “bipolar”, “mood”, “sleep”, “insomnia” and “circadian”. This was complemented by studies cited within the identified literature that did not appear in online searches (e.g. case reports and older reviews). This literature review should be considered in light of limitations such as publication bias (e.g. grey literature was not reviewed) and a reliance on studies published in English language studies.

1.4.1 *The Sleep-Reduction Model of Mania*

In 1987, Thomas Wehr and colleagues proposed that sleep disruption may be a 'final common pathway in the genesis of mania' (Wehr et al. 1987). This hypothesis was initially based on observations from case studies (Wehr et al. 1982; Wehr et al. 1987; Wehr 1989) in which Wehr observed that some patients appeared to have experienced sleep deprivation prior to the onset of manic episode. Selected examples are provided below:

Example 1: An attorney with no previous history of mental illness:

'The attorney was working on a difficult and important case. A trial date had been set, and as it approached, he realized that he did not have enough time to prepare in his usual thorough manner. Therefore, the night before the trial he decided to go without sleep and continue his preparations through the night. The next morning...he became increasingly manic, the police were called, and he was hospitalised involuntarily.' (Wehr 1989 p.11)

Example 2: Dr A, a bipolar patient who had been mildly depressed during the final year of medical school:

'During the first 2 months of his internship, he was on call at the hospital every third night. When on call, he was unable to obtain more than a few hours of sleep during the night. Each day after the on-call night Dr A became hypomanic; he became euthymic on the second day and mildly depressed on the third. Thus he developed a rapid-cycling course of manic-depressive illness that was driven by external factors regulating his sleep schedule.' (Wehr et al. 1987 p.202)

Example 3: Ms D

'Ms. D, a 50-year old woman who had been depressed for several months, took an overnight transatlantic flight from the United States to Europe to visit her family. Like many passengers, she slept very little (if at all) during the flight and by the time of her arrival the following morning she had switched into her first hypomanic episode.' (Wehr et al. 1987 p.202)

These case studies, in combination with other evidence (described in more detail below), led

Wehr and colleagues to propose that:

'Diverse psychological, interpersonal, environmental and pharmacological factors that appear to trigger the onset of mania could act via their capacity to cause sleep deprivation...Since mania in turn causes insomnia, the development of mania is potentially self-reinforcing and could become autonomous after being initiated by precipitating factors.' (Wehr et al. 1987 p.201)

The initial model proposed by Wehr and colleagues is shown in Figure 1-3.

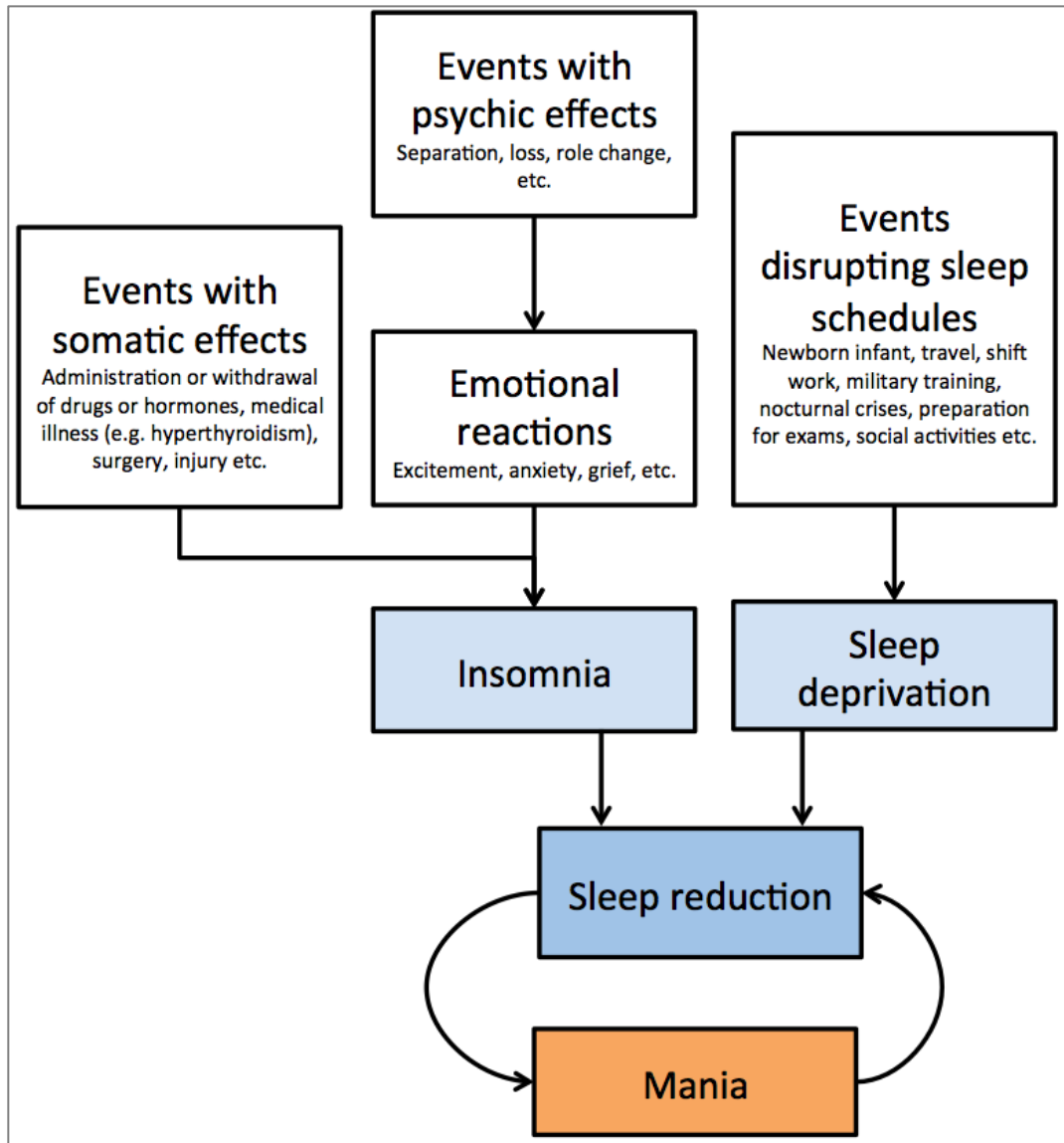


Figure 1-3. Proposed model of the relationship between sleep disruption and mania (Wehr et al. 1987).

As shown in Figure 1-3, Wehr et al. (1987) proposed multiple mechanisms (biological, psychological and environmental) by which an individual might experience a reduction in sleep. The model incorporates the possibility that the symptoms of mania result in further sleep disruption, thus providing a potential explanation for rapid escalation of manic episodes as well as drawing attention to the fact that mania can be both a symptom and cause of sleep disruption.

1.4.2 Supporting Evidence

In 1991, Wehr presented additional evidence to support the sleep-reduction model of mania from prospective observations of an inpatient over 16 weeks, shown in Figure 1-4 (Wehr 1991). Nurses monitored the patient's mood twice a day and the patient's sleep every 30 minutes. During the 16 weeks, the patient experienced five manic episodes. The first three episodes were preceded by reduced sleep, which Wehr proposed was the result of the stress of being admitted (first episode), and medication withdrawal (second and third episode). Following this, Wehr attempted to experimentally induce sleep deprivation by asking the patient to stay awake overnight on two separate occasions. On both of these occasions, the patient switched into mania the day after sleep deprivation, which was followed by depression once she had slept. Wehr concluded that, 'Although other interpretations are possible, the sleep-deprivation hypothesis appears to provide a parsimonious, unitary explanation for the patient's responses' (Wehr 1991 p.578).

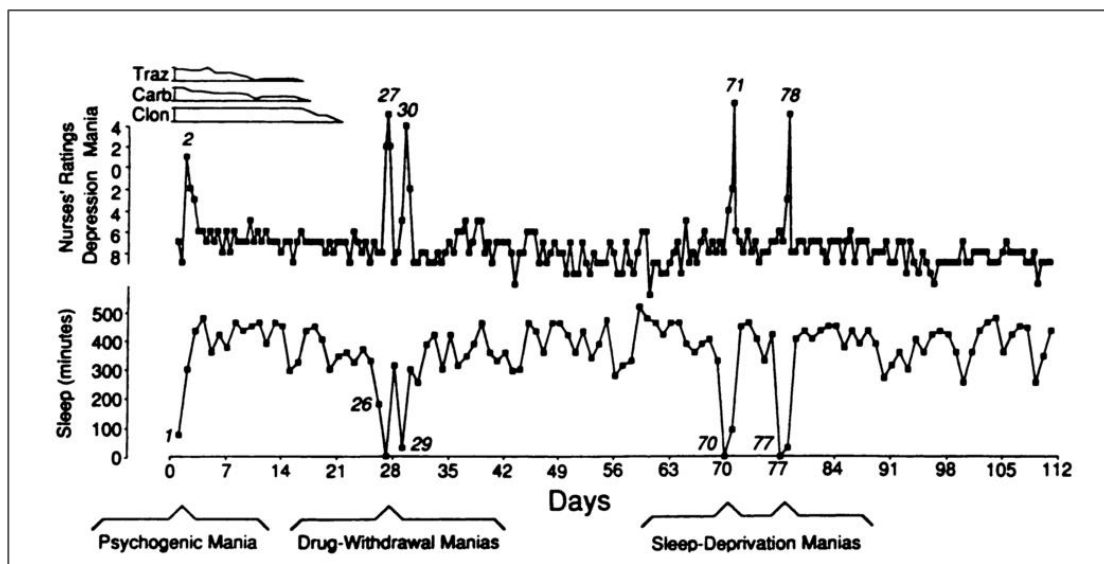


Figure 1-4. Longitudinal 16-week record of sleep duration and mood in 59 year old woman with bipolar illness (Wehr 1991).

Additional observational evidence has supported this model, with reports of mania following substance abuse, medications, long-haul travel, and bereavement (Hollender and Goldin 1978; Jauhar and Weller 1982; Rosenman and Taylor 1986; Wehr 1991; Young 1995). However, this evidence is limited by an inability to determine whether the observed sleep disruption is an early symptom of mania. For example, in a systematic review of prodromes, Jackson and colleagues (2003) concluded that sleep loss was one of the most common prodromes of manic episodes, reported by 77% of patients. Furthermore, sleep disruption may also be an epiphenomenon of other factors associated with manic episodes

However, more compelling evidence that sleep disturbance can trigger mania derives from the findings of (1) animal studies, (2) total sleep deprivation studies in healthy human populations, and (3) studies of bipolar patients undergoing total sleep deprivation therapy for depression.

Animal studies

Some researchers have reported manic-like behaviours in rats following enforced sleep-deprivation as produced by use of the 'platform method' (Jouvet et al. 1964) in which the rat is suspended on a small platform above water that it will fall into if it sleeps. For approximately 30 minutes after the protocol has ended, researchers have reported symptoms in the rats that mimic mania, such as hyperactivity, irritability (stimulation-induced aggression), hypersexuality and decreased need for sleep (Morden et al. 1968; Albert et al. 1970; Hicks et al. 1979; Fratta et al. 1987). In addition, Gessa and colleagues found that these symptoms could be alleviated following administration of lithium (Gessa et al. 1995).

Additional evidence for the role of sleep in the aetiology of mania is derived from mouse models in which researchers have induced mutations in genes involved in regulating circadian rhythms.

For example, Roybal and colleagues found that mice with a mutation in the *Clock* gene displayed manic-like behaviours, such as hyperactivity, decreased sleep, and increased value for rewards, which were alleviated following administration of lithium (Roybal et al. 2007). However, as noted in Section 1.3, the circadian system governs multiple processes throughout the body in addition to the sleep-wake cycle. Therefore mutations in circadian rhythm genes could incite manic symptoms via other processes.

Total Sleep Deprivation Studies in Healthy Human Populations

Total sleep deprivation (TSD) experiments in healthy participants have noted that some participants display manic-like behaviour such as euphoria, distractibility and disinhibited behaviour (Bliss et al. 1959; Kollar et al. 1966; Horne 1993). These findings have been corroborated by neuroimaging studies. For example, Gujar et al. (2011) found that TSD was associated with increased reactivity toward pleasure-evoking stimuli, with corresponding increases in mesolimbic reward brain networks.

Total Sleep Deprivation Therapy in BD Patients

Additional support for the mania-inducing effects of sleep loss derives from accounts of mood changes following sleep deprivation therapy (Wehr 1992). During sleep deprivation therapy, depressed patients are kept awake for either the entire night (total sleep deprivation, TSD, comprising at least 36 hours wakefulness) or half of the night (partial sleep deprivation). Sleep deprivation therapy has been used as a treatment for depression since the 1970s due to its antidepressant effects (Pflug 1972; Pflug 1976; Benedetti 2012). However, there are accounts of some patients with BD becoming manic or hypomanic following this treatment (Wehr 1989; Wu

and Bunney 1990; Kasper and Wehr 1992). Wu and Bunney (1990) reviewed the findings of 10 sleep deprivation studies (published from 1974 to 1982) and calculated that approximately 30% of the bipolar depressed patients had switched into mania. Table 1-4 includes the studies reported by Wu and Bunney (1990) in addition to subsequently published studies that have reported the percentage of BD inpatients who have become manic or hypomanic following TSD.

Table 1-4. Rates of mania and hypomania in BD inpatients following total sleep deprivation therapy for depression.

Study	Sample	Sleep Deprivation Protocol	Mood Measure	N (%) who became manic or hypomanic
Bhanji and Roy (1975)	<ul style="list-style-type: none"> • 2 BD-II • Male (100%) • Age 59 and 52 	<ul style="list-style-type: none"> • 1 night TSD therapy. • Medication kept constant. 	Mood measured by clinical observation and self-rated depression scale (Snaith et al. 1971)	1 (50%) 'mildly hypomanic'
Cole and Muller (1976)	<ul style="list-style-type: none"> • 3 BD • Gender and age not reported specifically for BD participants. 	<ul style="list-style-type: none"> • 36-hour TSD therapy under supervision of treating physician. • Treatment with antidepressant medication in "most cases". 	Hamilton Rating Scale for Depression (Hamilton 1960) and clinical notes.	1 (33%) manic
Colombo et al. (1999)	<ul style="list-style-type: none"> • 206 BD • 70 Male (34%) • Mean age 46.4 	<ul style="list-style-type: none"> • 3 cycles of TSD alone or in combination with supplemental medication. 	Mania and hypomania defined according to DSM-IV criteria with exception of temporal criterion for mania.	10 (4.85%) manic 12 (5.83%) hypomanic
Dessauer et al. (1985)	<ul style="list-style-type: none"> • 4 BD • Gender and age not reported specifically for BD participants. 	<ul style="list-style-type: none"> • 1 night partial sleep deprivation (5 sleep deprivation treatments in the second half of the night from 01.30h at 5-day intervals). 	Bojanovsky-Chloupkova mood rating scale (Bojanovsky and Chloupkova 1966) by examiner and patient self-report using Luria (1975) visual analogue mood scale.	1 (25%) manic 1 (25%) hypomanic
Gerner et al. (1979)	<ul style="list-style-type: none"> • 14 BD-I • Gender and age not reported specifically for BD participants. 	<ul style="list-style-type: none"> • 1 night TSD therapy (40 hours awake) monitored by nursing staff. • Medication-free for at least three weeks prior to study. 	Mood ratings every 2 hours by trained nurses or psychologists using Bojanovsky and Chloupkova (1966) rating scale.	No patients became manic or hypomanic.
Larsen et al. (1976)	<ul style="list-style-type: none"> • 3 BD • 2 Male (66%) • 2 < 60 years old • 1 > 60 years old 	<ul style="list-style-type: none"> • 1 night TSD therapy from 11pm until 5pm the following day, with supervision from medical student. • Medication-free 36 hours before sleep deprivation protocol. 	Björum and Lindberg Scale (reference not provided) rated by two psychologists.	No patients became manic or hypomanic.
King et al. (1982)	<ul style="list-style-type: none"> • 3 BD • Male (100%) • Mean age 39 (range 28-50) 	<ul style="list-style-type: none"> • 1 night TSD (36-42 hours). • Medication kept constant. 	Clinical notes (nurses and psychiatric resident) rated by independent raters.	1 patient became 'euphoric' (33%).

Study	Sample	Sleep Deprivation Protocol	Mood Measure	N (%) who became manic or hypomanic
Pflug (1976)	<ul style="list-style-type: none"> • 12 BD • 6 Male (50%) • Mean age 42 	<ul style="list-style-type: none"> • 1 night TSD therapy 	Bojanovsky and Chloukova (1966) mood rating scale.	1 (8%) manic
Post et al. (1976)	<ul style="list-style-type: none"> • 7 BD-I, 2 BD-II • 3 Male (33%) • Mean age 38 	<ul style="list-style-type: none"> • 1 night TSD therapy for at least 39 hours with continuous monitoring by nursing staff. • Medication-free. 	Ratings of depression, mania, psychosis, anxiety, anger, talkativeness, restlessness, drowsiness, somatic complaints, grandiosity, elation, retardation, agitation, and sadness obtained every two hours throughout the day by a trained research staff nurse using a 15-point scale designed to measure short-term behavioural and somatic changes.	1 (11%) 'mild hypomanic state' which lasted for two weeks.
Svendsen (1976)	<ul style="list-style-type: none"> • 17 BD • Gender and age not reported specifically for BD participants. 	<ul style="list-style-type: none"> • 1-6 treatments of 1-night TSD therapy with monitoring by nursing staff. • Medication kept constant. 	Mood rated by clinical observation and modified Cronholm-Ottosson rating scale (Cronholm and Ottosson 1960).	No patients became manic, unknown whether any became hypomanic.
Vovin et al. (1982)	<ul style="list-style-type: none"> • 7 BD • Gender and age not reported specifically for BD participants. 	<ul style="list-style-type: none"> • 1-night TSD therapy (36 hours) every 2-3 days for 2-3 weeks. • Medication (antidepressants) kept constant. 	Nurse observation every 2 hours.	1 (14%) manic, unknown whether any became hypomanic.
Wehr et al. (1982)	<ul style="list-style-type: none"> • 9 rapid-cycling BD (3 BD-I, 6 BD-II) • 1 Male (11%) • Mean age 39 	<ul style="list-style-type: none"> • 1-night TSD therapy (40 hours) with monitoring every 30 minutes by nursing staff. • Medication-free. 	Twice daily ratings of mania and depression by nurses using Bunney-Hamburg scale (Bunney and Hamburg 1963).	4 (44%) manic 3 (33%) hypomanic

Study	Sample	Sleep Deprivation Protocol	Mood Measure	N (%) who became manic or hypomanic
Yamaguchi et al. (1978)	<ul style="list-style-type: none"> • Sample of depressed patients (number with BD not reported) • Gender and age not reported specifically for BD participants. 	<ul style="list-style-type: none"> • 1 night TSD therapy with close supervision by at least one psychiatrist. • Medication kept constant 	Clinical observation (specific measure not reported).	1 manic
Zimanova and Vojtechovsky (1974)	<ul style="list-style-type: none"> • Sample of depressed patients (number with BD not reported) • Age and gender of BD patients not reported. 	<ul style="list-style-type: none"> • 28 nights TSD therapy with nurse observation • Medication: tricyclic antidepressants 	Questionnaire and self-rating mood scale (von Zeerson scale, references not provided).	1 manic 1 hypomanic

TSD, total sleep deprivation (i.e. at least 36 hours wakefulness); BD, bipolar disorder; BD-I, bipolar-I disorder; BD-II, bipolar-II disorder.

As shown in Table 1-4, in studies where the number of BD patients have been reported, the rate of switch into (hypo)mania varies widely from 0-44% for mania, and 0-50% for hypomania. However, these TSD studies are limited in a number of respects. First, apart from the study by Colombo et al. (1999) most of the studies have small sample sizes (ranging from 2 to 17 BD patients, with a median of 7 patients), thus they are underpowered and of insufficient representativeness to ascertain the rate of switch into (hypo)mania. Second, samples vary considerably in age, medications, and other clinical characteristics such as the presence of rapid-cycling and non-rapid cycling³ BD. Third, in all studies reviewed in Table 1-4, sleep deprivation therapy was administered to bipolar patients when they were depressed, therefore sleep loss may be more likely to trigger mania in euthymic bipolar patients (Plante and Winkelman 2008). Finally, characteristics of the sleep deprivation protocols may have influenced the rate of switch into mania. For example, in the study conducted by Svendsen (1976), the sleep deprivation protocol was described as follows, “The night’s social gathering comprises coffee parties, walks, music, card-playing, and various occupations according to the patients’ desires and skills. These activities are optional” (p.185). Although none of the patients in this study became manic, this raises the question of whether sleep deprivation protocols introduce additional factors that could incite mania, such as caffeine consumption and stimulating activities. Furthermore, patients were often fully aware of the purpose of these sleep-deprivation studies, thus any effects observed may have been a placebo effect.

³ The ‘rapid-cycling’ specifier for BD is described in section 1.2.3.

In light of these methodological limitations, the most robust study of rate of switch into mania was by Colombo et al. (1999), due to the relatively larger sample size and consideration of medication, which the authors concluded was not significantly associated with the rate of switches into mania. In this study, the rate of switching into mania was considerably lower than reported in the other studies (5-6%). However the authors concede that these rates could be higher in euthymic bipolar patients. Nevertheless, despite having a larger sample size than other studies available, the sample size in this study is still relatively small and had considerable heterogeneity in medications taken by patients, thus making it difficult to assess the true rate of switch into mania following sleep deprivation.

Prospective Studies of Sleep and Mood in BD

The findings outlined above prompted some researchers to examine the longitudinal relationship between sleep duration and mood in participants with bipolar disorder. Specifically, if sleep deprivation can trigger mania, then reduced sleep duration should predict subsequent increases in manic symptoms (Plante and Winkelman 2008). If so, clinicians and patients may be able to use this information to manage the condition. Some prospective studies have supported this hypothesis. For example, Wehr et al. (1982) reported that 13 out of 15 rapid-cycling patients experienced mania or hypomania following nights in which they could not sleep. In addition, Leibenluft et al. (1996) examined associations between sleep length and mood in a sample of 8 rapid-cycling bipolar patients over 18 months, finding that a decrease in sleep duration predicted a subsequent increase in manic symptoms the following day. Similarly, Bauer et al. (2006) examined associations between sleep and mood in 59 bipolar patients over a minimum of 100 days, finding that a 3 hour change in bed-rest predicted increased manic symptoms the following day. Other studies that have investigated the longitudinal relationship between sleep and mania

are summarised in Table 1-5. The studies presented in this table all demonstrate associations between reduced sleep duration and subsequent high mood. However, these studies are also limited in a number of respects. First, there is wide variation in the period of monitoring sleep and mood across studies; with the monitoring period of some studies as short as three days, and others as long as 18 months. Second, the frequency at which data on sleep and mood were monitored also varied widely between studies, ranging from 30-minute to 4-week intervals. Second, some of the studies (Wehr et al. 1982; Barbini et al. 1996; Leibenluft et al. 1996) rely on very small sample sizes, thus limiting the representativeness of the samples. Furthermore, the prospective studies of sleep and mood also suffer the same limitations as the sleep deprivation studies; in which the methodology includes samples that vary in age, medication use, and clinical features such as the presence of rapid-cycling BD. Finally, not all participants showed significant associations between reduced sleep and (hypo)mania. These issues will be discussed in further detail in section 1.6.

Table 1-5. Prospective studies between sleep and mania in participants with bipolar disorder.

Authors	N	Bipolar Subtype	Mood Measure	Sleep Measure	Monitoring Period and Frequency	Findings
[1] Bauer et al. (2006)	59	37 BD-I 22 BD-II	<i>Self-report</i> Visual analogue mood scale (0-100)	<i>Self-report</i> Sleep diary (awake, sleep, bedrest)	Daily measures of sleep and mood for 169 (mean) ± 59 days per participant	Decrease in sleep or bedrest followed by a shift towards mania/hypomania the next day in 59% of participants.
[2] Bauer et al. (2008)	101	64 BD-I 37 BD-II	<i>Self-report</i> Visual analogue mood scale (0-100)	<i>Self-report</i> Sleep diary (awake, sleep, bedrest)	Daily measures of sleep and mood for 265 (mean) ± 103 days per participant	Decrease in sleep duration (sleep and bedrest) associated with shift towards mania/hypomania the next day in 39% of participants.
[3] Barbini et al. (1996)	34	BD-I	<i>Clinician-report</i> Young Rating Scale for Mania (YRSM, Young et al. 1978). Nurses' Observation Scale for Inpatient Evaluation (NOSIE, Honigfeld and Klett 1965).	<i>Clinician-report</i> Nocturnal sleep duration and diurnal naps recorded by nursing staff.	Over 3 consecutive days: <ul style="list-style-type: none"> • Sleep checked at 60-minute intervals. • YRSM once daily at 12:00 • NOSIE twice daily at 12:00 and 19:00 	Significant correlations between decreased sleep duration and increased manic symptoms the subsequent day.
[4] Gruber et al. (2011)	196	126 BD-I 54 BD-II 16 BD NOS	<i>Self-report/Clinician-report</i> Clinical Monitoring Form (CMF, Sachs et al. 2002)	<i>Self-report</i> Average number of hours slept and sleep variability over preceding week.	Sleep and mood over preceding week reported at each routine psychiatric appointment over 12 months.	Shorter sleep durations associated with increased mania severity over 12 months. Greater sleep variability associated with increased mania and depression severity over 12 months.

Authors	N	Bipolar Subtype	Mood Measure	Sleep Measure	Monitoring Period and Frequency	Findings
[5] Houston et al. (2007)	401	Not reported	<i>Clinician-report</i> Young Rating Scale for Mania (YRSM, Young et al. 1978).	<i>Clinician-report</i> Decreased need for sleep item of the Young Rating Scale for Mania (YRSM, Young et al. 1978).	52 weeks Psychiatric appointments at 4-week intervals.	Decreased need for sleep item scores significantly predicted relapse in 7 participants.
[6] Leibenluft et al. (1996)	8*	Not reported	<i>Self-report</i> Visual analogue mood scale (0-100) (Whybrow and Guylia 1995)	<i>Self-report</i> Sleep diary (wake onset, sleep onset)	18 months Mood: twice daily Sleep: once daily upon awakening	Increased sleep duration was associated with a decreased probability of being in a hypomanic or manic mood state the following day in 5 patients.
[7] Wehr et al. (1982)	15*	Not reported	<i>Clinician-report</i> Twice-daily mood rating by nurses using Bunney-Hamburg Scale (Bunney and Hamburg 1963)	<i>Objective</i> Actigraphy <i>Clinician-report</i> Nurse observation	Exact monitoring period not reported. Authors report monitoring for 1 to 32 "manic-depressive cycles". Mood: twice daily Sleep: <ul style="list-style-type: none"> • Actigraphy: continuous • Nurse observation: every 30 minutes from 21:00 to 07:00. 	13 patients experienced one or more nights of wakefulness (i.e. total sleep deprivation) when switching from depression into mania or hypomania.

* rapid-cycling inpatients. BD-I, bipolar I disorder; BD-II, bipolar II disorder.

1.4.3 *Potential Mechanisms*

The mechanism by which sleep deprivation may precipitate episodes of mania remains unclear. However, current theories from neuroscience and chronobiology suggest that sleep deprivation may induce mania because:

1. As discussed in section 1.3.3, there is an overlap between the physiological systems involved in regulating emotion and sleep, therefore perturbations in sleep will affect mood regulation, and vice versa.
2. Individuals with mood disorders have an underlying instability in circadian rhythms that is 'reset' following sleep deprivation, resulting in increased positive affect (euthymia or mania).

Sections 1.3.3 - 1.3.4 outlined how sleep disruption may perturb emotion regulation more broadly, therefore the following section outlines the research that relates specifically to how sleep loss might trigger mania.

Neurophysiological Explanations

As discussed in section 1.3, neurophysiological theories posit that the physiological effects of sleep deprivation (on the immune system, neuronal signalling, HPA-axis etc.) interact with systems in the brain involved in emotion regulation (e.g. serotonergic, dopaminergic systems) to disrupt functioning in areas of the brain involved in emotion regulation (Dahl and Lewin 2002; Saper et al. 2005). This has been supported by behavioural and neurophysiological evidence from neuroimaging studies in healthy volunteers who are sleep deprived (Kahn et al. 2013). For example, using functional magnetic resonance imaging, Gujar and colleagues (2011) found that sleep deprivation was associated with increased positive reactivity to

stimuli, which corresponded with activity in mesolimbic regions of the brain (involved in reward processing). Sleep deprivation has also been associated with increased neurochemical dopamine activity (Gillin et al. 2001) with evidence that this increase occurs in brain networks associated with reward processing (Volkow et al. 2009; Krause et al. 2017). Serotonergic systems in the brain have also been implicated as a potential mechanism by which sleep deprivation could have antidepressant (or euphorogenic) effects (Benedetti and Smeraldi 2009; Harvey et al. 2011). This has been supported by animal studies which have found that sleep deprivation is associated with increased serotonin neurotransmission (Gardner et al. 1997; Adrien 2002).

The Social-Zeitgeber theory

Many of the same mechanisms proposed to account for state and trait characteristics of sleep disruption in BD outlined in section 1.3.4 may also apply here. However, with developments in circadian research since Wehr et al.'s (1987) original model, other researchers have reconceptualised the model as the 'social zeitgeber theory' in which life events are thought to trigger mood episodes through disrupting biological rhythms (Grandin et al. 2006). According to this theory, individuals with mood disorders have a circadian system that is overly sensitive to physiological or environmental changes, thus culminating in mood episodes. This might explain the associations between mutations in circadian rhythm genes and manic-like behaviour in animal models described previously in section 1.4.2. In addition, one of the therapeutic targets of lithium (a common treatment for BD) is glycogen synthase kinase Beta (GSK3-B), which plays a key role in the regulation of circadian rhythms (Gould and Manji 2005). Single-nucleotide polymorphisms in the GSK3-B promoter gene have been associated with response to sleep deprivation therapy (Benedetti et al. 2004; Benedetti et al. 2012).

However, lithium has several other targets, therefore the research in this area is still in its early stages (Jagannath et al. 2013).

1.4.4 Implications for Clinical Practice

The role of sleep disruption in relapse in BD has important clinical implications:

1. If sleep loss is involved in the aetiology and pathogenesis of bipolar disorder, then it is possible that efforts to normalise sleep may be accompanied by improvements in illness course. This has been supported by evidence that interpersonal and social rhythm therapy (IPSRT), which aims to stabilise sleep and other circadian rhythms, has been associated with improved prognosis in some patients (Frank et al. 2005).
2. If sleep loss triggers or precedes mania, sleep duration could be used as an indicator of when an individual is on-course to becoming unwell. With the advent of 'e-monitoring' techniques in which patients are encouraged to track their symptoms and identify early warning signs of impending illness (e.g. Hidalgo-Mazzei et al. 2015; Miklowitz et al. 2012), sleep duration might represent a useful variable for illness prevention as well as management.

1.5 Sleep Disturbance as a Pathway to Mania: Implications for Postpartum Psychosis

The sleep-reduction model of mania has important implications for our understanding of the causes of postpartum psychosis (episodes of mania or psychosis occurring in the postpartum period). As outlined in section 1.2.5, women with BD are at heightened risk of experiencing PP and the relationship between sleep loss and mania may explain this increased risk.

Episodes of PP are more often characterised by manic symptoms than psychotic symptoms (Brockington et al. 1981), suggesting that PP is a manifestation of a bipolar disorder triggered by childbirth. If this is so, then factors involved in the pathway to mania could also be involved in the pathway to episodes of PP. Sleep deprivation has been proposed as one such factor (Sharma and Mazmanian 2003). In fact, Wehr et al. (1987) include childbirth in the sleep-reduction model of mania (see Figure 1-3), stating that, 'Many of the factors believed to play a role in inducing mania interfere with sleep...Sleep is often disrupted in the postpartum period by the demands of feeding and caring for a newborn infant' (Wehr et al. 1987 p.201).

Sleep disruption is a common complaint during the perinatal period (Okun and Coussons-Read 2007; Reichner 2015), with the late third trimester and early postpartum period associated with the greatest sleep disruption (Hedman et al. 2002; Beebe and Lee 2007; Montgomery-Downs et al. 2010). This closely corresponds to the time that women are of greatest risk of developing PP, which, as mentioned in section 1.2.5, often emerges within the first few weeks of childbirth. A qualitative study of 13 women who had experienced PP reported that all women in the interviews discussed lack of sleep in the early stages of their illness (Engqvist and Nilsson 2013). In addition, in a study of 127 women who had

experienced PP, Heron et al. (2008) found that a lack of sleep was one of the most commonly reported early symptoms of PP, reported by 48% of women.

To date, few studies have examined the association between perinatal sleep loss and PP (Lawson et al. 2015). A retrospective study of parous women found that those who developed PP had significantly longer labours and were more likely to give birth during the night (Sharma et al. 2004), suggesting that women with PP experienced greater sleep disruption in the perinatal period. Furthermore, a case study of 3 women with a history of PP found that they became manic or hypomanic following experimentally-induced sleep deprivation (Strouse et al. 1992), suggesting that any sleep loss experienced during labour could have triggered the episodes of PP. However, in both of these studies, it was not known how long women had been kept awake prior to the onset of PP.

Conversely, one of the few prospective studies on PP and perinatal sleep comparing the sleep of pregnant women with a history of BD or PP (i.e. a group at high risk of PP) to pregnant healthy controls found no significant differences in sleep/wake patterns during pregnancy between these groups (Bilszta et al. 2010). However, due to a small sample size, the authors were unable to compare the sleep of women who relapsed following childbirth to those who remained well. Thus it remains unclear whether women who develop PP experience greater sleep disturbance prior to episode onset. This study highlights that the comparison group is important in research in this area, as in order to understand what makes some women with BD develop PP, we need to individualise risk. To do that, we need to compare characteristics of sleep within high-risk women. In addition, objective measures of sleep (such as actigraphy) are required to verify what level of sleep deprivation women experience.

Another explanation for how sleep loss might trigger episodes of PP is that women who develop PP are more sensitive than average to the sleep disturbances that typify the perinatal

period. This hypothesis is plausible for two reasons. First, research examining responses to sleep deprivation finds that there is considerable variation within healthy populations, with some individuals showing more pronounced neurobehavioural sequelae than others (Rupp et al. 2012) and emerging evidence suggests that this might be moderated by genetic factors (Groeger et al. 2008; Kuna et al. 2012). Second, although it is thought that individuals with psychiatric disorders are more vulnerable to the negative effects of sleep disturbance than healthy populations, there is evidence of variation in response to sleep deprivation within the BD population. For example, Benedetti and colleagues have found that an antidepressant response to sleep deprivation in individuals with BD is associated with genetic factors (Benedetti and Smeraldi 2009; Benedetti et al. 2012). This variation within the BD population in how individuals respond to sleep loss may extend to women in the perinatal period, with some women with BD being more sensitive to perinatal sleep disturbance and therefore potentially more susceptible to PP. The role of individual differences in the tendency for sleep loss to act as a pathway to mania is discussed in further detail in the following section, and analysis of this forms a key part of this thesis.

1.6 Limitations in Current Knowledge of the Sleep Reduction Model

As mentioned in section 1.4, there are a number of limitations in the body of literature that has been put forward to support the sleep reduction model of mania. These limitations include, small sample sizes (which are therefore of limited representativeness), heterogeneity in the use and dosages of medication, and a lack of information on other clinical features, such as bipolar subtypes.

Additional limitations of studies utilising therapeutic sleep deprivation include: the fact that the majority of these studies were not designed to detect mania, therefore these studies do not consistently report on the characteristics of BD participants, and sometimes used antidepressants as an additional treatment. Authors of these studies often comment that participants were informed that sleep deprivation was a treatment for depression, and this, in combination with the fact the studies could not be designed so that participants were blind to whether they had received sleep deprivation therapy, increased the likelihood of a placebo effect.

Additional limitations of prospective studies include variation in the frequency and length of the monitoring period, and variation in methods of measuring mood and sleep. It is also more difficult to ascertain causation from these studies, as observed associations between sleep and high mood could be the result of other triggering factors such as alcohol misuse, medications, stressors and other factors that may lead to circadian rhythm disruption, such as light exposure.

In summary, therefore, there is limited evidence on whether sleep deprivation can, in fact, trigger mania in individuals with BD. Existing studies, while suggesting that there might be an

association, are limited by methodological issues, thus making it difficult to determine causation.

Assuming that sleep deprivation can, in some cases, act as an early-warning sign or trigger of impending mood episodes, there are further limitations in our knowledge on this subject.

These can be summarised as follows:

1. Some evidence finds an association between reduced sleep and depression, Therefore, the nature of the association between sleep disruption and episode polarity is inconsistent (Gruber et al. 2011). There is a need, therefore, to understand what factors may cause individuals with BD to become depressed rather than manic following sleep disruption.
2. Not all individuals experience mood-elevating effects of sleep deprivation protocols (Benedetti and Smeraldi 2009), suggesting that some individuals have a lower threshold for the antidepressant effects of sleep loss compared to others.
3. The duration of sleep deprivation that is required to trigger mania is still unknown, with varying estimates provided in different studies.

These findings may be the result of (i) the type of sleep loss experienced (chronic vs. acute) and (ii) individual differences in the response to sleep disruption.

1.6.1 Sleep Disruption and Depressive Symptoms

Some studies find that reduced sleep is associated with increased depressive rather than manic symptoms. For example, Talbot et al. (2012) examined 49 patients with bipolar disorder over one week and found that decreased sleep predicted an increase in depressive, but not manic, symptoms the following day. Furthermore, Perlman et al. (2006), in a sample of 54 BD-I participants, found that reduced sleep duration predicted an increase in

depressive, but not manic, symptoms over a six-month follow-up period. This has also been noted in sleep deprivation therapy, where there are accounts of some patients becoming more depressed, rather than euthymic or (hypo)manic, following sleep deprivation (Wirz-Justice and Van den Hoofdakker 1999). Alternatively, sleep reduction might cause a manic or depressive polarity depending on characteristics of the sleep loss, such as whether it is chronic or acute (Boland and Alloy 2013).

1.6.2 Non-Manic Responses to Sleep Deprivation Protocols

Not all studies have found associations between sleep and subsequent mood. For example, (Klein et al. 1992) compared the sleep (from actigraphy) of patients who did and did not relapse following lithium discontinuation, and did not find significant differences between the groups (although this study may have been underpowered to detect differences, due to the small sample size of 10 participants). Studies of patients undergoing TSD for depression have also reported that some individuals do not experience antidepressant effects of sleep deprivation (Pflug 1976; Bhanji et al. 1978; Wirz-Justice and Van den Hoofdakker 1999) and it has been estimated that the treatment is effective for 50-60% of patients (Wu and Bunney 1990; Kasper and Wehr 1992). This further suggests that individuals vary in how they respond to sleep loss.

The fact that not all individuals respond to TSD in the same way might explain the varying estimates of the proportion of individuals with BD who will become (hypo)manic following sleep deprivation. However, most earlier studies of TSD were not designed to investigate what proportion of BD individuals would switch into mania, therefore included patients with a variety of diagnoses (e.g. major depressive disorder, BD-I, BD-II) and did not always report whether any patients had become hypomanic (Plante and Winkelman 2008). This, in addition

to issues with small sample sizes and varying methods, might explain the wide range in the proportion of individuals who become (hypo)manic following TSD.

1.6.3 *How Much Sleep Loss Triggers Episodes?*

The studies that report positive associations between sleep deprivation and mood also differ in their estimates of how much sleep deprivation will cause shifts in mood, with estimates ranging from three (Bauer et al. 2006) to 48 hours (Wehr et al. 1982). As discussed previously, this might be due to methodology and sample characteristics. It is also possible that the type of sleep loss (acute vs. chronic) may affect the polarity of the episode that is triggered, with chronic sleep loss being more likely to trigger depressive episodes, and acute sleep loss (i.e. total sleep deprivation) increasing the likelihood of manic episodes (Wehr 1992). In addition, the time that the sleep deprivation occurs may also be important; partial sleep deprivation therapy, where patients are restricted to 4 hours of sleep per night (Kasper and Wehr 1992), is more effective when patients are sleep-deprived in the second half of the night (i.e. woken after 1am) than in the first half of the night (Goetze and Tolle 1981; Sack et al. 1985; Sack et al. 1988).

1.6.4 *Individual Differences In Response To Sleep Disruption*

A possible explanation for why these studies show inconsistent results is that there is individual variation in the response to sleep loss within individuals with bipolar disorder. Vulnerability to the negative cognitive and emotional effects of sleep loss has been studied more extensively in the general population. Research in this area suggests that the differential vulnerability to sleep loss is trait-like (Van Dongen et al. 2004; Rupp et al. 2012; Taniyama et al. 2015) with tentative evidence suggesting that this is heritable (Kuna et al. 2012), associated with chronotype (Selvi et al. 2007), and associated with polymorphisms in

circadian rhythm genes (Groeger et al. 2008; Drake et al. 2015). This, in addition to evidence that BD is a heterogeneous condition, with a multi-factorial aetiology and clinical presentation, suggests that individuals within bipolar populations will show variation in their vulnerability to sleep disruption.

1.6.5 Summary

Therefore, despite being widely acknowledged as an important factor in the presentation, management and pathophysiology of BD, there is inconsistent evidence that changes in sleep reliably predict manic symptoms and/or episodes. Furthermore, the literature review undertaken in this thesis was non-systematic, therefore did not examine grey literature and was limited to studies published (or translated into) English. This means that the reported literature was predominantly conducted in Western populations and could be subject to publication bias.

The literature described in this section suggests that the role of individual differences in moderating the response to sleep disruption (e.g. polarity of response) requires further investigation, in addition to the characteristics of sleep loss that may influence whether it acts as a pathway to mania (e.g. duration, time in circadian night that sleep disruption occurs).

1.7 Aims and Structure of Thesis

In summary, the evidence I have outlined above suggests that sleep disruption may be one factor involved in the aetiology and pathogenesis of BD. However, a number of questions remain unanswered about the relationship between sleep disruption and BD. This thesis has the following aims:

Broad Aim: to examine the association between sleep disruption and mania in individuals with bipolar disorder.

Specific Aims:

1. To explore whether there is a subgroup of individuals who experience sleep disruption as a pathway to mania and, if present, to examine individual differences associated with this phenotype.
2. To determine whether experiencing sleep disruption as a pathway to mania is associated with vulnerability to postpartum psychosis (PP).
3. To conduct a pilot study using actigraphy to measure perinatal sleep in pregnant women at high risk of PP.
4. Within aims 1 and 2, to compare results for sleep disruption as a pathway to mania to those examining sleep loss as a pathway to depression.

I will address these aims using both retrospective and prospective data collected via the Bipolar Disorder Research Network (BDRN) (www.bdrn.org). In Chapter 3, I will examine the retrospective data on the tendency to report that sleep loss has triggered episodes of mania in a sample of 3,140 BDRN participants. In Chapter 4, I will examine data from 870 parous women to explore whether reporting that sleep loss has triggered episodes of mania is associated with experiencing PP. In Chapter 5, will utilise prospective data on symptoms of

insomnia and mania from 692 BDRN participants who monitored their mood using an online system. Finally, in Chapter 6, I conduct a pilot study using actigraphy to monitor sleep in a sample of pregnant women at high risk of PP.

2 GENERAL METHOD

2.1 Background

This thesis uses data from participants recruited to the Bipolar Disorder Research Network (BDRN). This is an ongoing study of individuals with bipolar disorder recruited from across the UK by research teams based at Cardiff University and the University of Worcester. In this chapter, I describe the BDRN sample recruitment and assessments. I will describe the methods and sample characteristics specific to individual analyses at the relevant points in subsequent chapters.

2.2 Sample Recruitment

Data in this thesis was obtained from participants who were recruited to the Bipolar Disorder Research Network (BDRN) (www.bdrn.org), a large-scale, ongoing study investigating the clinical and molecular genetic determinants of mood disorders (Jones et al. 2015).

Participants were recruited from across the UK, both systematically (via National Health Service, NHS, and Community Mental Health Teams) and non-systematically (via advertisements in local and national media and through patient support organisations, such as Bipolar UK).

The study has UK NHS Research Ethics Committee approval (MREC/97/7/01) and local Research and Development approval in all participating NHS Trusts/Health Boards. All participants provided written informed consent.

The study was funded by the Wellcome trust and Stanley Medical Research Institute. The principle investigators for this study are Professor Nick Craddock (Cardiff University), Professor Ian Jones (Cardiff University) and Professor Lisa Jones (University of Worcester).

2.3 Inclusion and Exclusion Criteria

Participants recruited to the BDRN were at least 18 years of age and met DSM-IV criteria for a major affective disorder (American Psychiatric Association 2013). Participants were of UK or Irish white ethnicity as the initial focus of the BDRN was to discover genetic determinants of affective illness within a relatively homogenous sample. Exclusion criteria were (i) affective illness experienced only in relation to alcohol or substance dependence, (ii) affective illness secondary to physical illness or medication, or (iii) a lifetime diagnosis of intravenous drug dependency.

2.4 Assessment Procedure

After obtaining written, informed consent, trained research psychologists or psychiatrists interviewed all participants. This semi-structured interview included questions on key clinical and demographic variables and relevant sections from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN, Wing et al. 1990). The SCAN questions were used to ascertain the presence of lifetime and worst-episode symptoms of mania, depression and psychosis. This information was then combined with case notes, and diagnostic and clinical ratings (such as age at illness onset and number of episodes of illness) were made based on all available information. Best-estimate lifetime diagnoses were made according to DSM-IV (American Psychiatric Association 2000), and ICD-10 (International Classification of Diseases, Tenth Revision; WHO, 1993) criteria. Diagnostic and clinical ratings were conducted for the majority of cases in this thesis prior to publication of the most recent edition of the DSM (DSM-5, American Psychiatric Association 2013), therefore DSM-IV (rather than DSM-5) criteria is used throughout this thesis.

In cases where there was doubt, diagnostic and clinical ratings were made by at least two members of the research team blind to each other's rating and consensus was reached via discussion where necessary. The inter-rater reliability for DSM-IV diagnoses, for both lifetime and perinatal mood episodes, was high ($\kappa = 0.85$ and 0.92 respectively). The mean kappa statistics for other key clinical variables (e.g. age of onset of psychiatric disorder and the number of episodes of mania and depression) ranged from 0.81-0.99 (Gordon-Smith et al. 2015).

2.5 BDRN Data and Samples Used in this Thesis

The sample of participants in the BDRN study with a DSM-IV diagnosis of BD-I or BD-II ($n=5,742$) were 66% female, 76% BD-I, and had an average age of 46 (range 18-89). The sample was also highly educated, with 41% having a level of higher education above A level standard. This sample may therefore differ from the population of individuals with BD as a whole, thus limiting the generalizability of results using these data.

The BDRN has encompassed multiple waves of recruitment over time, each including different targets and methods. This thesis is focused on data collected from the BDRN that could be used to investigate the relationship between sleep and mood. This comprises three methods of data collection:

1. Questions on whether sleep loss had triggered mood episodes, administered at original BDRN interview.
2. Weekly mood questionnaires administered via an online mood monitoring system (*'True Colours'*), which included questions on sleep disturbance (e.g. symptoms of insomnia symptoms).

3. Prospective estimates of sleep obtained via actigraphy during late pregnancy to early postpartum, combined with information on puerperal mood episodes.

The following sections outline brief information on each of these assessment methods and the samples used in this thesis. Further information is provided in each of the subsequent chapters.

2.5.1 Sleep Loss as a Trigger of Mood Episodes

In November 2007, a semi-structured question on triggers of (hypo)mania or depression was added to the main BDRN interview, in which participants were asked whether they had noticed anything that had triggered their mood episodes (Appendix A).

Interviewers highlighted to participants that the question related to triggers of mood episodes, rather than early signs or symptoms of a mood episode. In addition to the broad question on triggers, participants were also asked specifically whether sleep loss, physical illness, medication, non-prescription drugs, antidepressants or alcohol had triggered episodes of high or low mood. Participants responses were coded 'Yes', 'No', 'Unsure' or 'Not applicable' for each of the trigger options. The 'Not applicable' rating was used when individuals had not experienced the relevant mood episode or trigger (e.g. if a person with BD-I had never experienced a depressive episode, then questions relating to triggers of depressive episodes were rated 'Not applicable'). If participants could not differentiate between a trigger and early warning sign/symptom, interviewers coded responses as 'Unsure'.

Chapters 3 and 4 utilise the data derived from this measure. Chapter 3 examines responses to this question within 3,140 participants with a DSM-IV diagnosis of BD-I or BD-II. Chapter 4

examines responses to this question within a subsample of 870 parous women with a DSM-IV diagnosis of BD-I.

2.5.2 True Colours Online Prospective Mood Monitoring

True Colours is an online version of an SMS-based (Short-Message-Service/text message) symptom monitoring system developed by Professor John Geddes and colleagues at the University of Oxford Department of Psychiatry (Bopp et al. 2010). The True Colours system aimed to allow patients with BD to monitor mental wellbeing and aid illness management. The system was initially used by NHS patients within the Oxford Health Foundation Trust, and was adapted for use in research settings by the BDRN team from 2014-2015. From March 2015, participants enrolled in the Bipolar Disorder Research Network were invited (via newsletters and emails) to enrol in the research-adapted version of True Colours (bdrn.org/research/true-colours/).

Participants enrolled in the BDRN True Colours system were sent a weekly reminder email to complete two questionnaires on mood: the Altman Mania Scale (AMS) (Altman et al. 1997) and Quick Inventory of Depressive Symptoms (QIDS) scale (Rush et al. 2003) (Appendix B and C, respectively). These questionnaires included specific questions on sleep (e.g. insomnia).

In Chapter 5, I use data collected from the BDRN True Colours mood monitoring system to explore changes in insomnia symptoms that occur prior to episodes of high and low mood within individuals with BD-I or BD-II.

2.5.3 Prospective Sleep Monitoring in Pregnancy Study

From November 2014 to February 2016, women at high risk of developing PP (i.e. those who had a lifetime diagnosis of BD or a history of PP) were recruited during pregnancy to

participate in a prospective study that examined mood changes during pregnancy and the postpartum period. Women enrolled in this study were given the option to monitor their sleep patterns using an actigraph from week 37 of pregnancy until postpartum week 2. In Chapter 6, I conduct a pilot study to explore whether actigraphy can be used to collect information on sleep during the perinatal period in women at high-risk of PP.

2.5.4 *Summary of Samples*

To summarise, the analyses in this thesis were conducted on three samples of participants from the BDRN (illustrated in Figure 2-1):

Sample 1: BDRN participants who answered questions about sleep loss as a trigger of mood episodes as part of the interview assessment. Chapter 3 examines responses to these questions within participants with BD-I or BD-II (n=3140). Chapter 4 focuses on responses of parous women with BD-I (n=870).

Sample 2: A sample of 692 BDRN participants with BD-I or BD-II who were enrolled in the True Colours mood monitoring system (Chapter 5).

Sample 3: Actigraphy data from 10 pregnant women recruited to BDRN from 2014 as part of an ongoing project that examined pregnant women with a history of BD or PP (Chapter 6).

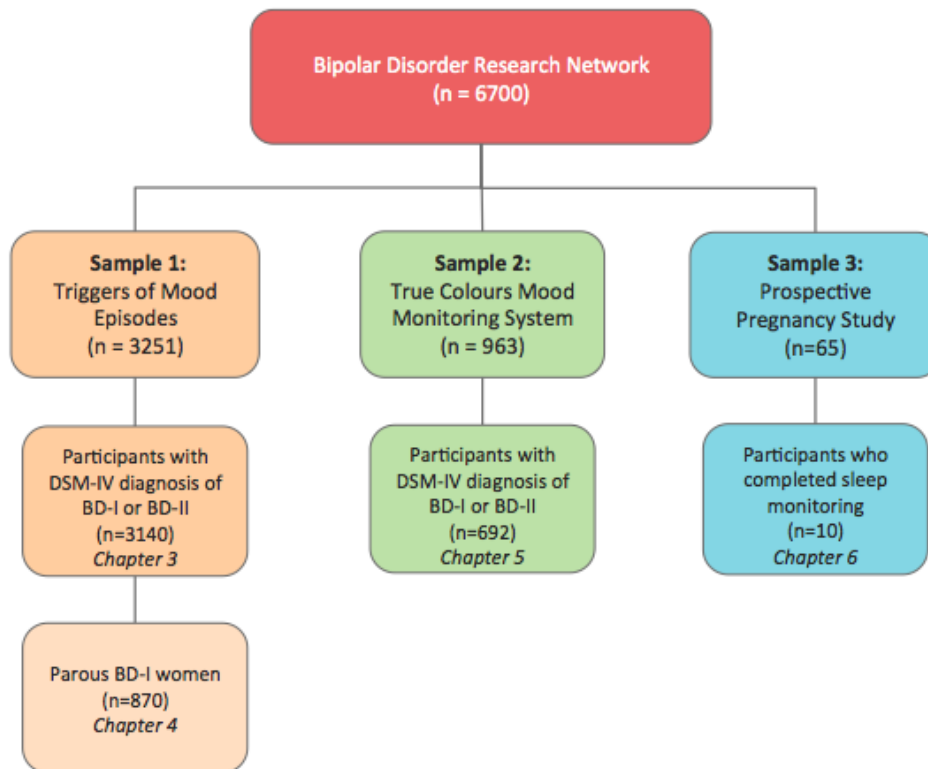


Figure 2-1. Diagram to illustrate the derivation of the samples used for each chapter of this thesis.

Further detail on methodology will be provided in the relevant sections of Chapter 3, 4, 5 and 6.

2.6 Statistical Analysis

I describe methods for statistical analysis in each of the relevant chapters to follow. Analyses in subsequent chapters were performed using SPSS version 20 (IBM 2011), Mplus version 7 (Muthén and Muthén 2012), or R version 3.2.2 (R Core Team 2017).

**3 SLEEP LOSS AS A TRIGGER OF MOOD EPISODES IN BIPOLAR DISORDER:
INDIVIDUAL DIFFERENCES BASED ON DIAGNOSTIC SUBTYPE AND GENDER**

Reported by (Lewis et al. 2017)

3.1 Introduction

In Chapter 1, I discussed the evidence that sleep loss is not only a symptom of mood episodes in BD, but can act as an early-warning sign of impending mood episodes (Jackson et al. 2003), and can trigger relapse, particularly mania (Wehr et al. 1982; Wehr et al. 1987; Gessa et al. 1995). However, sleep loss does not appear to be a trigger for all individuals with BD, and those who are vulnerable to this trigger may also differ in whether sleep loss triggers mania or depression (Perlman et al. 2006; Talbot et al. 2012).

In addition to aiding our understanding of the underlying mechanisms of bipolar illness, understanding what factors influence the relationship between sleep and mood episodes could (a) help clinicians predict which individuals are most likely to relapse following periods of sleep deprivation (e.g. due to long-haul travel or shift-work), and (b) inform self-management techniques such as ‘e-monitoring’ (Hidalgo-Mazzei et al. 2015).

In this chapter, I examine data on mood episodes triggered by sleep loss in a large sample of individuals with BD recruited to the BDRN (described in Chapter 2). In particular, I focus on whether sensitivity to sleep loss differs according to bipolar diagnostic subtype and gender. The reasons for comparing individuals on these characteristics are described in more detail below.

Bipolar Diagnostic Subtypes

As outlined in Chapter 1, bipolar-I disorder (BD-I) and bipolar-II disorder (BD-II) are subtypes of bipolar disorder that are distinguished via the presence of manic (BD-I) or hypomanic (BD-

II) episodes. Exploring whether there are differential reported effects of sleep disruption on mood episodes in BD-I and BD-II is important, given that they represent two well-defined diagnostic subtypes of BD with distinct clinical features, illness course, and physiology (T. H. Ha et al. 2009; Liu et al. 2010; Baek et al. 2011; Caseras et al. 2013). Furthermore, the majority of studies examining sleep and BD either include only BD-I participants, or do not distinguish between BD-I or BD-II, therefore it is unclear whether the effects of sleep loss are the same across the bipolar spectrum (Alloy et al. 2005). Of note is that one of the proposed mechanisms by which sleep loss affects emotion regulation is by disrupting emotion regulation systems in the brain (e.g. prefrontal and limbic areas) (Kahn et al. 2013). Recent neuroimaging studies have found that these same neurological systems vary between individuals with BD-I and BD-II, and correspond with behavioural differences in emotion regulation (Caseras et al. 2015). It is possible, therefore, that the effect of sleep loss on mood will also differ according to bipolar subtype.

Gender

The second characteristic I explore in this chapter is gender. There is evidence that the onset and presentation of bipolar illness differs between men and women, which may reflect different aetiology and pathology. For example, women are more likely to be diagnosed with BD-II rather than BD-I, spend less time well than men across their lifetime, and spend more time in the depressed polarity than men (Arnold et al. 2003; Benazzi 2006; Benazzi 2007; Altshuler et al. 2010; Di Florio and Jones 2010). In regards to mood episodes triggered by sleep loss, emerging evidence suggests that women are more prone to emotional dysregulation following sleep deprivation (Baglioni et al. 2010; Saunders et al. 2015; Short and Louca 2015) and more likely than men to experience insomnia (Mai and Buysse 2008). Women are also more likely to experience mood episodes following seasonal changes (Kerr-Corrêa et al. 1998; Suhail and Cochrane 1998; Morken et al. 2002), suggesting that

perturbations to the circadian system (described in Chapter 1) may have a more pronounced effect on mood in women than men. Only one study to date has examined gender differences in sleep loss triggering mood episodes in BD. Proudfoot and colleagues conducted an online survey of episode triggers in 198 individuals with (self-reported) BD (Proudfoot et al. 2012). They found that women were more likely than men to report that sleep loss had triggered episodes of depression than mania, whereas men were equally likely to report that sleep loss had triggered depression or (hypo)mania. However, these analyses were conducted on only 23 men, therefore may not be representative, and did not adjust for the total number of mood episodes experienced. In summary, the above evidence suggests that there could be a differential effect of sleep on mood between the genders, thereby warranting further investigation.

Episode Polarity

As discussed in Chapter 1, it is possible that inconsistent findings in observational studies are due to some individuals being more likely to experience depressive episodes in response to sleep loss, rather than manic episodes. Therefore, for each of the comparisons outlined above, I will compare the results for sleep loss triggering episodes of mania to sleep loss triggering episodes of depression.

3.2 Method

3.2.1 Sample

For further information on sample recruitment, see Chapter 2, section 2.2. The inclusion criteria for these analyses were that participants had a DSM-IV main lifetime diagnosis of bipolar disorder (BD-I or BD-II) and had been asked at interview about sleep loss triggering mood episodes. A total of 3,140 participants met these criteria.

3.2.2 Assessments

As described in Chapter 2, information on whether sleep loss had ever triggered episodes of high mood or low mood was derived at interview, where participants were asked about specific past triggers of their mood episodes (Appendix A). Response options, in addition to sleep loss, included physical illness, medication, non-prescription drugs and alcohol.

Participants responses were coded 'Yes', 'No', 'Unsure' or 'Not Applicable' for each of the trigger options. The 'Not Applicable' rating was used when individuals had not experienced the relevant mood episode or trigger (e.g. if a person with BD-I had never experienced a depressive episode, then questions relating to triggers of depressive episodes were rated not applicable).

3.2.3 Statistical Analysis

All analyses were performed using SPSS version 20. Initial analyses were calculated using chi-squared (χ^2) tests for independence to investigate associations between (i) bipolar subtype (BD-I vs. BD-II) and (ii) gender (male vs. female), and participant reports of sleep loss triggering episodes of (hypo)mania and major depression. Initial chi-squared tests for independence included all responses to the sleep trigger questions (i.e. 'Yes', 'No' and

'Unsure'). Tests that revealed significant associations were followed by partitioned chi-square tests that examined only 'Yes' and 'No' responses.

For analyses that were significant at the univariate level, I conducted a multivariate logistic regression analysis with bipolar subtype and gender as predictors and whether sleep loss had triggered mood episodes as the outcome. This enabled analyses to control for age, number of episodes of (hypo)mania or depression (depending on whether the outcome was sleep loss triggering episodes of high or low mood), and method of recruitment (systematic vs. non-systematic). These covariates were chosen due to their potential relationship with the likelihood of reporting sleep loss as a trigger. All tests were two-tailed with a $p < .05$ criterion for statistical significance.

3.3 Results

A total of 3140 individuals met the inclusion criteria described in section 3.2.1, of which 2075 (66%) had a lifetime diagnosis of BD-I and 1065 (34%) had a diagnosis of BD-II. Of this sample, 68% were female (n=2146), and the mean age at interview was 46.44 years (range 18-86, SD 12.40). Additional demographic and clinical information is provided in Table 3-1.

Table 3-1. Clinical and demographic information of participants with BD-I or BD-II who were asked about triggers of mood episodes.

		Sample Statistic (n = 3140)
% Female		68.0
Age at interview in years		
	Mean (SD)	46.4 (12.4)
	Median (range)	46.00 (18-86)
Age at illness onset		
	Mean (SD)	22.1 (9.1)
	Median (range)	20.0 (4-68)
Number of episodes of mania		
	Mean (SD)	12.6 (17.0)
	Median (range)	7.0 (1 -300)
Number of episodes of depression		
	Mean (SD)	15.9 (18.9)
	Median (range)	10 (0 -200)
Systematic recruitment, n (%)		806 (25.7)
Highest educational achievement, n (%)*		
	No secondary education qualifications	185 (5.9)
	CSE/O-level/GCSE	708 (22.5)
	A-level/AS-level	814 (25.9)
	Degree	864 (27.5)
	Postgraduate degree	408 (13.0)
	Unknown	161 (5.1)
Highest occupational attainment, n (%)		
	Professional	1534 (48.9)
	Non-professional	1367 (43.5)
	Never worked	102 (3.2)
	Unknown	137 (4.4)

* Grades of UK secondary education are specified as GCSE, General Certificate of Secondary Education; O-level, ordinary level; A-level, advanced level; AS-level, advanced subsidiary level; BD-I, bipolar-I disorder; BD-II, bipolar-II disorder.

3.3.1 Prevalence of Sleep Loss Triggering Mood Episodes in Bipolar Disorder

Within the total sample of 3140 individuals, 20% (95% CI 18.6-21.4%, n=627) of participants reported that sleep loss had triggered episodes of mania or hypomania. Of those who had experienced at least one major depressive episode (n=3064), 12% (95% CI 10.6-12.9%, n=359) reported that sleep loss had triggered episodes of depression. The rates of responses for other triggers are shown in Table 3-2.

Table 3-2. Response frequencies of triggers of mood episodes of participants with bipolar disorder.

Mood episode	Response	Triggers of Mood Episodes, n (%)				
		Sleep Loss	Physical Illness	Alcohol	Non-Prescription Drugs	Medication
(Hypo)mania (n = 3140)	Yes	627 (20.0)	82 (2.6)	231 (7.4)	175 (5.6)	114 (3.6)
	No	2325 (74.0)	2952 (94.0)	2706 (86.2)	2781 (88.6)	2881 (91.8)
	NA/Unsure	188 (6.0)	106 (3.4)	203(6.5)	184 (5.9)	145 (4.6)
Depression (n = 3064)	Yes	359 (11.7)	271 (8.8)	242 (7.9)	92 (3.0)	79 (2.6)
	No	2378 (77.6)	2553 (83.3)	2524 (82.4)	2691 (87.8)	2734 (89.2)
	NA/Unsure	327 (10.7)	240 (7.8)	298 (9.7)	281 (9.2)	251 (8.2)
NA, not applicable						

3.3.2 Differences Between Bipolar Subtypes

Episodes of High Mood

Bipolar diagnosis (BD-I or BD-II) was associated with self-reports of sleep loss triggering episodes of high mood ($\chi^2(2)=96.189, p <.001$). As shown in Figure 3-1A, individuals with a diagnosis of BD-I were more likely than those with BD-II to report that sleep loss had triggered episodes of high mood (24.7% vs. 10.8%). Partitioned chi-square analyses comparing ‘Yes’ and ‘No’ responses (n=2952) revealed that BD-I participants were 2.81 times more likely than those with BD-II to report that sleep loss had triggered episodes of high mood ($\chi^2(1)=90.808, p <.001, OR=2.81, 95\% CI 2.26-3.50$).

Episodes of Major Depression

Initial chi-squared tests for independence across all response options (i.e. Yes, No, Unsure) suggested that diagnostic subtype (BD-I or BD-II) was significantly associated with participants' responses on whether sleep loss had triggered episodes of depression ($\chi^2(2)=17.050$, $p < .001$). As shown in Figure 3-1B, there was a trend for participants with BD-II to be more likely than those with BD-I to report that sleep loss had triggered episodes of depression (13.6% vs. 10.7%) but this difference did not meet criteria for statistical significance in subsequent partitioned chi-square analyses comparing only 'Yes' and 'No' responses ($\chi^2(1)=3.716$, $p = .054$, OR=1.25, 95% CI 0.99-1.57, $n=2737$).

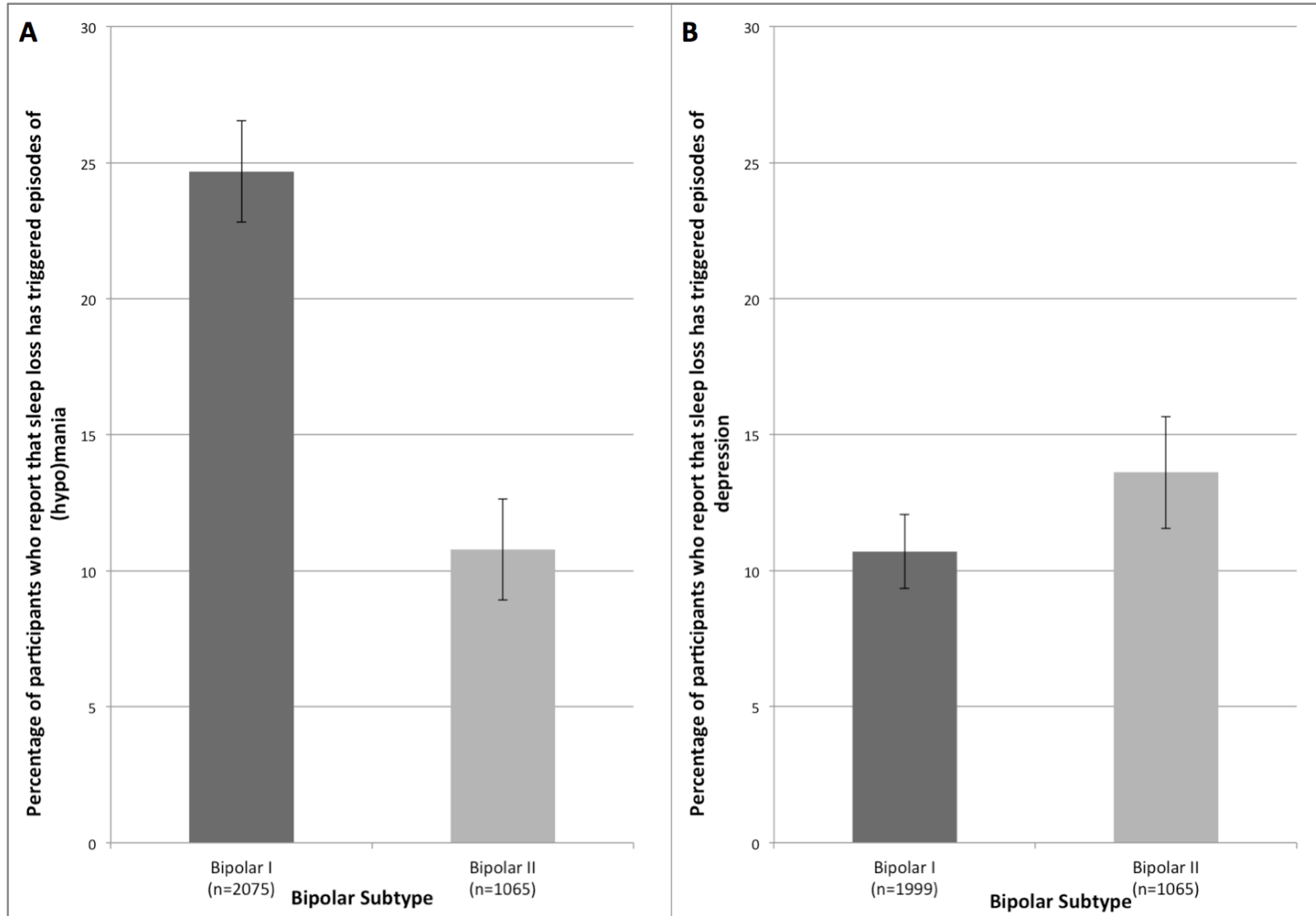


Figure 3-1. Percentage of individuals with bipolar disorder who report that sleep loss has triggered episodes of (hypo)mania (Panel A) or depression (Panel B) split by bipolar subtype. Error bars represent 95% confidence intervals.

3.3.3 Gender Differences

Episodes of High Mood

As shown in Figure 3-2A, I found an association between gender and reports of sleep loss triggering episodes of (hypo)mania ($\chi^2(2)=12.739$, $p=.002$), with women being more likely than men to report that sleep loss had triggered episodes of high mood (21.7% vs. 16.3%). A partitioned chi-square analysis comparing only 'Yes' and 'No' responses ($n=2952$) showed that this difference was statistically significant ($\chi^2(1)=12.668$, $p<.001$) with the odds of women reporting manic or hypomanic episodes triggered by sleep loss being 1.43 times greater than men (OR=1.43, 95% CI 1.17-1.75).

Episodes of Major Depression

Gender was significantly associated with self-reports of episodes of depression triggered by sleep loss ($\chi^2(2)=7.297$, $p=.026$). A partitioned chi-square analysis comparing only 'Yes' and 'No' responses ($n=2737$) showed that this difference was statistically significant ($\chi^2(1)=6.133$, $p=.013$) with women being more likely than men (12.7% vs. 9.5%, respectively, see Figure 3-2B) to report that sleep loss had triggered episodes of depression (OR=1.37, 95% CI 1.07-1.77)

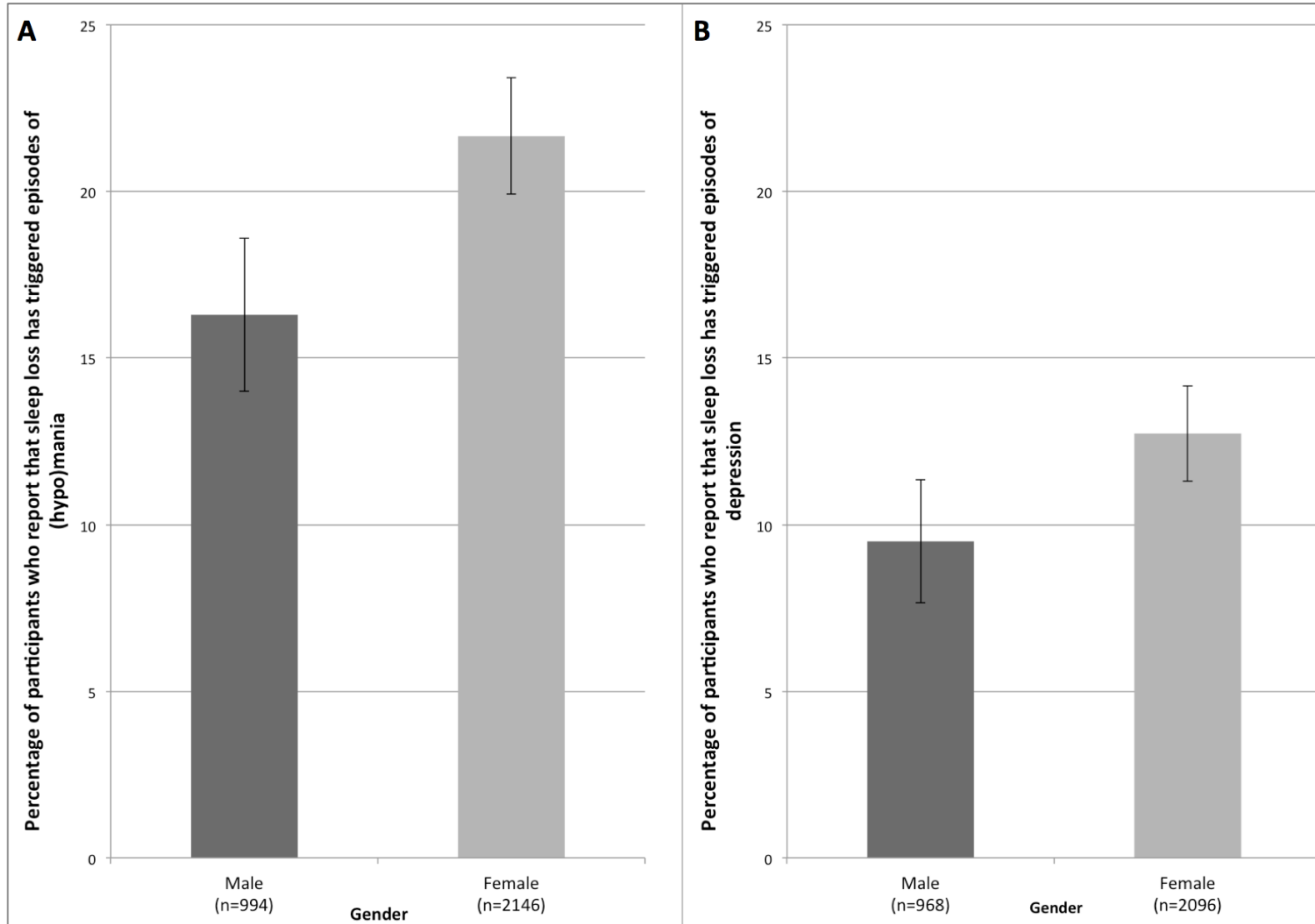


Figure 3-2. Percentage of individuals with bipolar disorder who report that sleep loss has triggered episodes of (hypo)mania (Panel A) or depression (Panel B) split by gender. Error bars represent 95% confidence intervals.

3.3.4 *Multivariate Binary Logistic Regression Models*

When adjusting for potential confounders (age, number of episodes of (hypo)mania, and method of recruitment), a multivariate logistic regression with (hypo)mania triggered by sleep loss as the outcome and including both bipolar diagnosis and gender as predictors found that the associations with (hypo)mania triggered by sleep loss remained significant for BD-I (OR=2.81, 95% CI 2.23-3.53, $p < .001$) and female gender (OR=1.30, 95% CI 1.05-1.61, $p = .015$). In contrast, the association between female gender and episodes of depression triggered by sleep loss was not significant when controlling for age, number of episodes of depression, and method of recruitment (OR=1.29, 95% CI 0.99-1.68, $p = .06$).

3.4 Discussion

Sleep loss has been proposed as a potential trigger of mood episodes (particularly high mood) in individuals with bipolar disorder (Wehr et al. 1987). Despite support from experimental research in animals (Gessa et al. 1995) and in healthy human populations (Kahn et al. 2013; Van Someren et al. 2015), longitudinal studies of clinical populations have not always found that reduced sleep predicts subsequent mania in all individuals with a bipolar diagnosis (Perlman et al. 2006; Talbot et al. 2012). It is possible, therefore, that some individuals with BD have increased vulnerability to experiencing high mood following sleep disruption whereas others may be unaffected or become depressed. If so, this would be consistent with research in healthy populations which finds individual differences in vulnerability to the neurocognitive effects of sleep loss (Van Dongen et al. 2004; Banks and Dinges 2007).

This study provides further evidence that some but not all individuals with BD experience sleep loss as a trigger of mania, with 20% of the sample reporting that sleep loss had triggered episodes of mania. Sleep loss was less commonly reported as a trigger of depression, with 11% of the sample who had experienced depressive episodes reporting that they had been triggered by sleep loss. Nonetheless, sleep loss was the most commonly reported trigger of (hypo)manic and depressive episodes (Table 3-2). It is difficult to compare these results to other literature, as few studies have reported the percentage of individuals with BD who report sleep loss as a trigger. Research to date has primarily focused on early symptoms of mood episodes (Jackson et al. 2003) or has explored the proportion of individuals with bipolar disorder who become manic or hypomanic following sleep deprivation therapy for depression. The proportion of individuals who become manic or hypomanic in these contexts is reported to range from 4.85% to 29% (Plante and Winkelman 2008). The aforementioned study on triggers of mood episodes by (Proudfoot et al. 2012)

does not report the percentage of individuals who endorsed a particular trigger, but the authors report that sleep loss was more frequently reported as a trigger of depression than mania. However, other triggers that the authors found were specific to mania (or common to both mania and depression) included events that are characterised by sleep loss, such as 'partying all night' or 'jet lag'.

A key finding of this study was that individuals with BD seem to differ in their tendency for sleep loss to trigger mood episodes depending on their gender and bipolar subtype. Specifically, I found that participants who were female or had a diagnosis of BD-I were more likely to report that sleep loss had triggered episodes of high mood than male participants or those with a BD-II diagnosis. In contrast, sleep loss triggering episodes of depression was more commonly reported by women and individuals with BD-II than men or those with BD-I, respectively. However, for sleep loss triggering depressive episodes, (1) the differences between BD-I and BD-II did not reach statistical significance, and (2) the differences for men and women did not persist when controlling for potential confounders.

3.4.1 Bipolar Subtype

In this sample, individuals with BD-I were significantly more likely than those with BD-II to report that sleep loss had triggered episodes of high mood, with 1 in 4 individuals with BD-I reporting this compared to around 1 in 10 individuals with BD-II. Differences between bipolar subtypes in the tendency for sleep loss to trigger high mood may reflect clinical and underlying neuroanatomical (and associated functional) differences between BD-I and BD-II that have been highlighted elsewhere (Liu et al. 2010; Baek et al. 2011; Caseras et al. 2013). One possibility is that the emotion regulation systems that are disrupted by sleep loss (Kahn et al. 2013) and have been found to vary between BD-I and BD-II subtypes (Caseras et al. 2015) are responsible for the different responses to sleep loss in BD-I and BD-II.

Alternatively, it is possible that fewer participants with BD-II reported sleep loss triggering high mood because they were generally less able to identify triggers of their episodes. However, analysis of the 'unsure' responses for this question revealed that 4.7% of participants with a BD-II diagnosis responded 'unsure' compared to 6.7% of those with BD-I ($p = .029$).

3.4.2 Gender

The results also suggest that women may be more susceptible than men to mood dysregulation following sleep loss, with women being significantly more likely than men to report that sleep loss had triggered episodes of high mood. These findings may have been due to women being more likely to over-report triggers, women generally being better at identifying triggers of mood episodes than men, or men being more likely to underreport triggers. However, when I examined responses for other triggers that participants were asked at interview (i.e. medication, antidepressants, alcohol or non-prescription drugs) I found that women did not consistently endorse triggers more than men (see Appendix D). In addition, analysis of 'unsure' responses revealed that men were not significantly more likely than women to respond 'unsure' when asked about triggers of high mood (5.8% vs. 6.1%, respectively, $p = .807$) or depressive episodes (11.6% vs. 10.3%, respectively, $p = .274$).

The findings are in agreement with previous research that has also found women to be at greater risk than men of mood disturbances following sleep loss (Saunders et al. 2015; Short and Louca 2015) and may partly explain why women with BD are at high risk of experiencing mania following childbirth (Jones et al. 2014), which is associated with sleep deprivation. Furthermore, there is evidence that women with BD-I are more likely to become manic following childbirth compared to those with BD-II (Di Florio et al. 2013) which is concordant with the results for BD subtype.

These gender differences provide interesting avenues to explore underlying mechanisms by which gender and sleep may interact to influence bipolar disorder phenotypes. For example, it has been suggested that ovarian hormones may interact with the circadian system to influence the sleep-wake cycle and responses to sleep deprivation (Bailey and Silver 2014).

3.4.3 Episodes of Depression Triggered By Sleep Loss

It is possible that the association between sleep loss and mania has been attenuated in some studies by the inadvertent inclusion of individuals who, following sleep loss, are more likely to experience shifts in mood towards the opposite polarity (i.e. depression). Therefore, I examined whether bipolar subtype and/or gender were associated with an increased likelihood of reporting episodes of depression triggered by sleep loss.

First, I found some evidence that individuals with BD-II were more likely than those with BD-I to report that sleep loss had triggered episodes of depression (14% vs. 11%, respectively) but this difference did not meet criteria for statistical significance ($p = .054$). Of note is that fewer participants reported sleep loss triggering episodes of depression ($n=359$, 11%) compared to high mood ($n=627$, 20%) and more participants responded 'unsure' when asked whether sleep loss had triggered episodes of depression (10.7%) compared to episodes of (hypo)mania (6.0%). The reasons for this are unclear, however, Jackson and colleagues (2003) reported that individuals with BD found it easier to identify early symptoms of mania than depression. Therefore, if the onset of depressive episodes is less noticeable than manic episodes, it may be more difficult for individuals to identify triggers.

Second, I found that women were more likely than men to report that sleep loss had triggered episodes of depression. This concurred with previous research finding that women are more likely than men to experience depressed mood following sleep loss (Saunders et al.

2015; Short and Louca 2015). These findings may be due to women being at a greater risk of experiencing insomnia, which has been associated with subsequent depressive episodes (Ohayon 2002). However, the association between gender and sleep loss triggering depression did not remain significant when controlling for potential confounding factors. This may be because rates of insomnia have been found to increase with age in both sexes (Ohayon 2002) and the sample included a wide age-range (median = 46 years, range = 18-86).

3.4.4 *Strengths and Limitations*

At the time of writing, this is the largest study to date reporting on the prevalence of sleep loss as a trigger of both manic and depressive episodes in individuals with BD. There are, however, studies that have examined this relationship using objective rather than subjective measures of sleep and mood, such as nurse observations (Wehr et al. 1982; Barbini et al. 1996) or have imposed sleep deprivation as part of treatment (e.g. Barbini et al. 1998). These studies have provided convincing evidence that sleep loss can trigger mood episodes, however, the labour-intensive nature of such studies results in relatively small sample sizes (typically fewer than 100 participants). This makes it difficult to ascertain what proportion of individuals with bipolar disorder may be vulnerable to the sleep loss trigger, and means there is limited power to make comparisons between bipolar subtypes and genders. The less-intensive nature of the self-report measure ensured that data were available on a large sample of individuals and therefore allowed comparisons of responses from men and women, as well as bipolar subtypes.

A further strength is that participant diagnoses were derived from rich clinical data. The only other study to date that has examined triggers of mood episodes relied on self-reported bipolar diagnoses that were reported online (Proudfoot et al. 2012). In contrast, in this study, information on diagnoses and other key clinical variables (e.g. age at illness onset) were

derived using a well-validated standardised psychiatric interview (Wing et al. 1990) and combined with information from case notes.

However, this study is limited by the retrospective nature of the data, hence there is a possibility that participants over- or underestimated the role of sleep loss in triggering mood episodes. For instance, the bidirectional relationship between sleep and mood (Wehr et al. 1987; Baglioni et al. 2010; Kahn et al. 2013) could have made it difficult for participants to judge whether sleep loss had been a trigger or prodrome of episodes (although participants had the option to respond 'unsure'). However, multiple experimental studies have provided supporting evidence that sleep deprivation can perturb emotion regulation (Harvey et al. 2009) and can be a risk factor for the development of BD in high-risk children (Levenson et al. 2015). In addition, if sleep loss is a prodrome rather than a trigger, it could nevertheless be a clinically useful warning-sign of incipient mood episodes. Therefore, if women and those with BD-I are more likely to report sleep loss triggering mania, this strongly suggests that there should be a concerted effort to monitor sleep in these individuals, as a change in sleep pattern – whether prodromal or as a result of external factors – could still signal the onset of an impending mood episode.

An additional limitation of the data used in this chapter is the representativeness of the dataset utilised for analysis. Participants in the sample used were highly educated and almost half of the sample had a professional occupation. Therefore the results may differ in more representative samples of individuals with BD.

Furthermore, although the multivariate analyses controlled for confounding factors such as age, number of episodes of illness, and method of recruitment, it is possible that other variables influenced the relationship between sleep and mood that were not available in this dataset, such as medication use or (as discussed below) differences in the amount of sleep

loss individuals were exposed to. Other confounders that were not controlled for, but could influence the relationship between sleep and mood include alcohol or other substance misuse, stressors, and other sources of circadian rhythm disruption such as light exposure.

3.4.5 Future Research

The results of the present study should inform future research investigating associations between sleep and mood in BD, as samples containing a mix of genders and bipolar subtypes might obfuscate associations between sleep and mood. However, the results need to be validated in longitudinal studies using objective measures of sleep such as actigraphy, as I did not have objective data on whether participants experienced sleep loss prior to mood episodes or the type of sleep loss that they experienced (e.g. total or partial sleep deprivation). Such research may also inform the rapidly expanding field of 'digital psychiatry' that aims to aid management of mental health by utilising information from technology (Bidargaddi et al. 2016). However, much more remains to be understood about the progression of mood episodes following sleep disruption (e.g. on how the pattern or circadian timing of sleep loss affects risk of relapse) and how to distinguish between sleep loss as a trigger, prodrome or early symptom of episodes. I will discuss this theme further in the General Discussion (Chapter 7).

It is unclear why some individuals become depressed following sleep deprivation and others become manic. It is possible that other triggers associated with relapse in BD (e.g. stressful or exciting life events, medication use or interpersonal conflict) may have coincided with the sleep loss that participants reported. However, vulnerability to the negative cognitive and emotional effects of sleep loss has been studied more extensively in healthy populations, which provides further support that differential vulnerability to sleep loss is trait-like and potentially genetic (Banks and Dinges 2007). Some studies have explored this in participants

with bipolar disorder, however to date this has been limited to candidate gene studies (e.g. Benedetti et al. 2012). Future research could potentially use manic or depressive responses to sleep loss as a sub-phenotype for genome-wide analyses or examine whether individuals at high familial risk of BD are more prone to mood dysregulation following sleep loss. In addition, there is a need to explore what factors underpin the differences in response to sleep loss between BD-I and BD-II individuals and between men and women.

Another intriguing avenue for future research is the relationship between sleep and pharmacology, as the data on medication use was limited in this dataset. For example, lithium is known to affect circadian rhythms (McCarthy and Welsh 2012) and there is preliminary evidence that patients are more likely to experience mood elevation following sleep deprivation therapy if they have single nucleotide polymorphisms in genes that encode enzymes targeted by lithium (Benedetti et al. 2004). Future research should explore the genetic underpinnings of this in genome-wide studies.

3.4.6 Implications for Clinical Practice

If replicated in subsequent research, the findings of this study may inform self-management strategies for bipolar disorder, particularly in light of recent attempts to engage patients with electronic self-monitoring tools, which aim to alert the individual of impending mood episodes based on their behaviour (e.g. Hidalgo-Mazzei et al. 2015). If future research reliably demonstrates that some individuals are more affected by sleep loss than others, then these self-monitoring tools could, for example, be tailored to send alerts if sleep starts to become disturbed. Clinicians should therefore discuss the importance of this trigger with patients, including encouraging a regular sleep pattern and considering the potential impact of specific situations such as shift work and long-haul travel.

However, additional research on burden to patients, clinicians and services will be required before the results of this study could be applied to clinical practice. One example of how research might take these results forward would be to use objective, longitudinal data on sleep and mood as a means of exploring the sensitivity, specificity, positive predictive value and negative predictive value of responding positively to whether sleep loss has triggered episodes of high mood.

The results of this study suggest that up to 1 in 4 individuals with BD at some point in their lifetime, have reported an episode of high mood that they attributed to sleep loss, with women and those with a bipolar-I diagnosis particularly at risk. Caution should be employed when interpreting this figure, however, due to the fact that this was a lifetime measure of triggers, could be referencing acute rather than chronic sleep loss, and this estimate may be higher or lower in more representative samples of individuals with BD.

3.4.7 Summary

In summary, I found that bipolar subtype and gender influence susceptibility to relapse following sleep reduction. In particular, the strongest effects were observed for sleep loss triggering mania, with female gender and BD-I diagnosis associated with a greater tendency to report this.

I also observed differences in the tendency to report that sleep loss had triggered episodes of depression, with this being associated with female gender and BD-II diagnosis. However, the effect for BD-II did not reach statistical significance, and the effect for gender was non-significant following controlling for confounders.

However, the results need to be interpreted with caution due to the limitations of the data (self-report, retrospective) and representativeness of the sample. These factors mean it is not

possible to determine whether sleep loss definitely triggered episodes of high mood in participants who reported this. To be able to adequately answer this question will require large-scale longitudinal studies in randomly sampled individuals or population studies (e.g. registry studies).

In the next Chapter, I will explore whether a tendency to report sleep loss triggering mania is associated with an increased risk of mania or psychosis in the postpartum period.

4 SLEEP LOSS AS A TRIGGER OF MANIA AND SUSCEPTIBILITY TO
POSTPARTUM PSYCHOSIS

Reported by Lewis et al. (In Press)

4.1 Introduction

As outlined in section 1.2.5 of Chapter 1, women with BD are at high risk of affective psychoses following childbirth, termed 'postpartum psychosis' (PP) (Jones et al. 2014). Although research has explored a number of factors that may explain this increased risk, sleep disruption during the perinatal period remains an understudied area of research.

Sleep disruption is a plausible candidate for triggering PP, as it has been associated with the onset of mania (Wehr et al. 1982; Wehr et al. 1987; Wehr 1989; Wehr 1991) and is characteristic of the perinatal period (Parry et al. 2006). Few studies have examined the association between perinatal sleep loss and PP (Ross et al. 2005; Lawson et al. 2015), however, one study suggested that women who develop PP may experience more sleep loss during labour than those who remain well; Sharma and colleagues (Sharma et al. 2004) derived information on length of labour and time of delivery from medical records of 42 women (21 PP, 21 healthy controls) who gave birth at three hospitals in Ontario, Canada between 1990-2000. Sharma et al. found that women who developed PP were more likely compared to healthy controls to give birth at night, and had longer durations of labour.

However, an important aim for clinicians is to be able to individualise risk within women who are at high risk of PP (i.e. women with BD or a history of PP). Within this high-risk group, it is possible that women who develop PP are more sensitive than average to the sleep disturbances that typify the perinatal period. This hypothesis is plausible for two reasons. First, research examining responses to sleep deprivation finds that there is considerable variation within healthy populations, with some individuals showing more pronounced neurobehavioural sequelae than others (Rupp et al. 2012) and emerging evidence suggests that this might be moderated by genetic factors (Groeger et al. 2008; Kuna et al. 2012).

Second, although it is thought that individuals with psychiatric disorders are more vulnerable to the negative effects of sleep disturbance than healthy populations, there is evidence of variation in response to sleep deprivation within the BD population. For example, Benedetti and colleagues have found that an antidepressant response to sleep deprivation in individuals with BD is associated with genetic factors (Benedetti and Smeraldi 2009; Benedetti et al. 2012). This variation within the BD population in how individuals respond to sleep loss may extend to women in the perinatal period, with some women with BD being more sensitive to perinatal sleep disturbance and therefore potentially more susceptible to PP.

In light of the above literature, and given that episodes of PP typically have a manic presentation (Brockington et al. 1981), I hypothesised that women with BD who report episodes of mania being triggered by sleep loss would be more likely to experience PP than those who do not report sleep loss as a trigger for manic episodes.

4.2 Method

4.2.1 *Recruitment and Inclusion Criteria*

Participants in this study were parous women who had been recruited to the BDRN and asked about triggers of mood episodes at interview. Evidence suggests that risk of PP is greatest for women with bipolar-I disorder (BD-I) (Di Florio et al. 2013), therefore I limited the current analyses to women with a lifetime DSM-IV diagnosis of BD-I. For further information on sample recruitment, see Chapter 2, section 2.2.

4.2.2 *Assessments and Definition of Postpartum Episodes*

Research psychologists or psychiatrists administered all assessments and diagnostic procedures. Data collected on all the pregnancies of each parous woman were used to make lifetime ratings of postpartum episodes. PP was defined as a lifetime DSM-IV manic, mixed, psychotic depression or other psychotic episode occurring within 6 weeks of delivery. Postpartum depression (PD) was defined as a lifetime DSM-IV episode of non-psychotic depression with onset within 6 weeks of delivery, with no lifetime episodes of PP. The temporal association of episodes to childbirth was chosen as 6 weeks based on previous research indicating that the majority of postpartum episodes occur within this time-frame and to include both DSM-IV and ICD-10 definitions of the postpartum period (Di Florio et al. 2013). Women were assigned to PP or PD categories in a hierarchical manner so that in instances where women had experienced both PP and PD, they were assigned to the PP group.

Information on triggers of past manic and depressive episodes was derived at interview, where participants were asked about triggers of their episodes of mania and depression, with

specific questions about sleep loss, physical illness, medication and alcohol. For these analyses, I focused on whether women had reported that sleep loss had triggered manic or depressive episodes. Responses were used to group women into (i) those who reported that their episodes of mania were triggered by sleep loss versus those who did not (i.e. 'sleep loss triggering mania') and (ii) those who reported that their episodes of depression were triggered by sleep loss versus those who did not (i.e. 'sleep loss triggering depression'). As data were retrospective, it is possible that women who reported sleep loss as a trigger of mood episodes were referring solely to episodes that had occurred in the postpartum period. To reduce the likelihood of this, I excluded women who had only experienced mood episodes in relation to childbirth.

4.2.3 Statistical Analysis

All analyses were conducted using SPSS version 20 (IBM 2011). In primary analyses, I used chi-square tests for independence to examine associations between sleep loss triggering mania and lifetime PP. Specifically, I compared the rates of PP in women who did or did not report that sleep loss had triggered episodes of mania. Significant associations were followed with multivariate logistic regression analyses that examined the association between sleep loss triggering mania (predictor) and lifetime PP (outcome) whilst controlling for number of deliveries, age, marital status, number of manic episodes experienced and method of recruitment. Data from other triggers of mood episodes (e.g. physical illness, medication, non-prescription drug use and alcohol use) were not included as covariates due to (1) low numbers of participants endorsing these triggers and (2) many people responding "not applicable" for trigger questions such as non-prescription drug use, thus including these as covariates would have increased missing data.

4.3 Results

4.3.1 *Sample Characteristics and Perinatal Episodes*

Within the BDRN cohort, 870 women met the inclusion criteria described in section 4.2.1.

Within the sample, 23.5% of women had experienced a lifetime episode of postpartum psychosis (n = 204) and a further 21.2% (n = 184), while not experiencing PP, had experienced non-psychotic depression within 6 weeks of delivery. The remaining women who did not meet criteria for PP or PD within 6 weeks of delivery had experienced (i) no perinatal episodes despite giving birth (n = 207, 23.8%) or (ii) while not meeting the criteria for PP or PD, had experienced an affective episode in pregnancy or later in the postpartum period, or there were insufficient data to reach a conclusion on perinatal episodes (n = 275, 31.6%).

Demographic and clinical information on the sample is presented in Table 4-1.

Table 4-1. Sample clinical and demographic information for 870 parous women with bipolar-I disorder.

Demographic/clinical characteristics (n=870)		
Age at interview in years, median (range)		49 (21-80)
Number of deliveries, median (range)		2 (1-8)
Number of episodes of mania		
	Median	7
	Range	1-100
Number of episodes of depression		
	Median	10
	Range	0-100
Age at illness onset, mean (SD)		22.53 (8.93)
Systematic recruitment, n (%)		261 (30.0)
Highest educational achievement, n (%)*		
	No secondary education qualifications	93 (10.7)
	CSE/O-level/GCSE	215 (24.7)
	A-level/AS-level	184 (21.1)
	Degree	218 (25.1)
	Postgraduate degree	96 (11.0)
	Unknown	64 (7.4)
Highest occupational attainment, n (%)		
	Professional	385 (44.3)
	Non-professional	416 (47.8)
	Never worked	15 (1.7)
	Unknown	54 (6.2)

* Grades of UK secondary education are specified as GCSE, General Certificate of Secondary Education; O-level, ordinary level; A-level, advanced level; AS-level, advanced subsidiary level.

4.3.2 Mania Triggered by Sleep Loss and Postpartum Psychosis

Within the sample of 870 women, 25.3% (n = 220) reported that sleep loss had triggered mania, 68.4% reported that sleep loss had not triggered mania (n = 595), and 6.3% of women reported that they were unsure whether sleep loss had triggered mania (n = 55). Subsequent analyses were conducted on women who had responded 'Yes' or 'No' to the sleep trigger question and had information on puerperal episodes, resulting in a sample of 732 for analysis.

Figure 4-1 shows the proportion of perinatal episodes within this sample, split according to

whether women had or had not reported sleep loss triggering mania. I found that women who reported sleep loss triggering mania were significantly more likely to experience PP than those who did not report this ($\chi^2(1)=17.191$, $p < 0.001$, 36.8% vs. 21.8%, respectively). Compared to women without a manic response to sleep loss, women who reported sleep loss triggering episodes of mania had more than twice the odds of experiencing a lifetime episode of PP (OR=2.09, 95% CI = 1.47-2.97). The association remained significant when controlling for number of episodes of mania, age at interview, number of deliveries, marital status and method of recruitment (OR=2.09, 95% CI=1.43-3.04, $p < 0.001$).

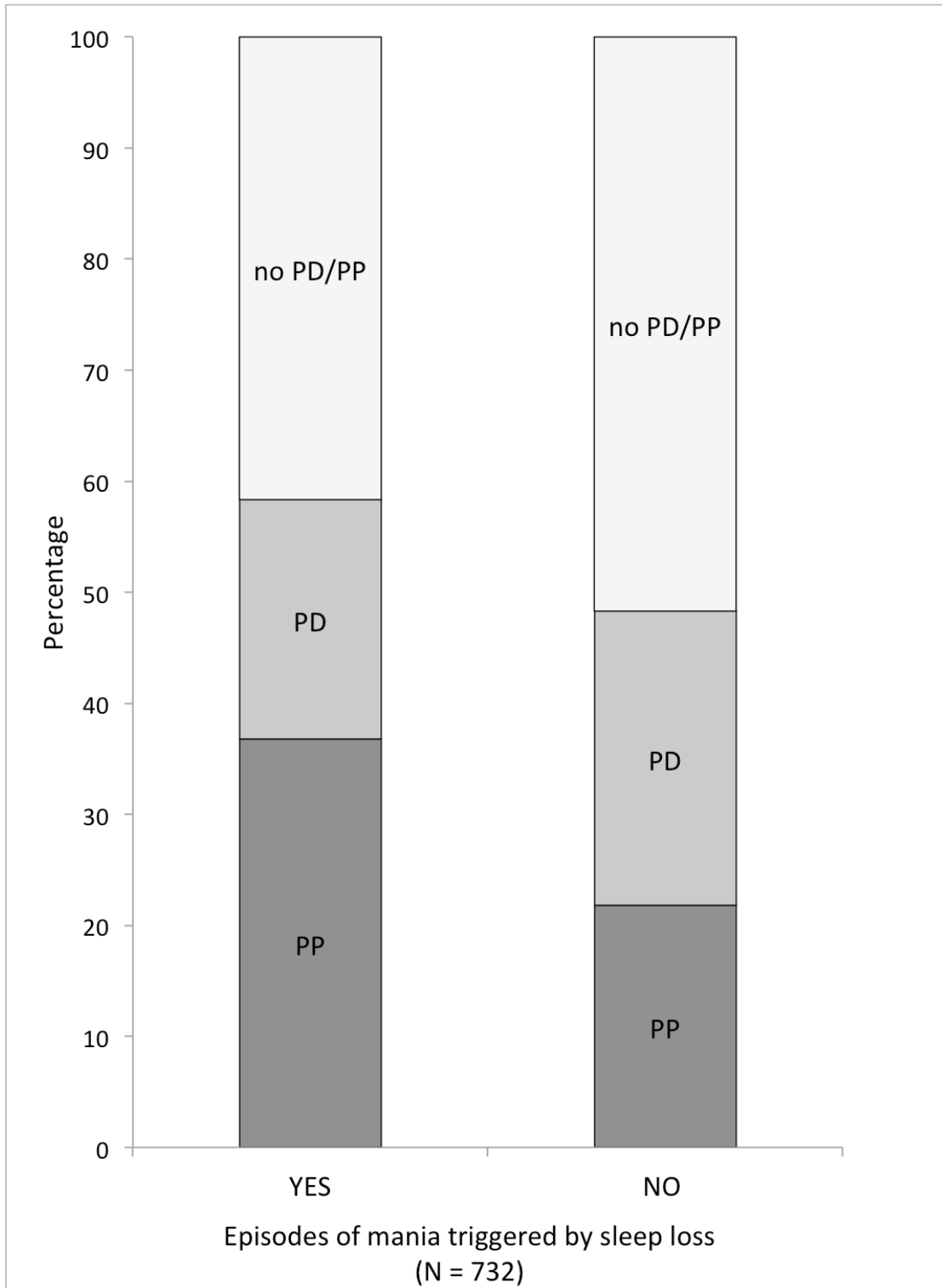


Figure 4-1. Proportion of women with perinatal episodes split by manic response to sleep loss. Abbreviations: PP, Postpartum Psychosis; PD, Postpartum Depression; no PD/PP, includes: no perinatal episode, any other psychiatric illness occurring in the perinatal period up to 6 months postpartum, or onset of PP or PD outside of 6 weeks of delivery.

4.3.3 *Specificity of Findings*

To examine the specificity of the findings for the trigger, namely mania triggered by sleep loss, and the outcome, namely episodes of PP, I conducted follow-up analyses examining (i) the association between reporting a depressive response to sleep loss (i.e. sleep loss triggering episodes of depression) and PP, and (ii) the association between depression or mania triggered by sleep loss and PD.

Depression Triggered by Sleep Loss and Postpartum Psychosis

Some women in the sample had not experienced depressive episodes, and therefore responded 'Not applicable' to whether sleep loss had triggered episodes of depression. The following analyses were conducted on the 669 women in the sample who had responded 'Yes' or 'No' to the sleep trigger question. As shown in Figure 4-2, in contrast to the findings for sleep loss triggering high mood, women who reported that sleep loss had triggered episodes of depression did not demonstrate higher rates of PP than women who did not report this (22.8% vs. 26.1%, respectively, $\chi^2(1)=0.401$, $p=0.526$).

Mood Episodes Triggered by Sleep Loss and Postpartum Depression

Compared to the rest of the women in the sample (i.e. those who had experienced no perinatal episodes or perinatal episodes that did not meet criteria for postpartum depression), women who experienced postpartum depression within 6 weeks of delivery were not more likely to report sleep loss triggering episodes of depression (25.3% vs. 25.6%, respectively, $\chi^2(1)=0.004$, $p=0.948$) or sleep loss triggering episodes of mania (25.7% vs. 20.9%, respectively, $\chi^2(1)=1.797$, $p=0.180$).

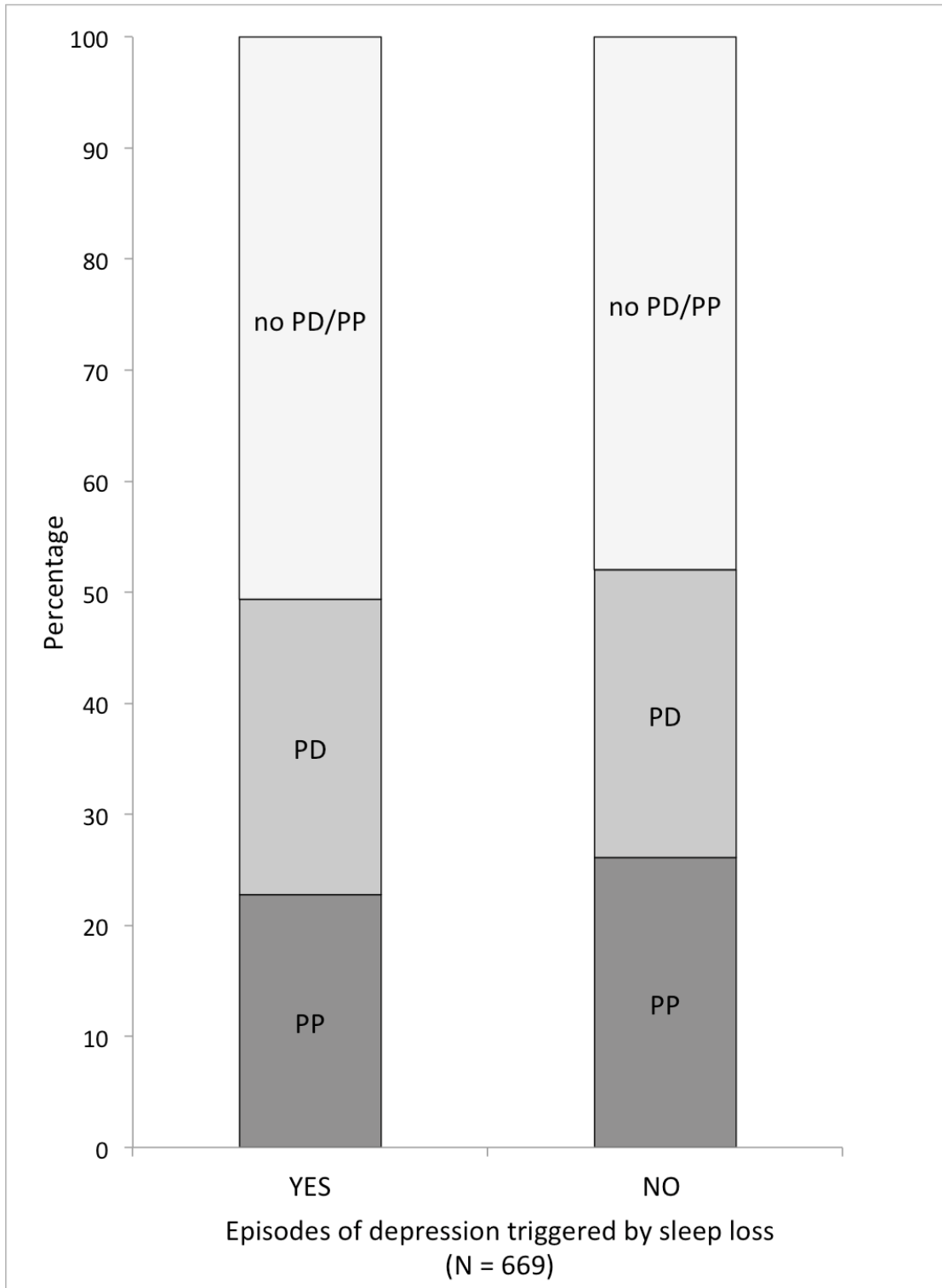


Figure 4-2. Proportion of women with perinatal episodes split by depressive response to sleep loss. Abbreviations: PP, Postpartum Psychosis; PD, Postpartum Depression; no PD/PP, includes: no perinatal episode, any other psychiatric illness occurring in the perinatal period up to 6 months postpartum, or onset of PP or PD outside of 6 weeks of delivery.

4.3.4 Analyses to Address Potential Recall Bias

I conducted further analyses to address the likelihood that reporting sleep loss as a trigger of mania was due to recall bias (i.e. due to women assuming that their postpartum episodes were caused by sleep loss they may have experienced in the perinatal period).

Episodes of Mania ‘Usually’ Triggered by Sleep Loss

First, I repeated the analyses on a sample of women who had said that sleep loss ‘usually’ triggered episodes of mania. This question was only asked to women who had experienced at least 3 episodes of mania (n = 547), reducing the likelihood that they were referring primarily to episodes that had occurred in the postpartum period. Among these women, those who reported that sleep loss had ‘usually’ triggered episodes of high mood were more likely to experience PP than women who did not report this ($\chi^2(1)=7.157$, $p = 0.001$, $OR=2.00$, $95\% CI=1.20-3.36$). This association remained significant when controlling for number of episodes of mania, age at interview, number of deliveries, marital status and method of recruitment ($OR=1.99$, $95\% CI=1.16-3.41$, $p = 0.012$).

Parous vs. Nulliparous Women

I compared the rates of reporting sleep loss triggering mania in parous and non-parous (nulliparous) women. If experiencing childbirth leads to an increased tendency to report that sleep loss triggers mood episodes, then I would expect parous women to be more likely to report this than nulliparous women (i.e. women who have not given birth). Parous women did not have higher rates of sleep loss triggering mania than nulliparous women – in fact, the opposite was true – with 30.7% of the non-parous BD-I women in the BDRN sample (n = 158/515) reporting that sleep loss had triggered episodes of mania compared to 25.3% of parous women (n = 220/870) ($\chi^2(1)=4.495$, $p = 0.034$, $OR=0.77$, $95\% CI=0.60-0.98$).

4.4 Discussion

I examined rates of lifetime postpartum mood episodes in parous women with BD-I according to self-report of sleep loss triggering episodes of mania or depression. Compared to those who did not report sleep loss as a trigger of mania, women who reported that sleep loss had triggered episodes of mania were more than twice as likely to have experienced PP. This effect remained significant when controlling for potential confounders.

The association between sleep loss and postpartum episodes was specific to (i) a vulnerability to sleep disturbance triggering mania rather than depression, and (ii) experiencing PP rather than PD. This suggests that a vulnerability to the mania-inducing qualities of sleep loss increases the risk of experiencing PP, and is consistent with previous research suggesting that PP is frequently a manifestation of manic or mixed episodes triggered by childbirth (Brockington 1996; Jones et al. 2001). Importantly, the results suggest that women with BD-I who report manic episodes triggered by sleep loss could be more vulnerable to developing PP, although this needs further investigation in prospective studies.

In contrast, I found that a lifetime history of depressive episodes being triggered by sleep loss was not associated with an increased rate of PD in this sample. Other research has found an association between perinatal sleep loss and PD (Skouteris et al. 2009; Khazaie et al. 2013), therefore it is perhaps surprising to find no significant lifetime associations between PD and depression triggered by sleep loss. It is worth noting, however, that fewer women in this sample reported depressive episodes triggered by sleep loss ($n = 93$) compared to mania triggered by sleep loss ($n = 220$), which will impact on power to detect a difference between the groups. In addition, it is possible that the mechanisms involved in triggering PD in BD women are different to women with unipolar depression. Finally, PD may be more likely to develop after exposure to chronic rather than acute sleep loss, which may not have time to

have its impact within the 6 weeks specified in the current study. In fact, previous studies examining the association between sleep and PD have used a broader onset criterion (Montgomery-Downs et al. 2010; Okun et al. 2011; Dørheim et al. 2014). However, expanding the definition of PD to include episodes that occurred within 6 months of birth did not result in significant associations between a depressive response to sleep loss and rate of PD ($\chi^2(1) = 0.006, p = 0.937$).

4.4.1 *Strengths and Limitations*

The strengths of this study are similar to those presented in Chapter 3, specifically the ability to analyse data from a large sample of parous women with BD with detailed clinical phenotype data. However, a major limitation is that the data on sleep loss triggering mood episodes were collected retrospectively at interview. It is possible that women with a history of PP over-reported that sleep loss had triggered mania due to attributing their postpartum episode(s) to sleep disruption that is typical in the perinatal period. However, I excluded women from the analyses if they had experienced manic episodes solely in relation to childbirth. Furthermore, secondary analyses provided support that this was not the major driver of the association I observed. First, if this were the case, women with PD may also over-report a depressive response to sleep loss. However, in this study, women who reported that sleep loss had triggered episodes of depression were no more likely to experience PD than those who did not report sleep loss triggering depression. Second, I performed additional analyses on a subsample of women who reported their manic episodes had *usually* been triggered by sleep loss, as opposed to on a single occasion, with the requirement that women had experienced at least three episodes of mania. This increased the likelihood that I selected a group of women with an underlying susceptibility to sleep loss triggering non-puerperal episodes of mania rather than those that occurred primarily in relation to PP. In this subsample, the association between reports of sleep loss triggering mania and PP remained,

even when controlling for potential confounders. Finally, if childbirth increases the likelihood of reporting that sleep loss triggers mood episodes, then one would expect parous women to report this more frequently than nulliparous women. However, I found that nulliparous women actually had higher rates of reporting sleep loss triggering mania than parous women.

Despite controlling for number of deliveries, age, marital status, number of manic episodes experienced and method of recruitment, it is possible that other factors which were not controlled for affected the results. These include (but are not limited to) social class, levels of family support, medication and substance use. I did not have available data on medication, substance use and levels of family support during perinatal episodes. Educational attainment and occupation could have been used as a proxy for social class but preliminary analyses revealed that these covariates were not significantly associated with reporting sleep loss as a trigger.

Another limitation is that I did not objectively measure sleep loss and relied on retrospective self-reporting. This means it is not possible to determine what level of sleep disruption women experienced around childbirth or at any other time. In addition to obtaining more detailed subjective measures of sleep, future prospective studies of pregnant women with BD should include objective measures of sleep such as actigraphy. Such prospective designs will be instrumental in establishing whether a history of sleep disruption triggering episodes of mood disorder is a clinically useful predictor of developing severe postpartum episodes.

4.4.2 Vulnerability to the Mania-Inducing Qualities of Sleep Loss

Further research on individual differences in vulnerability to sleep disturbance may provide markers of increased sensitivity to sleep loss in BD, thus allowing clinicians to predict vulnerable individuals prior to significant exposures to sleep loss. A particularly promising

area of interest is whether genetic variation (for example in circadian rhythm genes) predicts an individual's response to acute sleep loss (Benedetti et al. 2008; Benedetti and Terman 2013; Bunney and Bunney 2013). It will be of particular interest to determine whether genetic factors for vulnerability to mania following sleep loss overlap with those that predict episodes of PP in women with bipolar disorder.

4.4.3 Clinical Implications

If the findings of this study are replicated in prospective studies, a history of manic episodes triggered by sleep loss could be a potential screening question to identify pregnant women with BD at heightened risk of PP. This could help to individualise the risk of severe postpartum episodes in women with BD and potentially help with difficult decisions regarding the use of medication during the perinatal period. Furthermore, it may identify women for whom obstetric management may need to pay particular attention to sleep disruption in labour and for whom specific measures to protect sleep in the postpartum period may be indicated.

It could be argued that identifying women with BD for whom sleep loss has previously triggered episodes of mania is of limited clinical utility, given that these women are considered high risk of developing PP by virtue of having BD. However, estimates of the risk of PP vary within women with BD (Wesseloo et al. 2016) therefore the results of this study offer an opportunity to individualise risk within this group. In light of this, the finding that sensitivity to sleep loss could be associated with a two-fold increased risk of PP represents a moderate difference in risk. Understanding more about which factors can individualise risk may be helpful for women and clinicians when considering the risks and benefits of medication during pregnancy and postpartum. The finding that sensitivity to sleep loss could be associated with a two-fold increased risk further emphasises the need for services to

minimise sleep loss in this group and suggests that interventions that target sleep loss may be particularly beneficial for some women.

Nonetheless, further work is required in order to establish whether the results of this study would be helpful clinically and, if so, whether the method of assessing sensitivity to sleep loss that was used in this study would be applicable to clinical practice. For example, examination of case notes or more detailed questions on sleep and mood may be better measures of sensitivity to sleep loss. In addition, further research is required to determine whether interventions for improving sleep in women at high risk of PP are associated with decreased risk of relapse. There is preliminary evidence that cognitive behavioural therapy for insomnia (CBT-I) in pregnancy may help reduce symptoms of depression in pregnant women (Tomfohr-Madsen et al. 2017) and that CBT-I is preferred by pregnant women to medication as a treatment option for insomnia (Sedov et al. 2017). However, it remains to be seen whether this could be an option for pregnant women with BD. These issues will be discussed further in Chapter 7.

4.4.4 Future Studies

Future research needs to explore these findings further in samples with prospective data on sleep and postpartum episodes, in addition to multiple objective and subjective measures of sleep. Another important variable that was not available in this dataset was the use of medication in pregnancy and postpartum, which may have influenced the relationship between sleep and mood. Finally, future studies may also extend these findings by examining whether sleep loss triggering mania is associated with genetic factors, and whether these factors overlap with those implicated in risk for PP.

4.4.5 *Summary*

In summary, the results suggest that individual differences in vulnerability to mood dysregulation following sleep loss in BD may be a promising marker for identifying women at heightened risk of PP.

However, data were cross-sectional therefore may be subject to recall bias. I also did not have objective data on sleep disruption that had occurred during the postpartum period or prior to mood episodes. In Chapter 6, I further explore the relationship between sleep and postpartum episodes in a prospective study of pregnant women at high risk of developing PP using actigraphy (an objective measure of sleep loss).

5 TRAJECTORIES IN INSOMNIA PRIOR TO EPISODES OF HIGH MOOD:

RESULTS FROM AN ONLINE MOOD MONITORING SYSTEM

5.1 Introduction

As outlined in Chapter 1, there are numerous lines of evidence suggesting an association between sleep and mood in bipolar disorder (see section 1.6.1, Chapter 1). Seminal research in this area began with the work of Thomas Wehr and colleagues (Wehr et al. 1982; Wehr 1989; Wehr 1991) during which Wehr proposed the 'sleep reduction model of mania' (Wehr et al. 1987).

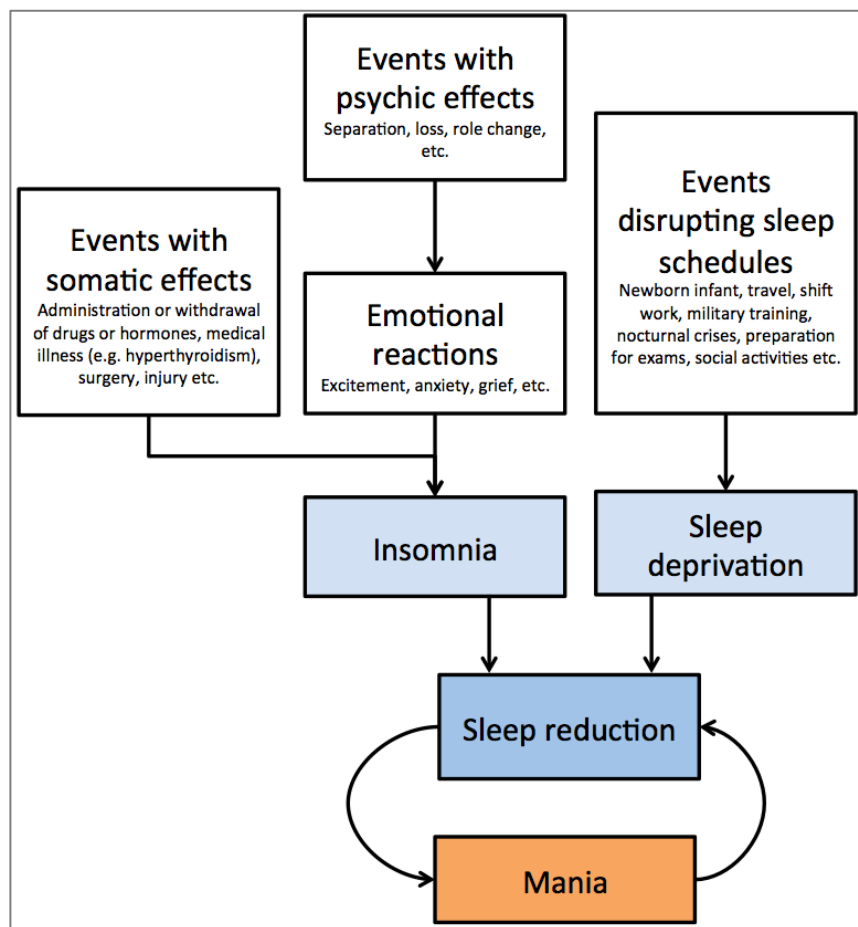


Figure 5-1. The sleep reduction model of mania (Wehr et al. 1987).

This model (Figure 5-1) proposed that the relationship between sleep and mania was bi-directional, such that sleep reduction as a result of insomnia or exogenous sleep deprivation could precipitate manic symptoms, and manic symptoms could, in turn, induce sleeplessness. The authors argued that this relationship culminates in a vicious cycle that explains the

tendency for manic episodes to escalate. Of note is that this model suggests that sleep loss can act as both a trigger and prodrome in the genesis of mania.

Evidence from (i) sleep deprivation experiments in animals and humans, and (ii) cases of mania following sleep deprivation therapy lend credence to the proposition that sleep deprivation via exogenous factors may trigger mania (e.g. Gessa et al. 1995; Colombo et al. 1999). In observational studies, however, it is more difficult to determine whether reduced sleep prior to an episode of mania is evidence of sleep loss acting as a trigger or prodrome. Regardless of whether sleep reduction does or does not 'cause' manic episodes, a pattern of sleep reduction prior to episodes of mania could be relatively easy to monitor by individuals and clinicians, and thus aid illness management.

To date, however, there are mixed findings from observational research, as some studies have found sleep reduction to be associated with subsequent depressive rather than manic symptoms (Perlman et al. 2006; Gruber et al. 2011; Talbot et al. 2012). One explanation for these findings is that, as the causes of BD are multifactorial, individuals will vary in how they respond to sleep loss; some individuals will become manic, some depressed, and others will remain euthymic. This is corroborated by research finding that only a subset of depressed bipolar patients become euthymic following total sleep deprivation therapy, whereas another subset become manic or hypomanic (Colombo et al. 1999). Likewise, if sleep reduction is a prodrome of mania, it is plausible that it may not be a prodrome for all individuals, and for some it may instead be a sign of an impending depressive episode.

This theory was supported in Chapter 3, in which I found that 20% of individuals with BD reported that sleep loss had triggered episodes of high mood, and that this was significantly more likely to be reported by women and those with BD-I (compared to those with BD-II). In addition, being female was associated with an increased likelihood of reporting that sleep loss

had triggered depression, however this finding did not persist following adjustment for confounders.

As shown in Figure 5-1, Wehr et al. (1987) also propose that sleep reduction can precipitate mania as a result of insomnia. This means that, in theory, some individuals will experience insomnia prior to episodes of mania. I explored the sleep deprivation aspect of the sleep reduction model of mania in Chapter 3, therefore in this chapter I present analyses examining the insomnia aspect of the model. In addition, as the research described in the previous chapter was limited by the use of retrospective data, in this chapter I examine these associations prospectively in individuals who completed weekly measures of their mood using an online mood-monitoring system, *True Colours*. Specifically, I examined whether there were different trajectories in sleep loss that can be observed prior to the development of mania. Specifically, this chapter aims to answer the following questions:

1: Are there groups of individuals with bipolar disorder who display different trajectories of insomnia prior to the onset of manic episodes?

The previous chapters and literature I have outlined suggest that there should be a group of individuals who experience disrupted sleep prior to episodes of mania. In the study described in this chapter, I hypothesised that a subgroup of individuals in the BDRN sample would show increasing insomnia symptoms prior to the onset of manic episodes.

2: If present, are particular insomnia trajectories associated with clinical characteristics such as bipolar subtype and gender?

In Chapter 3, I found evidence suggesting that women and individuals with BD-I are more likely to report that sleep loss triggers episodes of mania than men or individuals with BD-II.

Therefore in this chapter I aimed to explore whether gender and bipolar subtype were associated with different trajectories in insomnia prior to episodes of mania.

In addition, I examined any resultant classes for differences in the following characteristics:

- **Age:** Evidence suggests that the prevalence of insomnia increases with age (Ohayon 2002). Therefore, as there was a wide age range in the BDRN sample who completed True Colours, I examined whether individual differences in insomnia trajectories could be explained by age.
- **Symptoms of mania during the pre-illness period:** Although scores from participants were included only if they were euthymic during the pre-illness period, it is possible that reduced sleep during this time could have been the result of residual manic symptoms.
- **Symptoms of depression and presence of depressive episodes during the pre-illness period:** It is possible that insomnia symptoms occurring prior to the onset of a manic episode are the result of depressive episodes occurring during this time. This observation has previously been raised by Wehr et al:

‘...insomnia associated with depression should precipitate mania in bipolar patients. In fact, as many as half of all manic episodes are preceded by depressive episodes’
(Wehr et al. 1987 p.203).

Therefore any resulting differences in insomnia trajectories prior to episodes of mania were compared on depression symptoms in subsequent analyses.

3: Is the trajectory of insomnia symptoms prior to depressive episodes different to the trajectory observed prior to manic episodes?

Previous research has found that insomnia can increase the risk of depression in healthy individuals, and that persistent insomnia can increase the risk of depressive episodes in individuals with MDD (Franzen and Buysse 2008; Suh et al. 2013). There has been less

research examining this in individuals with BD, however, evidence to date would suggest that increasing insomnia symptoms would precede episodes of depression (Jackson et al. 2003; Perlman et al. 2006; Eidelman et al. 2010; Talbot et al. 2012).

5.2 Method

5.2.1 *The True Colours Online Mood Monitoring System*

True Colours is an online mood monitoring system that is an online version of the text based Oxford University Symptom Monitoring System (Bopp et al. 2010) developed by Professor John Geddes and colleagues at the Oxford University Department of Psychiatry (<https://oxfordhealth.truecolours.nhs.uk>), with the aim of allowing patients with BD to monitor mental wellbeing and aid illness management. The system was initially used by NHS patients within Oxford Health Foundation Trust, and was adapted for use in research settings in 2014-2015. From March 2015, participants enrolled in the Bipolar Disorder Research Network (BDRN, described in Chapter 2) were also invited (via newsletters and emails) to enrol in this version of True Colours (bdrn.org/research/true-colours/).

When enrolled in the True Colours system, participants are sent a weekly reminder email to complete two questionnaires on mood: the Altman Mania Scale (AMS) and Quick Inventory of Depressive Symptoms (QIDS) scale. These are described in detail below.

The Quick Inventory for Depressive Symptoms (QIDS)

The Quick Inventory for Depressive symptomatology (QIDS, Appendix B) is a questionnaire consisting of 16 items which correspond to the nine DSM-IV symptom criteria for major depressive episodes (low mood, poor concentration, self-criticism, suicidal ideation, anhedonia, low energy/fatigue, sleep disturbance, decrease/increase in appetite/weight, and psychomotor agitation/retardation) (Rush et al. 2003). Each item is measured on a 0-3 scale, with total scores ranging from 0-27 (see Appendix B for the algorithm used to calculate the total score). Total QIDS scores indicate varying levels of depression symptom severities based on the following ranges: 'mild' 6-10, 'moderate' 11-15, 'severe' 16-20, and 'very severe' 21-

27. The self-report version of the QIDS has demonstrated good psychometric properties and has been validated for use in bipolar samples (Rush et al. 2003; Trivedi et al. 2004; Bernstein et al. 2009). As shown in Figure 5-2, participants completed the QIDS based on how they had felt over the past week (see Appendix B for the full questionnaire).

The screenshot displays the 'True Colours' online mood monitoring system interface. At the top, the logo 'True Colours' is shown in a multi-colored font. Below it, the text reads 'Hello, you're about to take' followed by 'Depression (QIDS)' in a large, bold font. Underneath, the word 'INSTRUCTIONS' is followed by the text: 'Choose the response to each item that best describes you for the past seven days.' Below the instructions, the question 'Q5. Feeling sad' is displayed. To the right of the question is a 'Keyboard shortcuts' button. There are four response options, each with a corresponding score in a small box to its right: 'I do not feel sad' (0), 'I feel sad less than half the time' (1), 'I feel sad more than half the time' (2), and 'I feel sad nearly all of the time' (3). The option with score 3 is highlighted in green.

Figure 5-2. Welcome screen and example question from the Quick Inventory for Depression Symptomatology (QIDS) used in the True Colours online mood monitoring system.

The Altman Mania Rating Scale (AMS)

The Altman self-rating Mania Scale (AMS) (Altman et al. 1997) is a 5-item questionnaire that assesses each of 5 major symptoms of mania outlined in the DSM-IV (elevated mood, inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, and increased goal-directed activity, American Psychiatric Association 2000). The individual items for the AMS are shown in Appendix C). Each item is scored on a scale of 0 to 4, with total scores ranging from

0 to 20. Scores greater than 5 have been associated with 85.5% sensitivity and 87.3% specificity for detecting mania or hypomania (Altman et al. 1997).

True Colours

Hello, you're about to take

Mania (Altman)

INSTRUCTIONS

Choose the statement in each group that best describes the way you have been feeling for the **past week**. Please note: The word "occasionally" when used here means once or twice; "often" means several times or more; "frequently" means most of the time.

Q1. Happiness Keyboard shortcuts

- I do not feel happier or more cheerful than usual 0
- I occasionally feel happier or more cheerful than usual 1
- I often feel happier or more cheerful than usual 2
- I feel happier or more cheerful than usual most of the time 3
- I feel happier or more cheerful than usual all of the time 4

Figure 5-3. Welcome screen and example question from the Altman Mania Scale used in the True Colours online mood monitoring system.

Participants were able to view their current and previous answers to the QIDS and AMS online. Appendix E shows screenshots of True colours and the example graphs available to participants.

5.2.2 Sample

The sample presented in this chapter were participants with a diagnosis of type 1 or type 2 bipolar disorder (BD-I or BD-II, respectively) who were enrolled in the Bipolar Disorder Research Network (BDRN). Recruitment and assessment of this sample has been described in Chapter 2. The analyses presented in this chapter were conducted on data from BDRN participants who were enrolled in True Colours from 4 March 2015 to 3 February 2017.

During this time, 692 participants with a diagnosis of BD-I (n=429, 62%) or BD-II (n=263, 38%) completed the online mood monitoring system. This resulted in an initial dataset of 39,749 observations made over an average of 56 weeks (range 1 to 100 weeks).

5.2.3 Data Preparation

Data were downloaded from the True Colours server in February 2017. Initial data processing was conducted using a script prepared in R version 3.2.2 (R Core Team 2017), which was prepared with the help of Dr Katherine Tansey (Cardiff University).

Participants were sent a reminder email to complete the questionnaires each week, however, participants were able to log on to the system and complete the questionnaires at any time. This meant that some participants had responses in close succession (i.e. 1 or 2 days after the previous entry). To ensure that responses related to at least the majority of a preceding week, the R script specified that responses had to be a minimum of 4 days apart. This resulted in excluding 1.94% of the 39,749 responses, resulting in a final dataset of 38,994 responses. Out of the remaining responses, the average interval between responses was 7.13 days (SD = 1.16) with a range of 4-28 days. As shown in Table 5-1, 88% of responses occurred 6 to 8 days after the previous response, and 94% of all responses occurred 5-9 days after the previous response.

Table 5-1. Number of days between participant entries on the True Colours system.

Interval between entries	Percentage of responses in dataset (n = 38,994)
7 days	67.3
6 - 8 days	88.1
5 - 9 days	94.4
4 - 10 days	97.9
> 10 days	2.0

5.2.4 *Identifying Mood Episodes*

The presence of mood episodes was estimated based on two criteria:

- (1) A weekly summary score that was above a specified threshold, and
- (2) A specified duration for the above threshold score.

These criteria are described in more detail below.

Thresholds for Mood Episodes

The score thresholds for episodes of high and low mood were chosen based on the psychometrically validated threshold scores for the AMS and QIDS outlined in section 5.2.1 and previous work by the Oxford University True Colours research team (Bopp et al. 2010; Palmius et al. 2016). Specifically, AMS total scores that exceeded 5 were chosen as an index of hypomania or mania, and scores of 11 or more on the QIDS were chosen as indicators of moderate to very severe depression.

Duration of Episodes

The weekly scores for the AMS and QIDS do not assess duration, therefore to increase the probability that the duration criteria for an episode of (hypo)mania had been met (i.e. at least 4-7 days), AMS scores had to be above threshold for a minimum of two consecutive weeks. This increased the probability that symptoms had been present for at least one week. Likewise, as the DSM-IV duration criteria for major depressive episodes is at least 2 weeks, the total QIDS score had to be above-threshold for a minimum of 3 consecutive above-threshold weeks.

5.2.5 *Extracting Data Prior to Episode Relapse*

Once an episode that met the aforementioned criteria was identified, the R script extracted 4 weeks of data that had occurred prior to the episode onset, in order to allow examination of

trajectories in insomnia symptoms. To ensure that participants were euthymic during this time, participants whose scores were above threshold (i.e. had an AMS score greater than 5 or QIDS score greater than 10) for any duration in the weeks prior to mood episode were excluded. Out of the 692 participants enrolled in True Colours, 153 participants met these criteria for episodes of high mood, and 94 met these criteria for episodes of low mood.

Descriptives of the participants who met these criteria is detailed in Table 5-2.

Table 5-2. Descriptives of participants enrolled in True Colours who met symptom and duration criteria for likely episodes of high mood or low mood.

	High Mood	Low Mood
Total N who met criteria	153	94
Diagnosis, n (%)	BD-I: 91 (59.5) BD-II: 62 (40.5)	BD-I: 53 (56.4) BD-II: 41 (43.6)
Gender, n (%)		
Male	50 (32.7)	24 (25.5)
Female	103 (67.3)	70 (74.5)
Age, years	Mean 52.81 (SD 10.03) Median 53.00 Range 30-78	Mean 51.89 (SD 11.02) Median 52.00 Range 26-80
Response interval, mean (SD)	7.3 days (1.6 days)	7.0 days (1.1 days)
Response interval (% of responses)	7 days (60.3) 6 – 8 days (84.4) 5 – 9 days (91.5) 4 – 10 days (95.1)	7 days (64.3) 6 – 8 days (90.1) 5 – 9 days (97.0) 4 – 10 days (98.5)

5.2.6 Measuring Insomnia

The QIDS includes 4 items that assess sleep disturbance: initial insomnia, middle insomnia, terminal insomnia and hypersomnia. As the main aim of this chapter was to examine changes in insomnia that occur prior to episode relapse, I analysed data on initial, middle and terminal insomnia. The questions on these items are shown in Table 5-3.

Table 5-3. QIDS insomnia items and responses.

Question	Response (score)
Q1. Falling asleep [initial insomnia]	I never take longer than 30 minutes to fall asleep (0)
	I take at least 30 minutes to fall asleep, less than half the time (1)
	I take at least 30 minutes to fall asleep, more than half the time (2)
	I take more than 60 minutes to fall asleep, more than half the time (3)
Q2. Sleep during the night [middle insomnia]	I do not wake up at night (0)
	I have a restless, light sleep with a few brief awakenings each night (1)
	I wake up at least once a night but I go back to sleep easily (2)
	I awaken more than once a night and stay awake for 20 minutes or more, more than half the time (2)
Q3. Waking up too early [terminal insomnia]	Most of the time, I awaken no more than 30 minutes before I need to get up (0)
	More than half the time, I awaken more than 30 minutes before I need to get up (1)
	I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually (2)
	I awaken at least one hour before I need to, and can't go back to sleep (3)

QIDS, Quick Inventory of Depressive Symptomatology questionnaire (Rush et al. 2003)

Cross-product correlations between the insomnia items within the sample revealed that they were significantly correlated, with spearman correlation coefficients greater than 0.3 (see Table 5-4) and a Cronbach's alpha of 0.90.

Table 5-4. Correlations between QIDS insomnia items.

	Initial Insomnia	Middle Insomnia	Terminal Insomnia
Initial Insomnia	1.00		
Middle Insomnia	0.33***	1.00	
Terminal Insomnia	0.40***	0.44***	1.00

***p < .001, QIDS, Quick Inventory of Depressive Symptomatology questionnaire (Rush et al. 2003)

Given these associations, the items were summed to provide a total 'insomnia' score with possible scores ranging from 0 to 9. The insomnia score was calculated for each of the four weeks identified prior to the onset of mood episodes.

5.2.7 Statistical Analysis: Latent Growth Mixture Modelling

Following extraction of the relevant data using the methods described above, Growth Mixture Modelling (GMM) was used to examine trajectories in insomnia observed in the month prior to relapse. GMM is a statistical technique in which individuals are probabilistically assigned to categories (i.e. latent classes) based on intraindividual change over time (Jung and Wickrama 2008). Differences between individuals can then be explored based on class membership. Therefore, GMM is a person-centred statistical approach (in contrast to more traditional variable-centred approaches, Jung and Wickrama, 2008).

Determining the number of classes is an iterative process, in which a k-class model is tested (i.e. a model with one class) followed by models with k+1 classes. Each model is assessed by examining the following statistics (Berlin et al. 2014):

- *Log-likelihood*: values closer to 0 indicate a better model fit.
- *Bayesian information criterion (BIC)*: lower values indicate better model fit.
- *Entropy*: an index of classification accuracy ranging from 0 to 1. Values of at least 0.80 are preferable.

Models are also compared using likelihood ratio tests and bootstrapping procedures to determine whether a k+1 class solution provides a significantly better model fit than a k-class solution. The Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR-LRT) and Bootstrap likelihood ratio test (BLRT) were used in these analyses.

The optimum number of classes was informed by the statistics described above, theory and model parsimony (Bauer and Curran 2003). Missing data were handled using full information maximum likelihood estimation and all GMM analyses were conducted in Mplus version 7 (Muthén and Muthén 2012).

Differences Between Classes

Upon identifying an optimal class solution, differences between classes were tested in Mplus using pseudo-class Wald tests of equality of means. These tests use posterior probability-based multiple imputation in order to account for the fact that each individual will have a different probability of belonging to each of the resultant classes (Asparouhov and Muthén 2014).

5.3 Results

5.3.1 *Insomnia Trajectories Prior to Episodes of High Mood*

Out of the 153 participants, 8 had data missing at all 4 pre-illness weeks, therefore the final analysis was conducted on 145 participants. Figure 5-4 outlines the average insomnia trajectory in the sample prior to the onset of an episode of high mood.

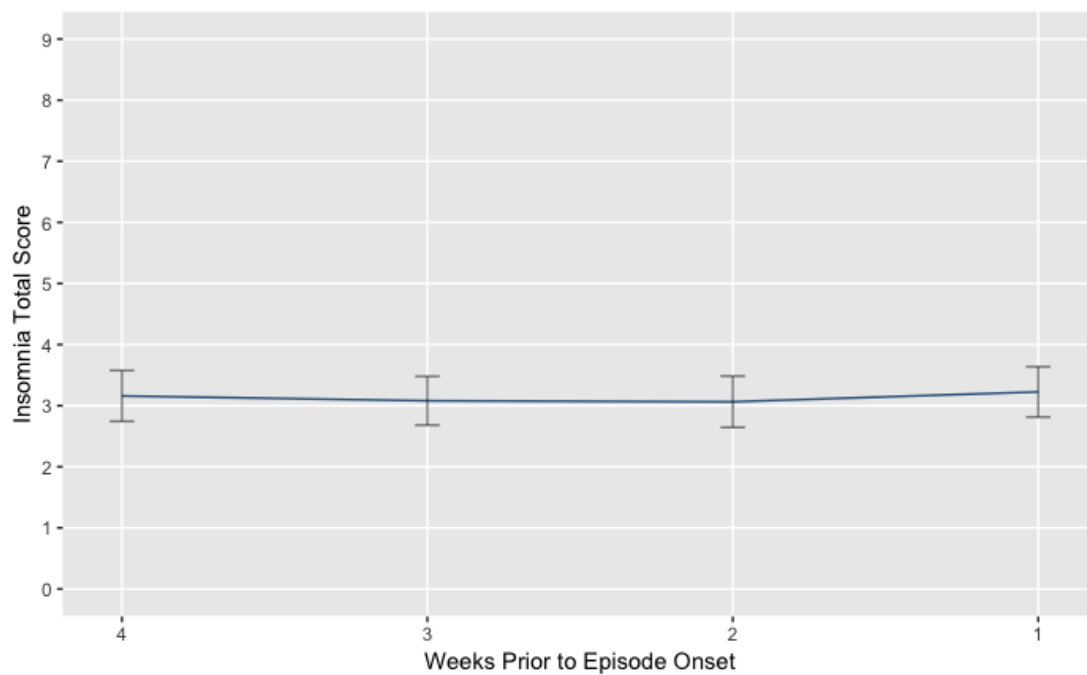


Figure 5-4. Mean insomnia score in weeks prior to episode of high mood. Error bars represent 95% confidence intervals.

Table 5-5 outlines the model fit statistics for each of the k class models that were tested using growth mixture modelling. The information in Table 5-5 (combined with assessment of the classes based on theory and parsimony) indicated that a 3-class solution of insomnia trajectories represented the best model fit, with the following model fit indicators:

- Classification accuracy (i.e. entropy) greater than 0.80 (0.85).
- Bayesian Information Criterion = 1963.477

- Vuong-Lo-Mendell-Rubin likelihood ratio test, $p = 0.017$ and Bootstrap likelihood ratio test, $p < .001$ compared to a 2-class solution.

Table 5-5. Model selection criteria to determine trajectory classes of insomnia prior to episodes of high mood.

Model	Log likelihood	BIC	VLMR-LRT	BLRT	Entropy
1-class	-977.000	1978.883	---	---	---
2-class	-964.435	1973.660	0.2711	< .001	0.873
3-class	-949.390	1963.477	0.0174	< .001	0.845
4-class	-941.378	1967.361	0.4438	0.020	0.845

BIC, Bayesian Information Criterion, VLMR-LRT, Vuong-Lo-Mendell-Rubin likelihood ratio test, BLRT, Bootstrap likelihood ratio test.

In addition, as shown in Table 5-5, the 4-class solution did not appear to represent a better model fit than the 3-class solution, as evidenced by:

- A higher Bayesian Information Criterion value (1967.361) than the 3-class solution.
- Vuong-Lo-Mendell-Rubin likelihood ratio test, $p = 0.44$ compared to the 3-class solution.

As shown in Figure 5-5, the classes identified for the 3-class solution were: (1) *low insomnia* ($n = 113, 78\%$) in which insomnia scores were consistently low throughout in the euthymic period, (2) *high insomnia* ($n = 24, 17\%$) in which insomnia score were consistently high during the euthymic period and (3) *increasing insomnia*, in which symptoms were initially low but increased throughout the pre-illness period ($n = 8, 6\%$).

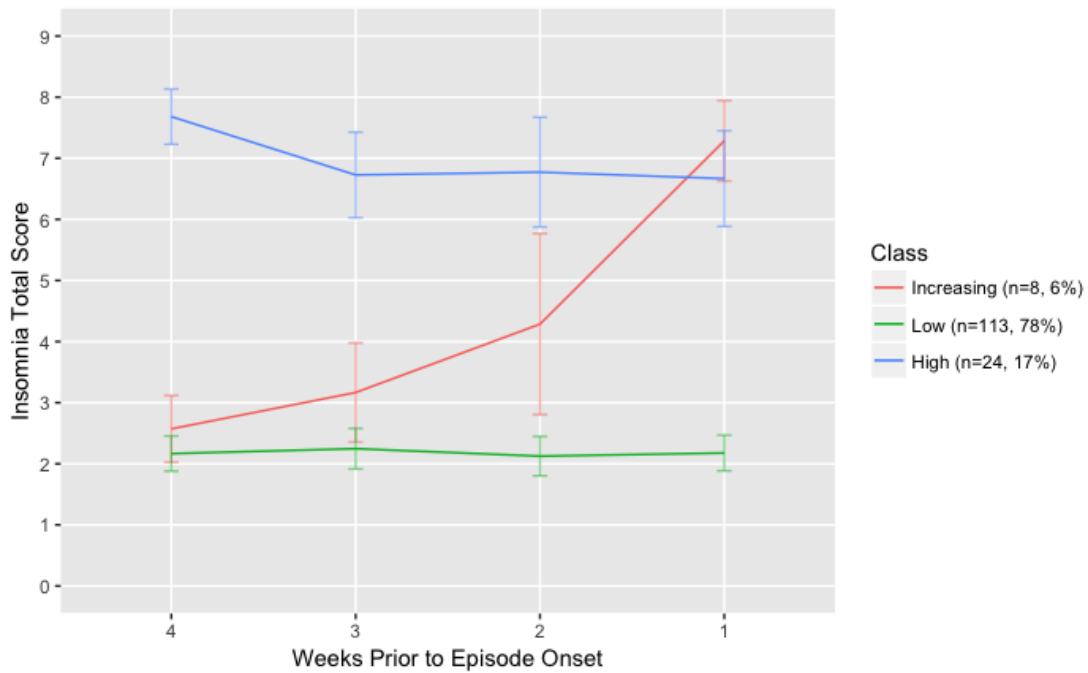


Figure 5-5. Mean insomnia scores prior to episodes of high mood, split by class. Error bars represent 95% confidence intervals.

5.3.2 Predictors of Insomnia Class Membership Prior to Episodes of High Mood

Bipolar Diagnosis and Gender

Results from Chapter 3 suggested that individuals with BD-I and women may be more likely to experience disturbed sleep prior to episodes of high mood, therefore I tested the groups to determine whether the increasing or high insomnia groups were more likely to include women and individuals with BD-I.

Pseudo-class Wald Chi-square tests revealed no significant differences between the classes in bipolar diagnosis ($\chi^2(2) = 1.98, p = 0.372$, see Figure 5-6) or gender ($\chi^2(2) = 0.566, p = 0.754$, see Figure 5-7).

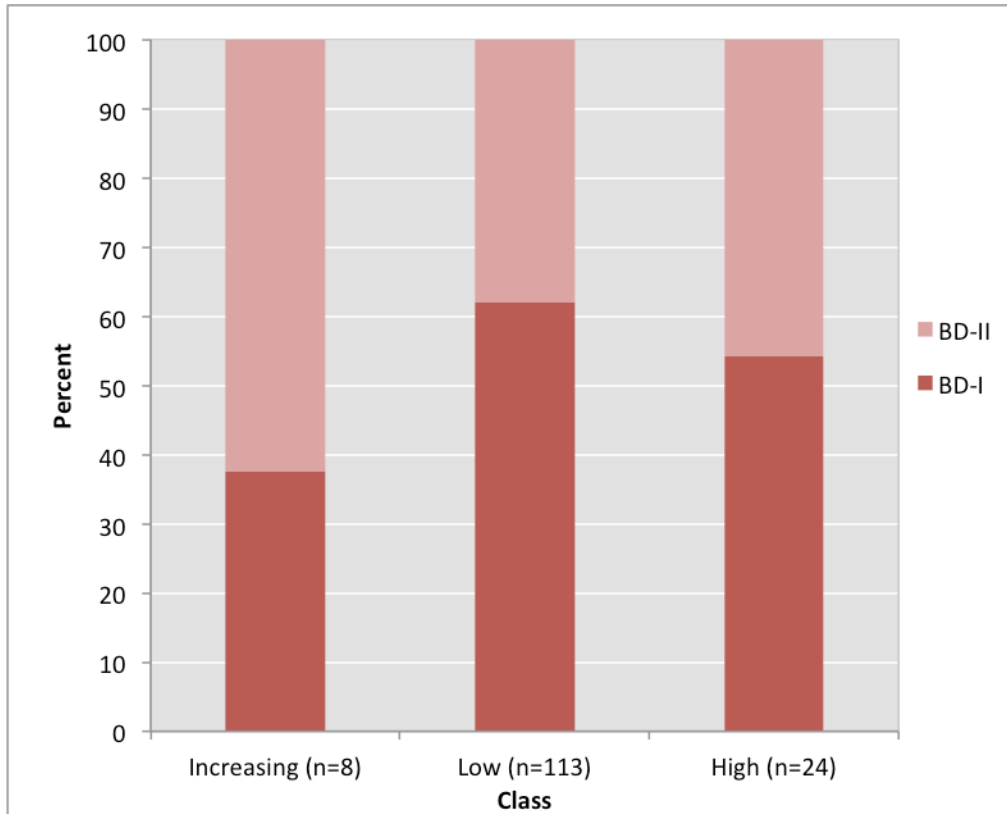


Figure 5-6. Insomnia trajectory class split by bipolar diagnostic subtype (BD-I, bipolar-I disorder, BD-II, bipolar-II disorder).

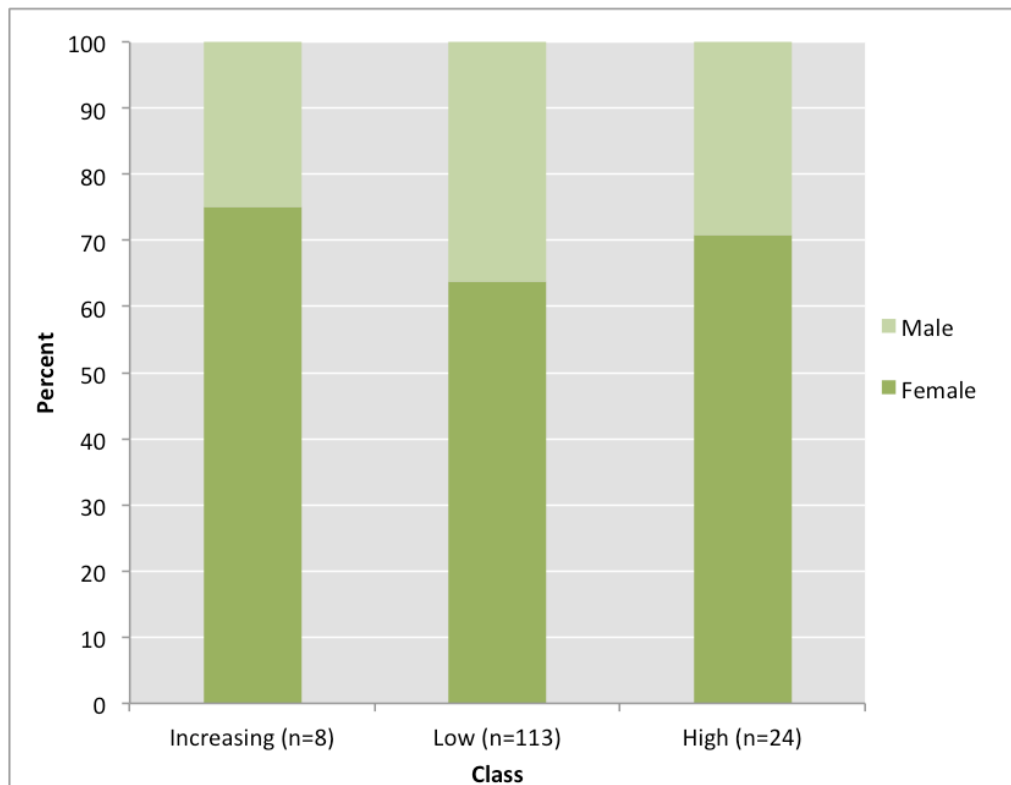


Figure 5-7. Insomnia trajectory class split by gender.

Age

As shown previously in Table 5-2, there was a wide age range in this sample and, given that old age is associated with a higher likelihood of insomnia, it is possible that the high or increasing insomnia classes were more likely to include older participants. However, a Pseudo-class Wald Chi-square test revealed no significant differences in age ($\chi^2(2) = 4.726$, $p = 0.094$) across the classes (see Table 5-6).

Table 5-6. Descriptives of age split by insomnia trajectory class.

	Class		
	Increasing (n=8)	Low (n=113)	High (n=24)
Mean (SD)	56.86 (10.30)	51.53 (9.89)	56.45 (9.98)
Median	52.00	52.00	58.50
Range	43-70	30-78	32-70

AMS Summary Scores in the Pre-Illness Period

It is possible that participants in the high or increasing insomnia classes were also more likely to display increasing residual manic symptoms during this time, therefore I compared the classes on AMS symptom scores during the pre-illness weeks. Figure 5-8 shows the AMS symptoms in the pre-illness weeks, split by class.

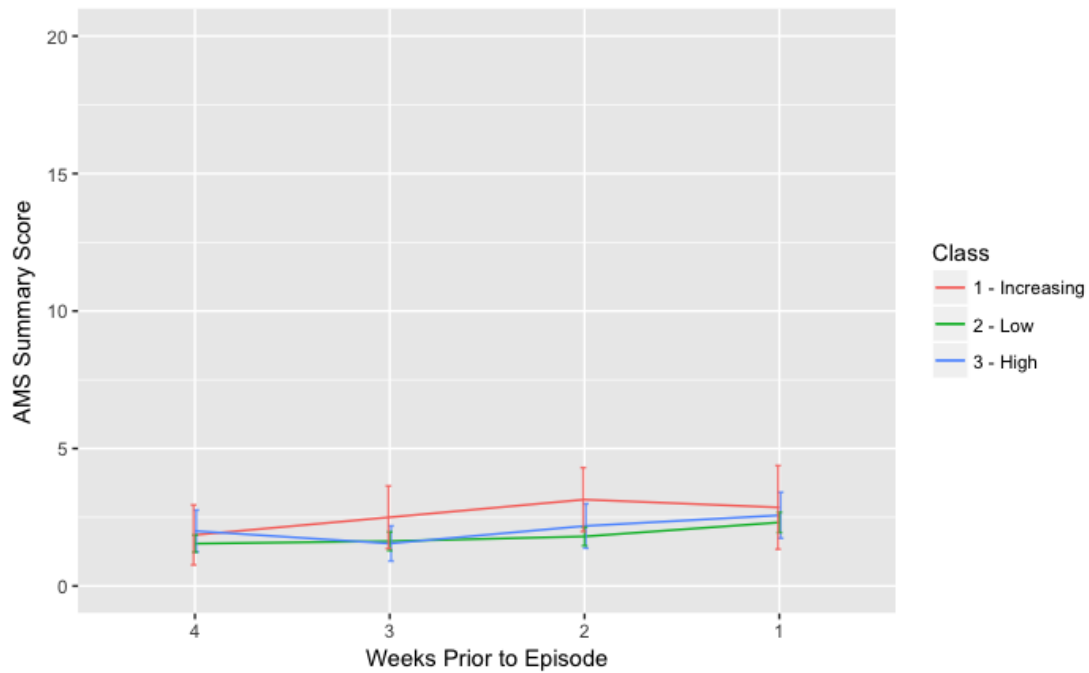


Figure 5-8. Mean Altman Mania Scale (AMS) scores prior to episodes of high mood. Error bars represent 95% confidence intervals.

A pseudo-class Wald test revealed that there were no significant differences in AMS summary scores between the classes ($\chi^2(2) = 1.43, p = 0.489$).

AMS Reduced Need for Sleep Score in the Pre-Illness Period

Despite there being no significant differences in AMS summary scores, it is possible that the insomnia groups showed corresponding differences in the 'reduced need for sleep' item of the AMS (see Appendix C). Figure 5-9 illustrates average scores for the 'reduced need for sleep' item of the AMS (with a score ranging from 0 to 3) during the pre-illness period according to class membership. A pseudo-class Wald test revealed that there were no significant differences in AMS 'reduced need for sleep' scores in the pre-illness period ($\chi^2(2) = 4.98, p = .083$).

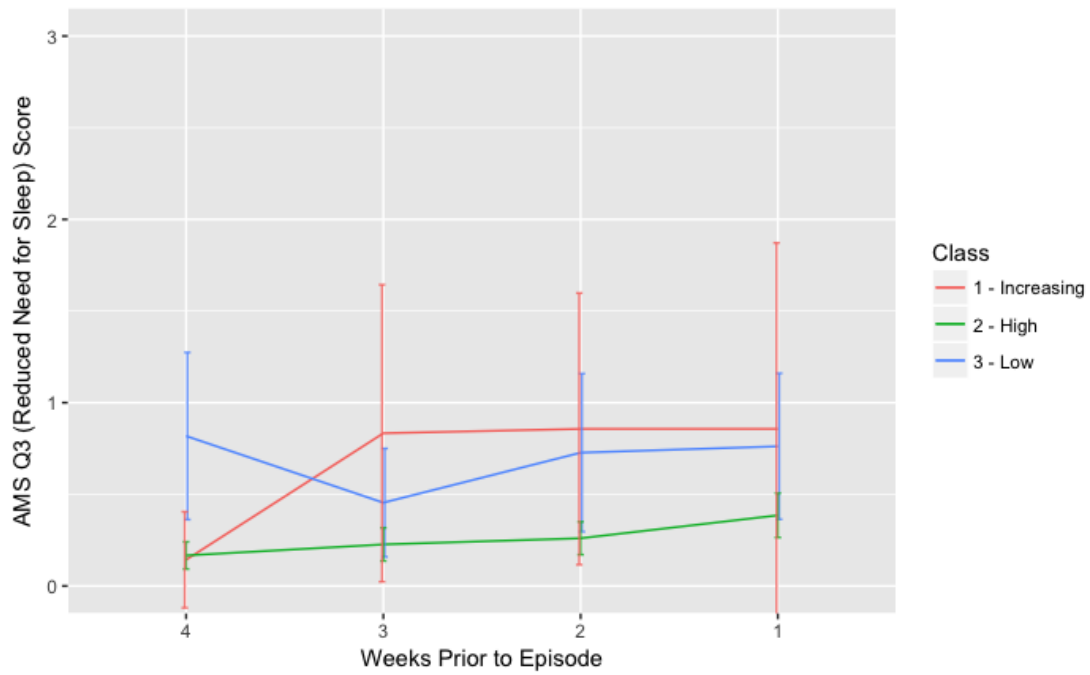


Figure 5-9. Average scores on the ‘reduced need for sleep’ item of the AMS. Error bars indicate 95% confidence intervals.

QIDS Total Scores in the Weeks Prior to an Episode of High Mood

A pseudo-class Wald test revealed that the distribution of QIDS summary scores (minus insomnia items) in the pre-illness period were significantly different across classes ($\chi^2(2) = 10.356, p = .006$), with a significant difference between Class 2 (‘Low insomnia’) and Class 3 (‘High insomnia’) ($\chi^2(1) = 10.441, p = .001$).

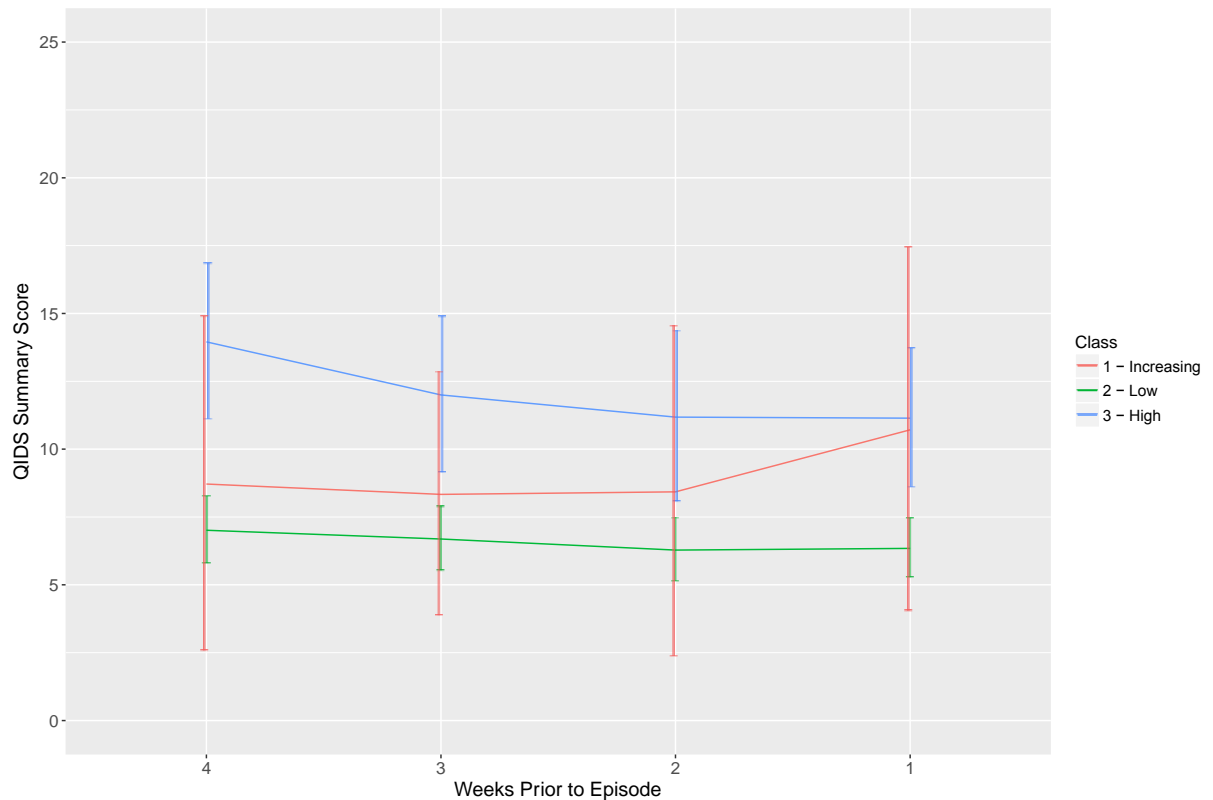


Figure 5-10. Average QIDS summary scores (minus insomnia items) by class during 4 weeks prior to an episode of high mood. Error bars indicate 95% confidence intervals.

Examination of the QIDS total scores in the weeks prior to the episodes revealed that 21.4% of the sample met criteria for an episode of low mood (i.e. reported QIDS scores > 10 for at least 3 consecutive weeks) during the 4 weeks prior to the episode of high mood.

A pseudo-class Wald test revealed that the proportion of participants who met criteria for a depressive episode during the pre-illness period was significantly different across classes ($\chi^2(2) = 8.76, p = .013$), with a significant difference between Class 2 ‘Low insomnia’ and Class 3 ‘High insomnia’ ($\chi^2(1) = 8.89, p = .003$), with 46% of the ‘high insomnia’ class meeting criteria for a depressive episode compared to 16% in the ‘low insomnia’ class.

5.3.3 Insomnia Trajectories Prior to Episodes of Low Mood

Of the 94 participants who met the criteria outlined in section 5.2.5, 12 had missing data at all 4 weeks prior to episode onset, therefore the analysis was conducted on the 82 participants.

Figure 5-11 outlines the average insomnia trajectory in the sample prior to the onset of episodes of low mood.

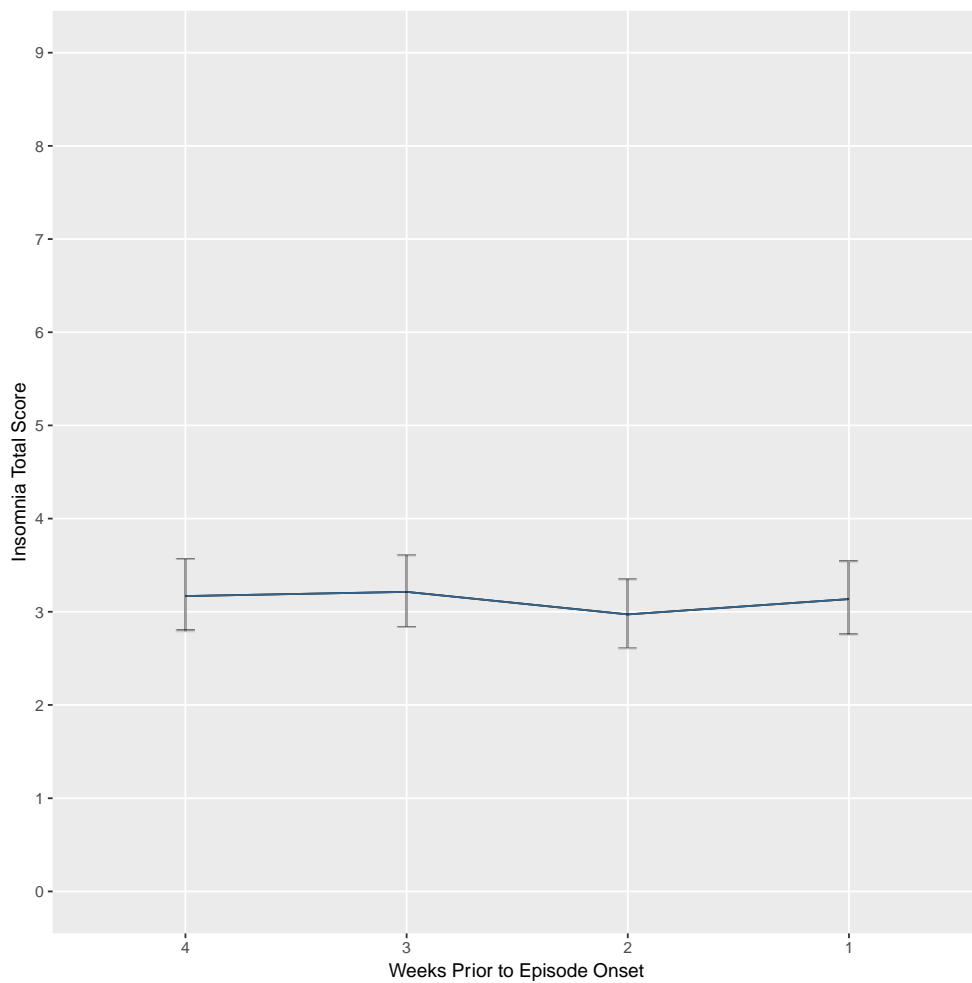


Figure 5-11. Average trajectory in insomnia severity over 4 weeks preceding episodes of low mood. Error bars represent 95% confidence intervals.

As shown in Table 5-7, the model fit statistics for each of the k+1 models did not appear to provide better solutions to the data than a 1-class solution. Specifically, (1) the BIC value increased for each additional class, (2) the 3-class and 4-class solutions did not show

significantly better fit than a 2-class or 3-class solution, respectively, and (3) although the VLMR-LRT and BLRT tests were significant, inspection of the 2 classes revealed that one class consisted of only one individual.

Table 5-7. Model selection criteria to determine trajectory classes of insomnia prior to episodes of low mood.

Model	Log likelihood	BIC	VLMR-LRT	BLRT	Entropy
1-class	-538.341	1098.716	---	---	---
2-class	-529.754	1099.169	0.0017	0.0000	0.989
3-class	-525.948	1109.184	0.3528	0.2500	0.883
4-class	-522.736	1120.386	0.7431	0.6667	0.760

BIC, Bayesian Information Criterion, VLMR-LRT, Vuong-Lo-Mendell-Rubin likelihood ratio test, BLRT, Bootstrap likelihood ratio test.

5.4 Discussion

The aim of this chapter was to examine the prospective association between sleep disturbance and episode relapse in individuals with bipolar disorder. Specifically, I examined trajectories in symptoms of insomnia prior to episodes of high mood and low mood. The three questions that I aimed to address are discussed below.

Are there different trajectories in insomnia prior to the onset of manic episodes?

The results indicate that individuals with bipolar disorder can be grouped into three classes based on their insomnia trajectories: 'low insomnia', where insomnia symptoms remain low (e.g. low scores on insomnia questions in the weeks prior to episodes); 'high insomnia', where insomnia symptoms are consistently high prior to episodes; and 'increasing insomnia' where insomnia symptoms start low but increase in the weeks prior to manic episodes. The majority of individuals were in the 'low insomnia' class (78%), with 6% in the 'increasing insomnia' class and 17% in the 'high insomnia' class. These results suggest that there are distinguishable patterns in sleep disturbance prior to episodes of mania.

Few other studies have reported on the proportion of bipolar individuals who experience sleep disturbance prior to episodes of high mood. In a systematic review, which comprised over 1100 participants, Jackson et al. (2003) reported that a median of 77% of bipolar individuals report sleep loss as a prodromal symptom of mania. This figure is considerably higher than that observed in the present study, however the authors conceded that the studies included in the systematic review varied considerably in methodologies and relied primarily on retrospective data (Jackson et al. 2003). In addition, 'sleep loss' is a broad term that can encompass both symptoms of insomnia and sleep loss incurred through other

factors (e.g. shift work), whereas the results of the present study consider only symptoms of insomnia.

In studies which have examined the rates of mania and hypomania in individuals receiving total sleep deprivation therapy for depression, the rates of switching from depression into hypomania or mania range from 5-29% (Wu and Bunney 1990; Kasper and Wehr 1992; Colombo et al. 1999). These figures are more consistent with the results of the present study, but the studies are not directly comparable, given that they assessed rates of switching into mania that occurred following sleep deprivation, and in these cases all patients were depressed. Furthermore, prodromal insomnia may have different psychological and physiological sequelae to sleep deprivation imposed in a therapeutic setting.

An additional point that warrants further exploration is the characteristics of the 'high insomnia' group. It is possible that, for these participants, high levels of insomnia signalled the impending onset of episodes of high mood. Conversely, it is possible that these individuals always experienced this level of sleep disturbance and continued to do so after the episode of high mood abated. Sleep disturbance for longer periods before and after episodes could be explored in future work on these data.

Chapter 3 of this thesis found that 20% of individuals with BD reported that sleep loss had triggered episodes of high mood, therefore the results of this chapter, in which 6% report increasing insomnia symptoms prior to episodes of high mood, could be interpreted as weaker evidence for the role of sleep loss as a pathway to mania. Whilst this may be correct, it is also worth considering that the results of Chapter 3 considered lifetime triggers of mania, whereas the results of this chapter examine sleep loss occurring prior to one episode. Therefore, one would expect a lower proportion of participants to report sleep loss prior to episodes of high mood when examining one mood episode compared to all those

experienced in a participant's lifetime. Furthermore, the definition of a 'mood episode' differed in this study, and subsequent research might wish to use more robust measures of mood episodes than scores on questionnaires.

Are particular insomnia trajectories associated with clinical characteristics such as bipolar subtype and gender?

The insomnia classes did not differ according to bipolar subtype, gender, age or AMS symptom scores during the pre-illness period. However, the classes significantly differed on QIDS symptom scores, with individuals in the high insomnia group demonstrating significantly higher QIDS symptom scores compared to individuals in the low insomnia group, even when removing insomnia items from the QIDS summary score. Further examination of these scores revealed that the high insomnia group were also more likely than those in the low insomnia group to meet criteria for a depressive episode during this time.

This is in accordance with the sleep reduction model of mania, in which Wehr hypothesises that insomnia that occurs as a result of depressive symptoms could precipitate mania in some bipolar individuals (Wehr et al. 1987). Future analyses could aim to delineate whether insomnia predicts episodes of mania over and above depressive symptoms within this sample, as has been done in studies of patients with MDD (Franzen and Buysse 2008). However, the 'low' and 'increasing' insomnia subgroups had small sample sizes, which compromised power to detect differences between the subgroups, therefore these results need to be replicated in larger samples before conclusions can be made.

Is the trajectory of insomnia symptoms prior to depressive episodes different to the trajectory observed prior to manic episodes?

In contrast to episodes of high mood, the analyses did not suggest more than one insomnia trajectory prior to episodes of low mood. This trajectory was consistently low, with an average of 3 out of a possible 9 on the insomnia scale during the pre-illness period. This finding is in contrast to research finding that reduced sleep duration is associated with subsequent depression (Perlman et al. 2006; Talbot et al. 2012; Gershon et al. 2017). However, it should be noted these analyses were conducted on a sample of 82 participants, therefore were likely underpowered. Future analyses could aim to rerun the analyses in a larger sample.

5.4.1 *Strengths and Limitations*

There are a number of strengths of this study. First, this is one of the first studies to examine prospective associations between insomnia and relapse in bipolar disorder. Despite evidence that sleep loss is both a prodromal symptom and trigger of mania (Wehr et al. 1987; Jackson et al. 2003), few studies have examined the relationship between sleep and mood in a prospective sample. Second, data were collected over an extensive period, spanning an average of 56 weeks, with mood ratings collected at weekly intervals. Third, the findings highlight the importance of recognising heterogeneity in sleep loss that may occur prior to episodes of high mood. Specifically, the analysis lent credence to the theory that only a subgroup of individuals display sleep loss as a pathway to mania. Finally, although weekly mood symptoms were completed online, information on diagnoses were derived from rich clinical data collected via diagnostic interviews and case notes.

However, the findings of this chapter need to be considered in light of the following limitations. First, the option for participants to answer the mood questionnaires at any time point resulted in unequal intervals between entries, which will have introduced additional error within the analyses. However, the rate of compliance with providing weekly mood ratings was high, with 94% of all responses occurring 5-9 days after the previous response. Future analyses in large samples may attempt to model this variation through the use of a latent variable.

Second, a major limitation of secondary analyses which compared classes is the small sample sizes within the derived classes (e.g. $n=8$). This means that the results for class comparisons need to be interpreted with caution, as they are likely to be underpowered to detect differences between the classes. Power calculations indicate that a larger sample size would be required in order to make adequately powered comparisons between the classes. For example, based on the effect size achieved in this study, analyses with 80% power to detect whether individuals with BD-I (or BD-II) are overrepresented in particular classes would require a minimum sample size of 62 participants in each class (see Appendix F for the method used to calculate sample sizes). Until this is achieved it is not possible, therefore, to reliably interpret the results of class comparisons.

Third, the AMS may not be the optimum measure of 'high mood' episodes, as it does not assess other symptoms of mania such as irritability, racing thoughts, distractibility, and excessive involvement in pleasurable activities with high potential for painful consequences. In addition, the threshold of a score of 5 or more may have been too liberal a criterion for manic episodes. This may explain why, using this criterion, more participants in the sample met criteria for (hypo)manic episodes than depressive episodes (see Table 5-2).

Finally, of note is that the sample consisted of a wide age range, with an average age of 52-53 in both samples. Although further analyses did not reveal significant differences in age between the samples, it would be prudent to attempt to replicate the results in younger samples. In addition, it was not possible to adjust results for the effects of medication, as these data were not collected as part of this version of the True Colours system. However, a study by Sylvia and colleagues (Sylvia et al. 2012) on the relationship between sleep duration and course of illness in BD found that only anticonvulsants were associated with reduced sleep duration, with no significant associations found with other medications such as lithium or atypical antipsychotics. Nevertheless, routine collection of medication via the True Colours system would be beneficial for disentangling the relationship between sleep and mood.

5.4.2 Future Research

Aside from the aforementioned recommendations, future research could improve upon the current study through the following:

1. **Increasing the sample size:** Aside from recruiting more participants or waiting for more participants to experience episode recurrence, other methods to increase the sample size might involve using less stringent criteria for mood episodes (e.g. requiring only one week instead of two weeks above threshold) or the pre-illness period.
2. **Further exploration of the insomnia classes:** It is possible that individuals in the 'high insomnia' class experienced high levels of insomnia both prior to and following the 4-week pre-illness period. It would be interesting to explore whether these individuals experience persistently high sleep disturbance prior to, during and following episodes of high mood.

3. **Utilising other statistical methods:** Selecting data prior to one episode per participant may be limited due to not being able to make use of the full data for each participant – other statistical methods for intensive longitudinal data may provide additional insight into the relationship between sleep and mood (e.g. multilevel modelling, cross-lagged panel models, dynamic structural equation models).
4. **Frequency and characteristics of sleep and mood measures:** In this study, ratings for insomnia symptoms and mood were made on a weekly basis. Previous research suggests that the time lag between sleep and mood may be best observed using daily measures (Leibenluft et al. 1996; Bauer et al. 2006). Furthermore, other types of sleep disturbance in addition to insomnia may display different relationships with subsequent mood episodes (e.g. hypersomnia for depression, acute versus chronic sleep deprivation).

5.4.3 *Conclusions*

In summary, the results in this chapter support the theory that only a subgroup of individuals with BD will display sleep disturbances prior to the onset of manic episodes. The results suggest that high or increasing levels of insomnia may be a more useful prodrome for detecting the onset of manic, rather than depressive episodes. However, the analyses presented here are of limited statistical power to examine the characteristics of the identified subgroups, and need to be further explored in larger samples that include at least 62 participants in each subgroup. Nonetheless, the results highlight the importance of considering both intra- and interindividual variation in sleep prior to episodes of high mood. If replicated in larger samples, further characterisation of individuals who are at a heightened risk of relapse following sleep disturbance may help illness management and prevention.

6 USING ACTIGRAPHY TO MEASURE SLEEP DISTURBANCE IN PREGNANT

WOMEN AT HIGH-RISK OF POSTPARTUM PSYCHOSIS

6.1 Introduction

Previous chapters highlighted the relevance that sleep research may have for predicting and preventing postpartum psychosis (PP). In Chapter 4, I analysed data from the Bipolar Disorder Research Network (BDRN) sample on parous women with bipolar disorder (BD). These results suggest that a history of sleep loss triggering episodes of high mood (i.e. sensitivity to sleep loss) may indicate increased risk of developing PP. However, these results were limited by the retrospective nature of data collection, therefore may have been subject to recall bias. Furthermore, as measures of sleep loss were not available for these data, it was not possible to determine what level of sleep loss women in this sample had been exposed to.

The next step in this area of research, therefore, is to explore these findings using prospective measurements of sleep and subsequent mood episodes in the perinatal period. In this chapter, I will first outline existing research in this area, followed by a description of the use of actigraphy for this area of research. I will end this section by describing the aims for this chapter.

6.1.1 Prospective Studies of Sleep and Risk of Postpartum Psychosis

To date, only two studies have examined the prospective relationship between perinatal sleep and PP. First, Sharma and colleagues compared the obstetric records of 21 women admitted to hospital with PP to matched controls (Sharma et al. 2004). They found that women with PP had experienced significantly longer labours and were also more likely to give birth at night (defined by the authors as a delivery occurring between 12:30am and 7:30am). However, this study inferred sleep loss based on the timing and duration of labour, and did

not measure sleep directly. It also did not consider sleep patterns in the days or weeks preceding labour.

Second, Bilszta and colleagues (Bilszta et al. 2010) asked 23 women at high-risk of PP (i.e. with a history of BD and/or PP) and 15 healthy controls to record their sleep during pregnancy and the postpartum period using sleep diaries. The authors reported no significant differences in sleep parameters between the high-risk and control groups, but reflected that 80% of women in the high-risk group were taking medication, and that this group's past experiences with PP may have made them hyper-vigilant to minimise any potential triggers of mood episodes.

There is evidently a need for more studies in this area and the existing studies have a combined sample size of 80 women (44 with PP), thus limiting power and generalisability. Furthermore, both studies used healthy controls as the comparison group, therefore are of limited use for individualising risk within women who are already at high risk of developing PP (i.e. women with a history of PP or diagnosis of BD). It was not possible for Bilszta and colleagues to compare sleep parameters between women who did and did not relapse in the high-risk group because only 3 out of 23 women in this group relapsed). Comparing women who do and do not experience episode recurrence is crucial for understanding what factors precipitate PP in high-risk women. It is therefore necessary to examine whether changes in sleep patterns could be used as a risk marker *within* women at high risk of PP.

Furthermore, neither study used objective measures of sleep. The study by Sharma and colleagues inferred sleep loss based on the timing and length of labour, whereas the study by Bilszta et al. used sleep diaries. Currently available objective measures of sleep may be less prone to recall-bias or poor compliance than sleep diaries.

In summary, the above studies highlight the need for further research on sleep and PP that (a) compares the perinatal sleep of high-risk women who develop PP to those who remain well, and (b) complements subjective measures of sleep with objective measures.

The two main methods for objectively measuring sleep are polysomnography (PSG) and actigraphy. PSG is considered the gold standard method for assessing sleep and combines information from multiple sensors to elucidate sleep stages. These generally include electrical brain activity, eye movements, and muscle activation, but may also use information from oxygen saturation sensors, video recordings and other sensors (Sadeh 2015). However, PSG involves high participant burden, high costs, and the requirement to sleep in an unnatural environment, thereby making it a questionable assessment of normal sleep patterns (Millar et al. 2004; Sadeh 2015). In contrast, actigraphy provides a cost-effective and non-invasive method to assess sleep over long periods of time in naturalistic settings (Millar et al. 2004; Sadeh 2011; Miller et al. 2012; Sadeh 2015). Actigraphy is described in further detail in the next section.

6.1.2 Actigraphy and Sleep

The term 'actigraphy' (also referred to as actimetry or activity monitoring) refers to the use of electromechanical devices, typically worn on the wrist, which monitor and analyse movement (Sadeh 2011). Collected data is then analysed via validated algorithms to estimate sleep parameters such as sleep onset, total sleep time and sleep efficiency. The first use of actigraphy was documented in the 1950s (Tryon 1991), with subsequent development in the 1970s (Littner et al. 2003) and was approved by the American Academy of Sleep Medicine for research purposes in 1995 (Thorpy et al. 1995). Actigraphy has previously been successfully used to measure sleep patterns in women in pregnancy and the postpartum period (Insana and Montgomery-Downs 2010; Montgomery-Downs et al. 2010; Insana et al. 2011; Insana

and Montgomery-Downs 2013; McBean and Montgomery-Downs 2013) and in individuals with BD (e.g. Gershon et al. 2012; Jones et al. 2005).

Actigraphy enables non-invasive long-term monitoring of sleep, which is advantageous for research on sleep loss occurring due to childbirth. This is because delivery dates may vary significantly from due dates, with only 27% of births in the UK occurring at gestational week 40 (Moser and Hilder 2008). This variation means that devices need to monitor sleep for a sufficient period of time in order to capture sleep loss occurring around childbirth. Recent technological advances mean that monitoring periods of several weeks are now possible with some actigraph models. However, the extended monitoring period of the newer actigraph models currently cannot capture the entire gestational period; therefore it is still necessary to limit actigraphy monitoring to a specific period of interest. The available literature suggests that the most crucial timeframe to measure the association between sleep patterns and PP is the *immediate perinatal period* (i.e. the week prior to, including, and following labour). This is because the greatest degree of sleep loss occurs in this period (Hedman et al. 2002; Beebe and Lee 2007), and the first symptoms of PP often emerge in the first postpartum week (Heron et al. 2007; Heron et al. 2008). Evidence from sleep deprivation studies mentioned previously (e.g. Kasper and Wehr, 1992) suggest that acute sleep deprivation (i.e. total sleep deprivation or sleep deprivation in the latter half of the night) can trigger mania after one night. It is plausible, therefore, that the acute sleep loss often experienced during labour (Sharma et al. 2004; Beebe and Lee 2007) and in the early postpartum days, may trigger PP in some women.

At the time of writing, there were no published studies using actigraphy to measure sleep in women at high risk of developing PP. This could be due to a confluence of factors. First, this might reflect difficulties of recruiting clinical populations (particularly, women at high-risk of PP) as well as asking individuals to partake in research during a significant life event. Second,

this may be due to difficulties capturing sleep at a particular stage of pregnancy and postpartum that can be difficult to coordinate within the limits of actigraphy battery life and memory storage. Although allowing relatively long-term measurements of sleep, until recently, the length of time that actigraphy was able to measure was limited to around 1-2 weeks. This means traditionally it has been logistically difficult to measure sleep continuously during the weeks immediately before and after birth.

6.1.3 *Aims*

In summary, the results presented in Chapter 4 were limited by the lack of direct data examining sleep, and there is a dearth of research that has used objective measures of sleep to examine sleep patterns in women at high risk of developing PP. Therefore, the aim of this study was to pilot the use of assessing sleep using actigraphy in pregnant women at high-risk of developing PP. Specifically, I aimed to measure changes in sleep that occurred during the time of parturition which has been associated with the greatest disruption to sleep; the weeks immediately before and after childbirth.

Initially, I also aimed to use the prospective sleep data to investigate whether changes in sleep patterns during pregnancy and postpartum could be used as a marker for developing PP. However, difficulties with recruitment meant that this project was not able to progress beyond the pilot stage. This chapter will therefore describe the process of designing and conducting the pilot study, followed by recommendations for future research based on the experiences of conducting this study and examining preliminary results.

~~In particular, I will discuss:~~

1. Whether it is feasible to collect actigraphy data in this population and, if so, to identify which indicators of sleep disturbance may be useful to target in larger studies.
2. The barriers to conducting this type of research, and what could be done to facilitate this research in the future.

6.2 Method

The study described in this chapter formed part of the ongoing programme of research conducted by the BDRN. Specifically, this study prospectively investigated the factors associated with postpartum mood episodes in pregnant women at high risk of PP (i.e. women with a lifetime diagnosis of BD or a history of PP). Women enrolled in this study were given the option to monitor their sleep patterns using an actigraph and sleep diary. The following sections describe the main study from which participants were recruited, followed by the methods specific to the sleep monitoring aspect of the study. The study had UK National Health Service (NHS) Ethics Committee approval (West Midlands Multi-Centre Research Ethics Committee, Ref MREC97701) and local R&D approval in NHS Trusts and Health Boards throughout the UK (described below).

6.2.1 Recruitment

Participants were primarily recruited systematically via specialist psychiatric perinatal services and community mental health teams. Trusts and Health Boards approached included: Abertawe Bro Morgannwg; Aneurin Bevan; Birmingham and Solihull; Derbyshire; Devon; East London; Glasgow; Greater Manchester; Hampshire; Leeds; Lothian; Northumberland; Nottinghamshire; Sheffield; South Staffordshire and Shropshire; Tyne and Wear; West Hub and Bath; and Worcestershire. Participants received an invitation letter and information sheet from their perinatal psychiatrist and contacted the research team if they wished to participate. In addition, individuals referred to the Cardiff University second opinion clinic run by Professor Ian Jones were informed of the study and referred if they wished to participate.

Participants were also recruited non-systematically via websites and social media relating to postpartum psychosis and mental health (e.g. www.app-network.org, www.ncmh.info,

www.bdrn.org, and www.bipolaruk.org). Written informed consent was obtained from all participants prior to enrolment in the study.

6.2.2 Inclusion and Exclusion Criteria

In addition to general inclusion and exclusion criteria for inclusion to the BDRN research programme (described in Chapter 2, section 2.3), participants in the prospective pregnancy study had to meet the following criteria:

- Be at least 12 weeks pregnant
- Have a lifetime diagnosis of bipolar disorder (BD-I, BD-II or schizoaffective disorder bipolar type) according to DSM-IV or DSM-5 criteria (American Psychiatric Association 2000; American Psychiatric Association 2013) or a history of PP (defined according to the same criteria described in Chapter 4, section 4.2.2). Diagnoses were ascertained by participant interview and case notes (described below).

6.2.3 Antenatal Interview

The antenatal assessment occurred during the second or third trimester (depending on time of recruitment). In this assessment, trained research psychologists interviewed participants using the Schedules for Clinical Assessment in Neuropsychiatry interview (SCAN, Wing et al. 1990), a psychiatric interview used to ascertain lifetime psychiatric history. This interview included questions regarding any history of mood episodes occurring in relation to childbirth and any previous and currently prescribed medication use during pregnancy.

6.2.4 Sleep Monitoring

During the antenatal interview, participants were given the option to monitor their sleep patterns during late pregnancy, birth and postpartum using an actigraph and sleep diary. This

aspect of the study was not mandatory in order to safeguard against overburdening participants. Participants who expressed interest were referred to myself to be given further details on what the sleep monitoring would involve.

Sleep Disorder Screening Questions

For participants who decided to monitor their sleep, at approximately 36 weeks gestation I conducted a brief phone interview (see Appendix G) containing five screening questions to ascertain the potential presence of sleep disorders such as obstructive sleep apnoea or periodic limb movement disorder (Wilson et al. 2010). These sleep disorders are common in pregnancy (Pien and Schwab 2004; Parry et al. 2006; Facco et al. 2010; Hutchison et al. 2012) and may influence subjective and objective sleep estimates.

Actigraphy

From week 37 of pregnancy until two weeks postpartum, sleep-wake patterns were measured objectively using the Actiwatch Spectrum Plus actigraph by Philips Respironics (shown in Figure 6-1). This model of actigraph was chosen based on the following features:

- Extended monitoring period (up to 60 days)
- Off-wrist detection feature
- Waterproof
- Ability to function as a watch



Figure 6-1. Actiwatch Spectrum Plus Actigraph (Philips Respironics).

Each actigraph was set to record data from 37-weeks gestation for 56 days (8 weeks) in 60-second epochs as recommended by American Academy of Sleep Medicine practice parameters for actigraphy (Littner et al. 2003). Participants were advised that they were able to adjust or remove the device if they found it uncomfortable.

In order to remove artefacts from actigraphy data (i.e. distinguish periods of wakeful inactivity from periods where the individual is resting and attempting to sleep), it is recommended that actigraphy research is complemented with sleep diaries (Littner et al. 2003). Therefore, participants were asked to complete a daily (paper-based) 'sleep grid' to record their sleep times, rise times, and nap times (Beebe and Lee 2007), Figure 6-2) whilst wearing the actigraph. Actigraphs, sleep diaries and instructions were sent to participants by post (Appendix H).

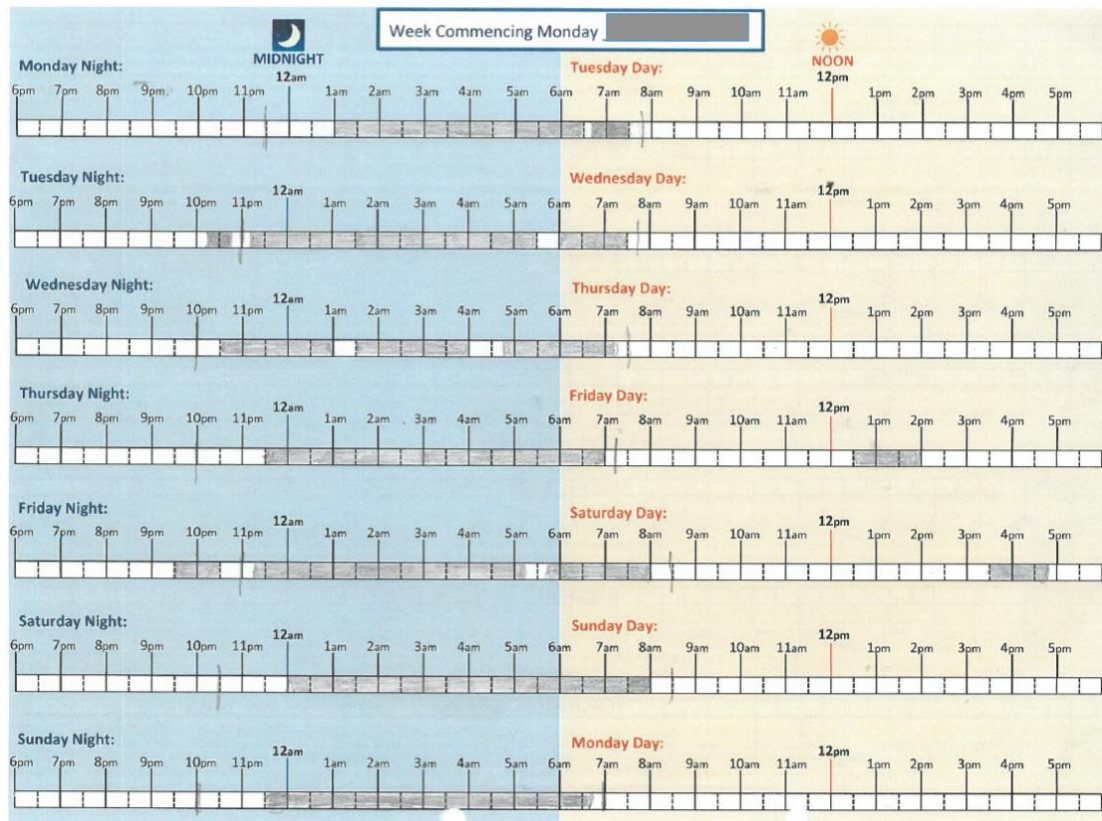


Figure 6-2. Example sleep diary. Shaded regions indicate sleep, vertical lines indicate bed times and rise times.

Following the expected due date, participants were sent freepost envelopes to return the actigraph and diaries. Participants also had the option to return the materials via courier.

6.2.5 Postnatal Interview

Approximately 8 weeks following the expected delivery date, the participant's GP and psychiatrist were sent a questionnaire pack which asked for information regarding the participant's pregnancy outcome and postpartum symptoms or treatment (Appendix I).

Providing that the patient's clinicians did not indicate that the pregnancy had resulted in an adverse outcome (e.g. miscarriage, still birth), research psychologists conducted a telephone interview 12 weeks after the expected due date. This interview included:

- Questions relating to delivery (e.g. length of labour, method of delivery, pain relief, birth complications).
- Questions relating to the postpartum period (e.g. medication prescribed) and relevant sections of the SCAN to determine whether the participant experienced a postpartum mood episode.

Figure 6-3 provides a brief summary of the assessment measures used in the pilot study.

6.2.6 *Lifetime Diagnoses and Postpartum Episodes*

Lifetime Diagnosis and History of PP

Following initial interview, GP and/or psychiatric records were requested to gather further information on psychiatric history. Information from the interview and case notes was then collated into a written vignette for each participant and used to determine lifetime diagnoses and whether participants had a history of PP. The procedure for rating diagnoses was the same as for other participants recruited to BDRN (described in Chapter 2, section 2.4) and the criteria for postpartum episodes that occurred prior to the prospective study were the same as outlined in Chapter 4, section 4.2.2.

Mood episodes occurring during the prospective pregnancy study

Mood episodes that occurred during the course of the prospective study were rated using the same methods described in previous chapters. Specifically, trained research psychologists independently rated psychiatric symptoms from participant interviews, clinician reports, and case notes, and these were used to determine the presence of DSM-IV and DSM-5 (American Psychiatric Association 2000; American Psychiatric Association 2013) episodes of mania, hypomania and depression. Episodes of ‘baby blues’ (which are not defined by DSM-IV or DSM-5) were defined as an episode of self-limiting mood symptoms (e.g. tearfulness,

dysphoric mood, fatigue) lasting no longer than one week, with onset in the first postpartum week (Robertson et al. 2004; Heron et al. 2005).

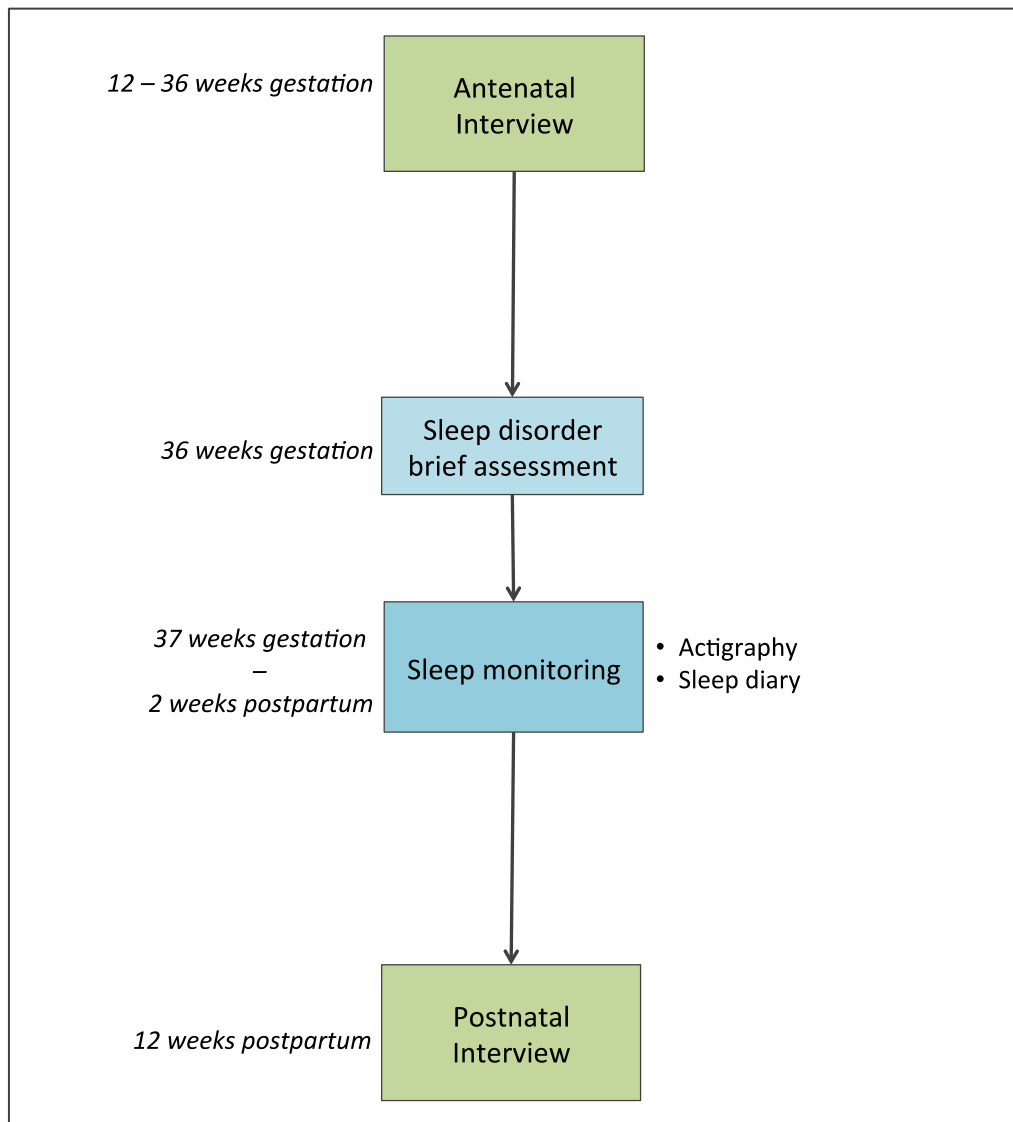


Figure 6-3. Brief summary of assessments used in the prospective pregnancy study.

6.2.7 Preparation of Actigraphy Data

Prior to analysis, actigraphy data were imported into proprietary software (Actiware version 6.0, Philips Respironics). Data were cleaned by setting ‘rest intervals’ in the software, which were informed by information from participants’ sleep diaries. This is a requirement for actigraphy data analysis as actigraphy is not reliable for distinguishing periods of wakeful

inactivity (e.g. reading, watching television) from periods where the individual is resting and attempting to sleep (Littner et al. 2003). The protocol applied for correcting actigraphy is outlined in Appendix J. In cases where there were discrepancies between participant's self-reported bed/rise times and activity data, I made informed judgements on where to allocate rest intervals in the program based on:

1. the general level of concordance between each participant's diary entries and activity.
2. the level and persistence of activity (i.e. high and persistent vs. low and fragmented).
3. examination of activity around previously reported bed/rise times to determine whether participants showed a common 'activity signature' during these times.

I applied the actigraphy data cleaning protocol to the actigraphy data for each participant.

When correcting and analysing the actigraphy data, I was blind to participants' diagnoses and psychiatric outcomes in the prospective pregnancy study.

6.2.8 Analysis

Following data cleaning, actigraphy data were analysed using the proprietary software (Actiware version 6.0) to calculate 'activity counts'. The criteria used to identify sleep were (i) a 40-activity count wake threshold and (ii) at least 10 minutes of immobility.

Once corrected, the Actiware software was used to derive the following sleep parameters:

- *Sleep onset latency*: Number of minutes to fall asleep
- *Number of awakenings per night*: Number of nocturnal awakenings after sleep onset
- *Time awake after sleep onset*: Total minutes awake per night after sleep onset
- *Total Sleep Time*: Number of hours asleep whilst in bed
- *Sleep Efficiency*: Percentage of time asleep whilst in bed

The resulting sleep parameters were extracted from the software and analysed using R version 3.2.2 (R Core Team 2017).

6.3 Results

6.3.1 Recruitment and Retention

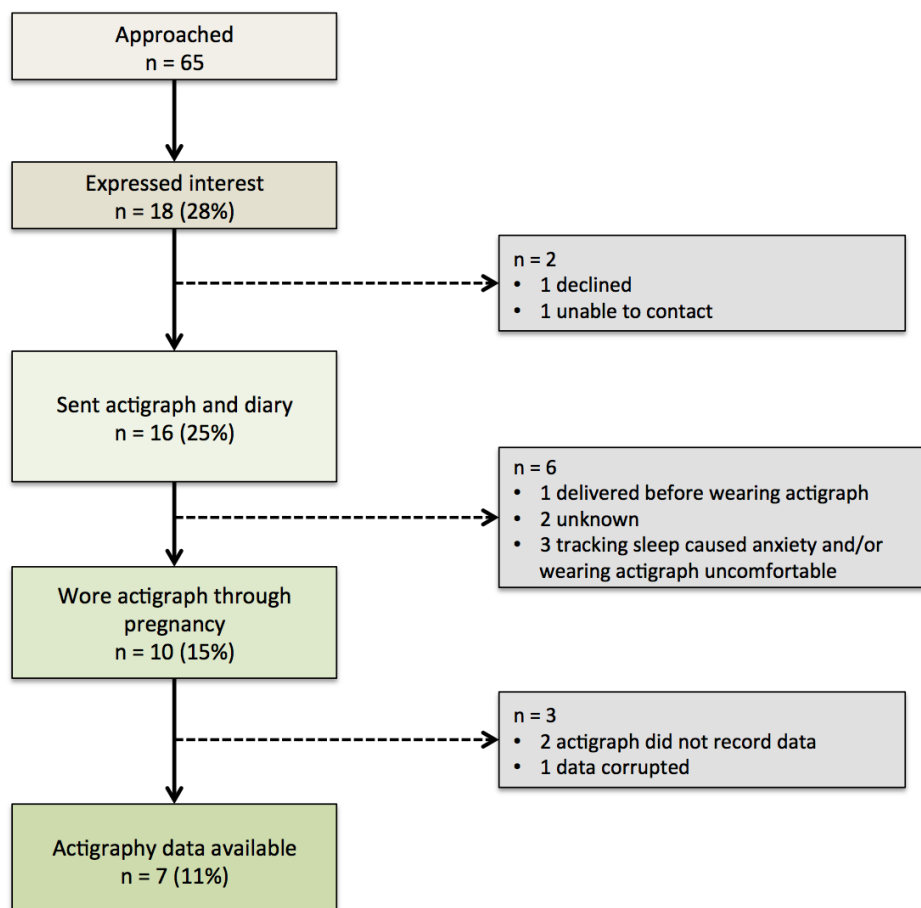


Figure 6-4. Recruitment chart for actigraphy study.

As shown in Figure 6-4, during the course of the pregnancy study, 65 women were given the option to record their sleep during pregnancy and postpartum. Of these 65 women, 28% ($n = 18$) expressed interest. Characteristics of the 18 women who expressed interest in monitoring sleep are shown in Table 6-1. All women had a partner at the time of recruitment.

6.3.2 *Retention and Acceptability*

As shown in Figure 6-4, out of the 18 women who initially expressed interest in recording their sleep, one woman later declined due to personal circumstances and another was unable to be contacted. Of the remaining 16 women:

- One woman was unable to partake in sleep monitoring due to giving birth before receiving the study materials.
- Two women did not complete sleep monitoring but did not provide a reason.
- Three women did not complete sleep monitoring due to anxiety about monitoring sleep and/or finding the watch uncomfortable.

Two of the three women who withdrew from sleep monitoring due to anxiety or discomfort voluntarily provided written correspondence outlining their reasons for withdrawing (full quotes from written correspondence are provided in Appendix K. The key reasons for withdrawing reported by these two women were:

- Finding the actigraph hot and uncomfortable to wear at night.
- Becoming anxious about tracking sleep times on the diary or not having the time to complete the sleep diary.
- Worry that the anxiety and restlessness caused by being 'aware' of sleep patterns would have a detrimental effect on their mental health.

6.3.3 *Women who Completed Sleep Monitoring*

Of the original 18 who expressed interest in sleep monitoring, 10 (56%) wore the actigraph and completed a sleep diary during pregnancy and postpartum. Demographic and clinical characteristics of these women are provided in Table 6-1.

Table 6-1. Demographic and clinical characteristics of women who expressed interest in sleep monitoring.

	Expressed interest in sleep monitoring (n = 18)	Completed sleep monitoring (n = 10)	Did not complete sleep monitoring (n = 8)
Age, median (range)	34.5 (18-43)	34.5 (32-40)	35 (18-43)
Method of recruitment, n (%)			
Systematic	9 (50)	3 (30)	6 (75)
Non-systematic	9 (50)	7 (70)	2 (25)
Gestational week at recruitment, mean (range)	25 (14-38)	21 (14-27)	30 (16-38)
Primiparous, n (%)	4 (22)	2 (20)	2 (20)
DSM-V diagnosis			
Bipolar-I	16 (89)	8 (80)	8 (100)
Bipolar-II	1 (6)	1 (10)	0 (0)
Bipolar NOS	1 (6)	1 (10)	0 (0)
History of postpartum psychosis, n (%)	5 (28)	2 (20)	3 (38)
Illness onset in the postpartum period, n (%)	2 (11)	2 (20)	0 (0)
Time since last mood episode, n (%)			
Currently unwell	0 (0)	0 (0)	0 (0)
Less than 1 month	4 (22)	2 (20)	2 (25)
1-3 months	2 (11)	1 (10)	1 (13)
4-6 months	2 (11)	1 (10)	1 (13)
7-12 months	4 (22)	2 (20)	2 (25)
More than 1 year	5 (28)	3 (30)	2 (25)
More than 5 years	0 (0)	0 (0)	0 (0)
Unknown	1 (6)	1 (10)	0 (0)
Age at first contact with secondary services, median (range)	26 (15-37)	29 (19-34)	25 (15-37)
Highest educational attainment, n (%)			
CSE/O-level/GCSE	1 (5.6)	0 (0)	1 (13)
A-level/AS-level	4 (22.2)	1 (10)	3 (38)
Degree	9 (50.0)	7 (70)	2 (25)
Postgraduate Degree	4 (22.2)	2 (20)	2 (25)
Highest occupation, n (%)			
Professional	15 (83)	8 (80)	7 (88)
Non-professional	1 (6)	1 (10)	0 (0)
Never worked	2 (11)	1 (10)	1 (13)

Sleep Disorder Screening

The sleep disorder screening questions did not indicate the presence of narcolepsy, sleep breathing disorder, or restless legs syndrome in any of the 10 women who completed sleep monitoring. One participant screened positive for delayed sleep phase disorder and parasomnia, however, the actigraphy data for this woman were not analysed due to the actigraph malfunctioning and corrupting the data.

6.3.4 Actigraphy

As shown in Figure 6-4, 3 out of the 10 actigraphs returned by women who completed sleep monitoring malfunctioned. This resulted in data from 7 women (11% of the original 65 approached) available for analysis. An example actogram for one participant is shown in Figure 6-5. As shown in this figure, each actogram plots activity (black lines) over time. For reference, the participant's self-reported bed times and rise times were added to the actogram within the Actiware program, shown as horizontal blue lines.

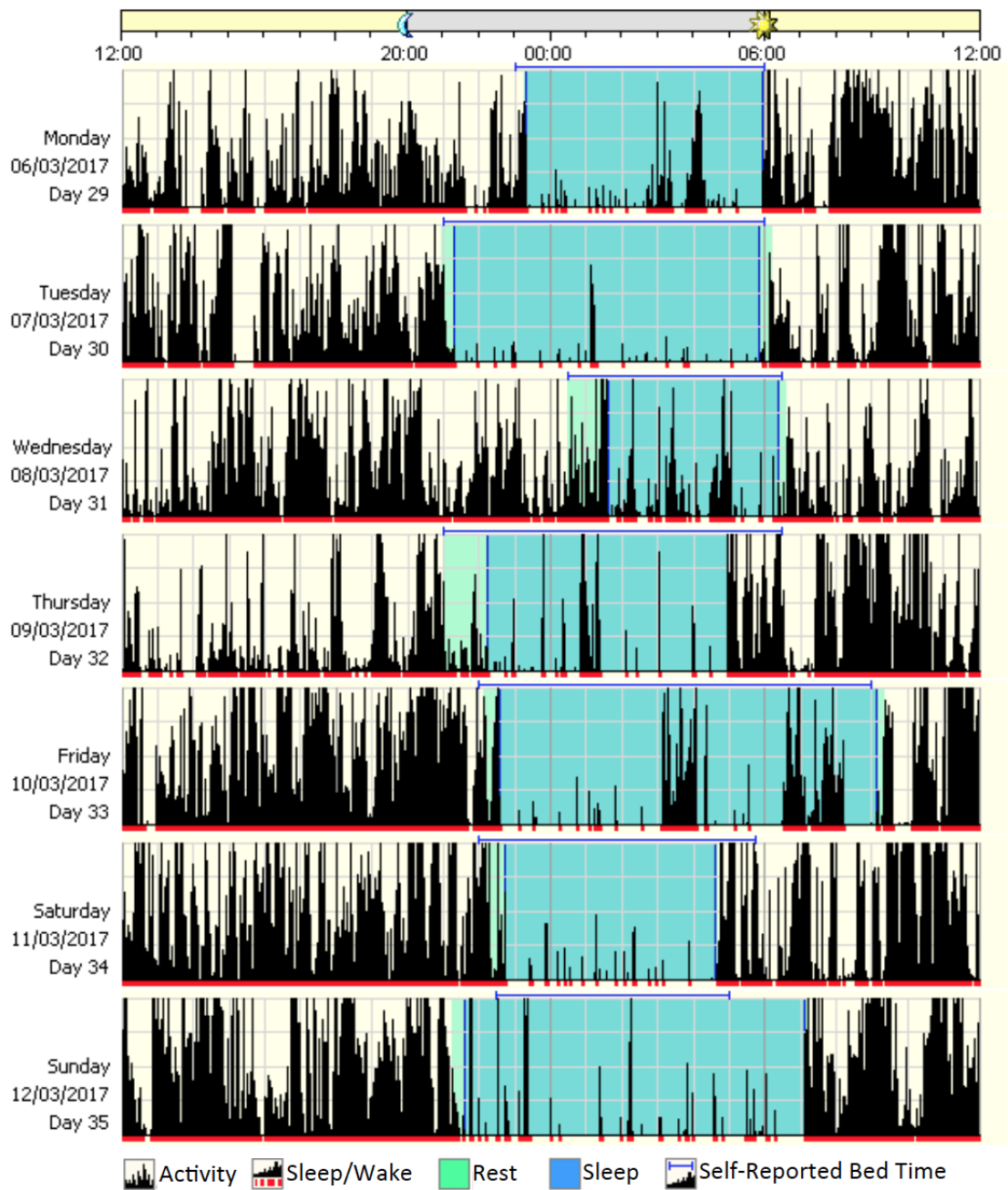


Figure 6-5. Example actogram of one participant during the postpartum period. Day numbers indicate days of monitoring.

The sleep parameters outlined in section 6.2.8 (sleep onset latency, number of awakenings per night, time awake after sleep onset, total sleep time, and sleep efficiency) were plotted for each participant (Appendix L) using R. An example is shown in Figure 6-6.

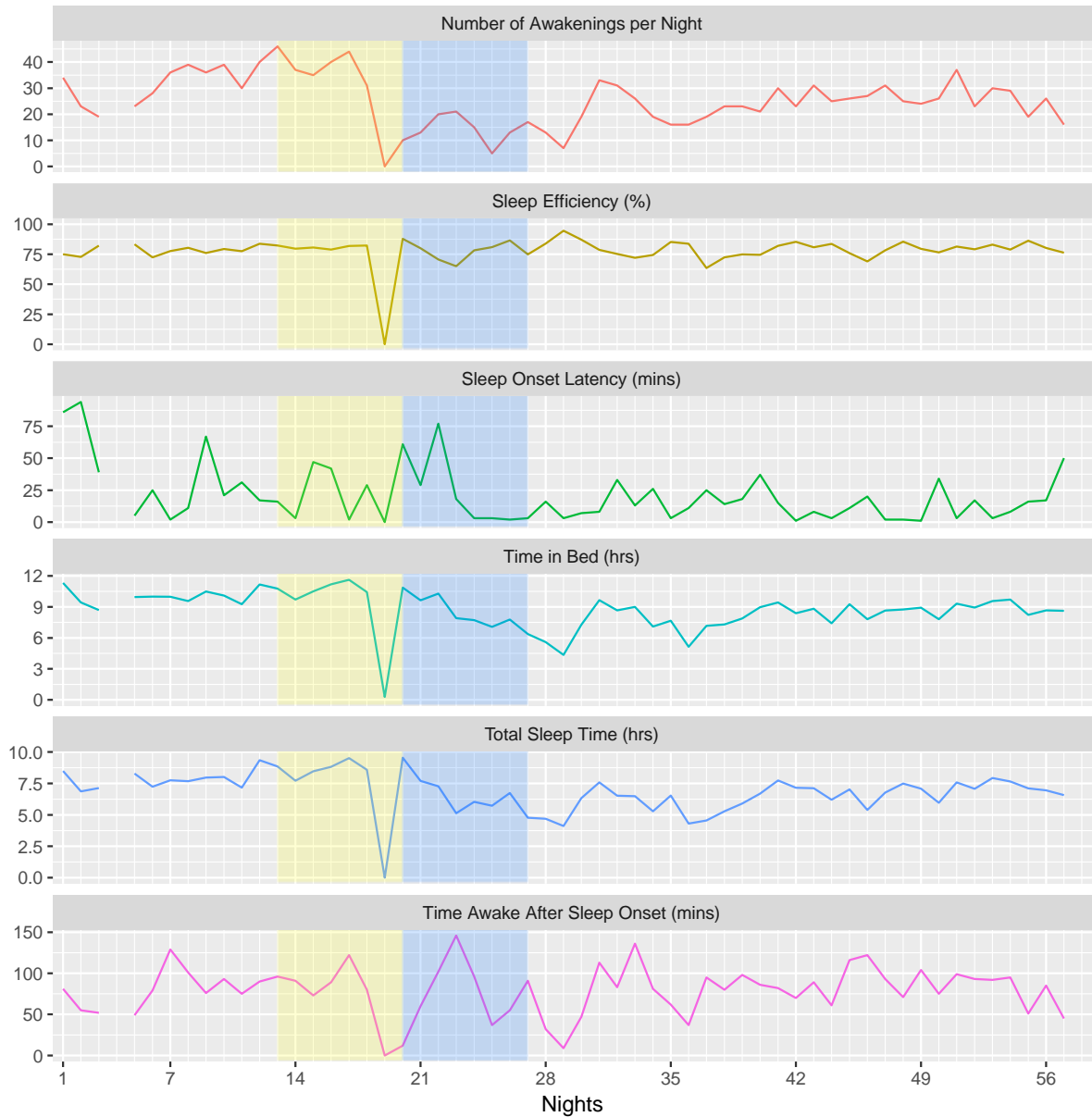


Figure 6-6. Example sleep parameters derived from actigraphy for one participant during pregnancy and the postpartum period. The yellow shaded region indicates the week prior to delivery, the blue shaded region indicates the week following delivery.

The sleep parameter of most relevance to research on sleep and postpartum episodes is the total number of hours slept per night. Figure 6-7 shows the total sleep time for each participant, centred on delivery date with psychiatric outcomes and onset labelled.

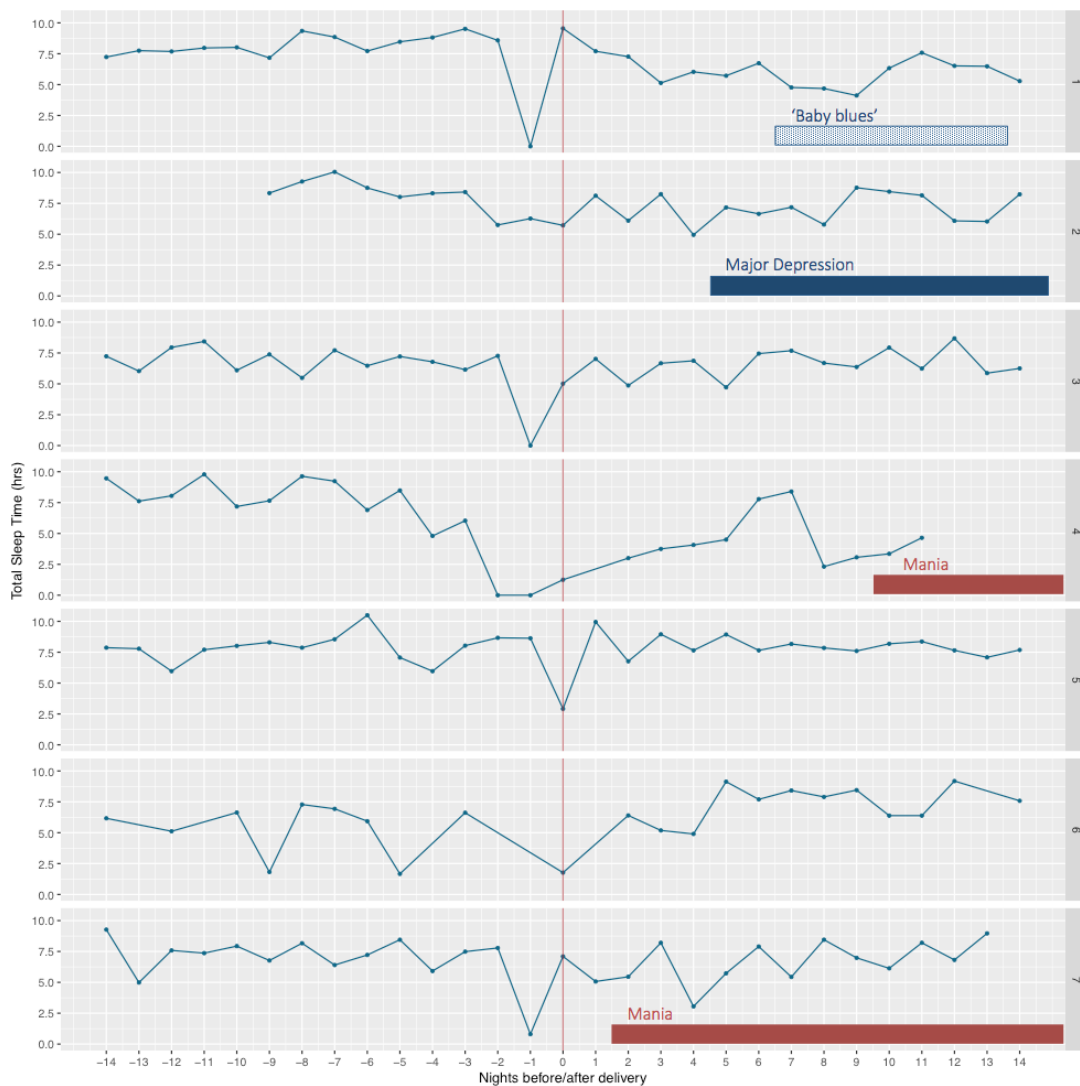


Figure 6-7. Total number of hours slept per night two weeks before and after delivery date in 7 women, measured using actigraphy. Onset of DSM-5 psychiatric episodes is labelled if women became unwell.

This figure illustrates that:

- 6 of the 7 women experienced a marked decrease in sleep one or two nights preceding or on the night of delivery.
- Some women have more variable antepartum sleep than others (cf. participant 6 vs. participant 1).
- Some women appear to have more variable sleep durations in the postpartum vs. antepartum period (e.g. participant 7).

- Excluding the days immediately surrounding childbirth, some women's sleep duration remains relatively similar in the postpartum to antepartum period (e.g. participant 3), whereas others experience more marked changes (e.g. participant 4).

6.3.5 *Psychiatric Sequelae and Sleep Duration*

As shown in Figure 6-7 and Table 6-2, four women experienced episodes of mood disturbance following childbirth, and three women remained well. Of the three women who remained well, participant 3 and 5 both showed relatively similar sleep patterns before and after childbirth. Of note is that participant 5 had a night-nurse to feed the baby for the first few weeks postpartum, and was given prophylactic olanzapine and Zopiclone following delivery. In contrast, participant 6 also remained well but her sleep was more disturbed in pregnancy compared to the postpartum period. This participant's medication remained stable before and after birth.

As shown in Figure 6-7 and Table 6-2, four of the seven women who completed sleep monitoring experienced some form of psychiatric disturbance during the two weeks following delivery. A summary of these women's sleep patterns that can be derived from Figure 6-7 is provided below:

Participant 1 – 'Baby blues'

- Antepartum: experienced relatively consistent sleep duration ranging between 7 and 9 hours each night.
- Delivery: 0 hours sleep (emergency caesarean section)
- Postpartum: sleep duration returned to pre-delivery levels on the night following delivery and first two nights postpartum. From the third to fifth postpartum night, sleep duration reduced to 5-7 hours, which was followed by an episode of 'baby

blues' lasting one week. During this time, her sleep duration ranged between 4 and 7 hours.

Participant 2 – Major depression

- Antepartum: Sleep duration of approximately 8-10 hours that decreased to approximately 6 hours in the two nights preceding delivery.
- Delivery: Approximately 6 hours sleep (elective caesarean section)
- Postpartum: sleep duration became more variable, ranging from 5-8 hours, followed by an episode of major depression lasting 4 weeks. Sleep duration during this episode (that overlapped with sleep monitoring) ranged between 6 and 9 hours.

Participant 4 - Mania

- Antepartum: Sleep duration initially ranged from 7-10 hours then decreased in the 4 nights prior to delivery (0-5 hours).
- Delivery: 1 hour of sleep (emergency caesarean section).
- Postpartum: Apart from approximately 8 hours sleep on postpartum nights 6 and 7, sleep duration ranged from 2-4 hours on postpartum nights 1-9. The participant became manic on day 10, at which point she completed sleep monitoring for a further two nights (sleep duration ranging from 3-4 hours).

Participant 7 - Mania

- Antepartum: Sleep duration on average around 7.5 hours per night until the night prior to delivery, in which sleep reduced to 0.80 hours.
- Delivery: 7.1 hours sleep (emergency caesarean section after a 14 hour labour)
- Postpartum: 5 hours sleep on the first night after delivery. Participant became manic the following day (which lasted 6 weeks). Sleep duration becomes more variable at this point, ranging from 3-8 hours.

Further information on obstetric and psychiatric outcomes, medication use and diagnosis is provided in Table 6-2.

Table 6-2. Additional information on medication, delivery and psychiatric sequelae of women who completed sleep monitoring.

N	Diagnosis	Medication (Pregnancy)	Medication (Postpartum)	Delivery	Psychiatric Sequelae
1	BD-I	<ul style="list-style-type: none"> • Sertraline^P • Quetiapine^P 	<ul style="list-style-type: none"> • Sertraline^P • Quetiapine^P 	<ul style="list-style-type: none"> • Delivered at 6:00 AM • 6 hour labour • Emergency C-section 	Baby blues <i>Onset:</i> 7 days after delivery <i>Duration:</i> 1 week
2	BD-II	<ul style="list-style-type: none"> • Lamotragine^P (stopped at 5 weeks gestation) • Quetiapine^P • Mirtazapine^P 	<ul style="list-style-type: none"> • Quetiapine^P • Mirtazapine^P • Sertraline^T (postpartum day 7) 	<ul style="list-style-type: none"> • Elective C-section 	Depression <i>Onset:</i> 5 days after delivery <i>Duration:</i> 4 weeks
3	BD-I	No medication.	No medication.	<ul style="list-style-type: none"> • 24 hour labour • Vaginal delivery 	Remained well.
4	BD-I	<ul style="list-style-type: none"> • Lithium^P • Duloxetine^P (changed to Olanzapine^P at 6.5 weeks gestation) 	<ul style="list-style-type: none"> • Lithium^P • Olanzapine^T (postpartum day 10) 	<ul style="list-style-type: none"> • Delivered at 12:41 AM • 24 hour labour • Emergency C-section 	Mania <i>Onset:</i> 10 days after delivery <i>Duration:</i> 4 weeks
5	BD-I	No medication.	<ul style="list-style-type: none"> • Olanzapine^P (postpartum day 1) • Zopiclone^P (start date unknown) 	<ul style="list-style-type: none"> • Delivered at 10:17 AM • 7 hour labour • Vaginal delivery 	Remained well.
6	BD NOS	<ul style="list-style-type: none"> • Venlafaxine^P • Quetiapine^P 	<ul style="list-style-type: none"> • Venlafaxine^P • Quetiapine^P 	<ul style="list-style-type: none"> • Delivered at 12:00 PM • 40 hour labour • Forceps delivery 	Remained well.
7	BD-I	<ul style="list-style-type: none"> • Zopiclone^P (late in 3rd trimester for poor sleep) 	<ul style="list-style-type: none"> • Olanzapine^P (postpartum day 1) • Zopiclone^T (postpartum day 4) • Diazepam^T (postpartum day 4) 	<ul style="list-style-type: none"> • Delivered at 08:06 AM • Emergency C-section 	Mania <i>Onset:</i> 2 days after delivery <i>Duration:</i> 6 weeks

^P Prophylactic, ^T Treatment

6.4 Discussion

This study aimed to pilot the use of actigraphy to obtain longitudinal objective measures of sleep in pregnant women at high risk of developing PP. In particular, I aimed to use this method during the latter weeks of the third trimester and initial postpartum weeks.

Findings from this study suggest that actigraphy is a challenging methodology for measuring sleep in women at high risk of PP. Specifically, this study demonstrated that recruitment was difficult, with only 28% (n=18) of the women approached expressing interest in monitoring sleep patterns. Of this sample, issues with acceptability and technical failures meant that data were available on 7 of the 18 women who expressed interest (11% of total sample approached). This suggests that, for the majority of women at high-risk of PP, it is not possible to use actigraphy to measure sleep loss during the perinatal period (although feasibility studies are needed in order to adequately assess this), and that to obtain large enough samples for statistical analysis would require multi-site collaboration.

However, this study also demonstrates that, in women who opt to monitor their sleep, actigraphy was a useful method of measuring sleep. In these cases, actigraphy was well tolerated for multiple weeks and allowed the derivation of multiple sleep parameters (e.g. sleep efficiency, total number of hours slept per night). Closer examination of sleep duration for each woman revealed particular characteristics that may be of interest to explore in larger samples. These are outlined in further detail below.

6.4.1 *Sleep Deprivation in the Perinatal Period*

Although the small sample size precluded statistical analyses, the women's sleep patterns unveiled interesting features that could be explored in larger samples. First, in line with

previous research (e.g. Hedman et al. 2002; Beebe and Lee 2007), the majority of women in this sample experienced the most sleep deprivation on the night before or of delivery. However, this was not the case for all women; one participant, who became depressed 5 days postpartum (Participant 2), appeared to have the least sleep deprivation in the nights surrounding delivery compared to the other women (of note is that Participant 2 was the only woman in the sample who had an elective caesarean section). These findings demonstrate that not all women will experience dramatic decreases in sleep during childbirth, therefore the day immediately before or after delivery will not necessarily be associated with the most sleep loss in the perinatal period.

Second, the actigraphy data highlighted the potential role of intra-individual sleep variability and its relationship with postpartum mood episodes. The three women in this sample who experienced major affective episodes (1 major depression, 2 mania) demonstrated marked variability in sleep duration in the nights preceding episode onset. Intra-individual variability in sleep has previously been associated with BD and mood dysregulation (Jones et al. 2005; Kalmbach et al. 2014; Bei et al. 2016). Research in larger samples may therefore wish to explore sleep variability in the pre- and postpartum period and its relationship with mood episodes.

In concordance with literature on sleep and mood (Wehr et al. 1987; Wehr 1989), the two women who became manic did show short total sleep durations in the nights preceding episodes onset (i.e. 0-2.5 hours). Surprisingly, however, both women also showed increased sleep durations (~ 7.5 hours) in the nights preceding mania. As mentioned above, this may reflect the effects of sleep variability on mood, and requires further examination in larger samples.

In addition, the women in this study who had disturbed sleep did not always relapse, and some women had more variable sleep patterns than others in the antepartum and/or postpartum period in general. It would therefore be of interest in future studies to explore additional factors that may contribute to more or less disturbed sleep in pregnancy and postpartum, such as medication and symptoms of anxiety. Future research could also explore which variables are associated with resilience to sleep loss in the perinatal period.

Finally, although the initial aim was to examine sleep loss one week either side of delivery, the long monitoring time of the actigraph model allowed examination of a slightly larger time span of 2 weeks either side of delivery, which provided useful additional information on sleep patterns and postpartum mood episodes. Therefore it is important for future research to utilise these data if they are available.

6.4.2 Barriers to Using Actigraphy in Women at High Risk of Postpartum Psychosis

This study highlighted the following factors that may limit the ability to estimate sleep disturbance via actigraphy in this population.

Recruitment

An area of concern in this study was the low recruitment rate. During a recruitment period of 2 years, 18 of the 65 women approached expressed an interest in sleep monitoring (28%). One reason for this low recruitment rate could have been due to the timing of when women were approached about sleep monitoring; women were approached after they had completed a long research interview, by which point they may have been reluctant to commit to additional research demands. Women may also have been less likely to commit to sleep monitoring during this time due to the burden of pregnancy. Future research should assess

this systematically (e.g. via focus groups or questionnaires) to determine the barriers to recruitment.

Discussion with research psychologists suggested that women declined because (a) they thought they would forget to wear the actigraph and/or complete the diary, or (b) did not normally wear a watch and would therefore find it uncomfortable to wear an actigraph.

Future research might conduct a feasibility study to systematically record reasons for declining this and explore whether women who are less likely to partake in sleep monitoring are more likely to become unwell in the postpartum period and/or differ in other characteristics (e.g. illness severity, socioeconomic status, primiparity).

Retention/Acceptability of Sleep Monitoring

Of women who opted to monitor their sleep, a subsequent barrier was the acceptability of wearing the actigraph and tracking their sleep using a diary. Three out of the 16 women who opted to complete sleep monitoring (19%) later discontinued due to finding the actigraph uncomfortable to wear at night and/or finding that keeping a sleep diary disturbed their sleep. An approach to minimise these issues in the future might be to use smaller actigraph models and emphasise to women that they do not have to keep a sleep diary if it disturbs their sleep. One alternative to keeping a sleep diary is to record bed times and rise times using an event-logging button, which is available on some actigraph models.

Technical Issues

Technical issues also compromised this study. Out of the 10 actigraphs worn throughout pregnancy and the postpartum period, three did not record data. A 30% failure rate is particularly problematic in this area of research, given the difficulties with recruitment and time-dependent nature of data collections (i.e. during late-pregnancy and postpartum). These

problems may have been confined to this study, as the actigraph model that I used was a newly developed version and, in the initial stages of the study, the devices malfunctioned primarily due to problems with the new software and firmware.

6.4.3 Strengths

Despite the small sample size, this study has several strengths. First, the study provides a starting point for understanding the barriers to conducting actigraphy research in women at high-risk of PP. Second, the preliminary data from this pilot study highlight which indices of sleep may be most useful to examine in larger samples. Third, the prospective design using an objective measure of sleep offers an advantage over retrospective designs using self-report measures of sleep, which are subject to participant attributions and recall bias.

Fourth, the model of actigraph used in this study allowed sleep monitoring to be conducted over an extended period (up to 60 days), thus ensuring the continuous measurement of sleep from late-pregnancy to postpartum. This is one of the first studies to date that has used actigraphy to monitor sleep during this period in women at high-risk of PP. Finally, in line with the data from previous chapters in this thesis, this study utilised detailed clinical information on women both before and after delivery (derived from case notes and interview).

6.4.4 Limitations

The limitations of this study are first, due to the sensitive nature of the data collection period, there was a greater need to ensure that participants were not over-burdened or contacted too frequently. This meant that, although participants were able to contact me if they had any problems with the actigraph or sleep diary, I did not contact them once sleep monitoring had begun. This may have contributed to some women discontinuing sleep monitoring (e.g. if they required additional support using the actigraph or completing the sleep diary).

Second, the results of this chapter and future work in this area may not be generalizable, as it is possible that women who opted to do sleep monitoring are not the most representative of women at high-risk of PP. An extension of the work presented in this chapter might compare demographic and clinical information on the women who opt to monitor sleep and those who do not, to determine which women are more likely to take part in this type of research.

Finally, although referred to as an 'objective' measure of sleep, actigraphy is the measure of movement, not sleep, and the final data processing requires researchers to use judgments to remove artefacts from the data and interpret inconsistencies between participants' diary data and activity data (Littner et al. 2003). These procedures are not widely reported in actigraphy literature and vary in literature that does report them, leading to some researchers to call for standardised procedures to be published (Sadeh 2011). This issue will be discussed in further detail in the General Discussion. In this study, I used a procedure for processing actigraphy data based on the protocol used by the Sleep and Circadian Neuroscience Institute at Oxford University (shared with permission from Dr Katharina Wulff). However, a key part of this protocol involves regular reliability checks between researchers who process actigraphy data, which would need performed on these data in future work.

6.4.5 Future Research

In addition to the suggestions for future research outlined above, further work in this area might explore the following topics:

Feasibility of Using Actigraphy in Pregnant Women at Risk of PP

An important limitation of this study was the inability to adequately assess the feasibility of using actigraphy in this population. Future research should systematically assess this through conducting a feasibility study. This would include qualitative interviews and focus groups with

stakeholders, in addition to systematic assessment of acceptability and efficacy (Bowen et al. 2010).

Sleep Loss in Women who Develop PP

In sufficiently large samples, it might be possible to compare the sleep of women who develop PP to those who remain well. In addition to measures of total sleep duration, additional sleep parameters should be considered, such as intra-individual variability in sleep that occurs in pregnancy and postpartum (Mezick et al. 2009), sleep fragmentation, and circadian timing of sleep loss (Sack et al. 1988). For example, it has been proposed that sleep loss at particular phases of circadian timing (e.g. from 1am-4am) might increase risk of mania more than sleep loss at other times (9pm-12am) (Kasper and Wehr 1992; Wehr 1992). It is possible, therefore, that women who are kept awake from 1am-4am during childbirth are more likely to develop PP than those who are sleep deprived at earlier stages in the night. Other indices of disrupted circadian function may also be important, such as temperature and hormonal circadian rhythms (Parry et al. 2006).

Individual Differences in Sensitivity to Sleep Loss

Previous research and the results of previous chapters in this thesis suggest that only a subset of individuals with BD experience manic episodes in response to sleep loss, hence, some individuals may be more sensitive to the effects of sleep loss than others. This appeared to be the case in the data in this study, as some women experienced disturbed sleep but did not relapse. Future research might explore clinical characteristics that may modify any association between sleep disruption and PP, such as diagnostic category, chronotype, or a history of manic episodes being triggered by sleep loss.

Women at Risk of Other Postpartum Episodes

The present study examined women at high risk of PP, therefore all women in the sample had a history of BD or PP. However, other groups of women may also experience an increased risk of mental illness in the postpartum period that is exacerbated by sleep loss, such as women with major depressive disorder (MDD, Okun et al. 2011). A further avenue to explore using this methodology might be to compare perinatal sleep in women with MDD or BD who develop postpartum depression to those with BD who develop PP.

Fathers

A related research question is whether the effects of postpartum sleep loss extend to fathers, who have also been reported to suffer sleep loss once the infant is born (Insana and Montgomery-Downs 2013). Examining males provides an opportunity to examine the effects of sleep loss in a population that is not experiencing the same hormonal fluctuations in response to childbirth, an avenue of research that has also been explored as a possible cause of PP, although with mixed results. Fathers with bipolar disorder have rarely been examined, although a case study (Stevens et al. 2014) reported that a father had become manic after his sleep was repeatedly disturbed by his newborn daughter.

Alternative Measures of Sleep Loss

Finally, the fact that the majority of women approached in this study did not want to monitor their sleep on a daily basis suggests that less-intensive measures of sleep may be more amenable to this population. These might include online questionnaires (such as the Pittsburgh Sleep Quality Index (Buysse et al. 1989) administered at weekly or monthly intervals during pregnancy, or the option to only use a sleep diary instead of wearing an actigraph.

6.4.6 Clinical Implications

It should be noted that although a prospective design does not allow researchers to infer a causal role between sleep disruption and PP, identifying characteristics of sleep loss (whether causal or prodromal) that are important in the pathogenesis of PP could inform postpartum relapse prevention plans. If followed up in larger samples, the findings of this study could ultimately inform prevention strategies for pregnant women at heightened risk of postpartum psychosis. These might include night time help with infant feeding, improving sleep hygiene in pregnancy and postpartum, CBT-I, or pharmacological interventions that improve sleep (Reichner 2015; Wesseloo et al. 2016).

In addition, understanding more about which indices of sleep are likely to signal the onset of a postpartum episode, and which women will be most vulnerable to these, could help perinatal teams make the best use of resources to treat and prevent postpartum episodes.

6.4.7 Conclusions

In conclusion, the findings from this study suggest that actigraphy is a challenging methodology for measuring sleep in women at high risk of PP due to low levels of recruitment (28%) and feasibility studies are required in order to further explore barriers to recruitment. Whether women who opted to monitor their sleep using actigraphy are representative of the population of interest needs to be determined, and larger samples are needed in order to statistically determine which indices of sleep (if any) can be used to predict the onset of postpartum episodes. If this is achieved, there is opportunity to derive in-depth information on sleep parameters, which may inform prevention strategies for PP and aid understanding of the role of sleep disturbance in the pathway to mania more generally.

7 GENERAL DISCUSSION

7.1 Introduction

In this chapter, I will summarise the main findings of each of the studies presented in this thesis and discuss how they addressed the primary thesis aims. I will then discuss the strengths, limitations, and themes that emerged during the course of this thesis. I will end this chapter with suggestions for future research and the clinical implications of the findings.

The broad aim of this thesis was to examine the association between sleep disruption and mania in individuals with bipolar disorder (BD). In Chapter 1, I outlined the following thesis aims:

1. To explore whether there is a subgroup of individuals who experience sleep disruption as a pathway to mania and, if present, to examine individual differences associated with this phenotype.
2. To determine whether experiencing sleep disruption as a pathway to mania is associated with vulnerability to postpartum psychosis (PP).
3. To pilot the use of actigraphy to measure perinatal sleep in pregnant women at high risk of PP.
4. Within aims 1 and 2, to compare results for sleep disruption as a pathway to mania to those experiencing sleep loss as a pathway to depression.

I investigated these research aims in the studies presented in Chapters 3, 4, 5 and 6. In the following sections, I outline the findings from each chapter in relation to the research aims, followed by limitations and suggestions for future research. A summary of the findings from each chapter is provided in Table 7-1.

Table 7-1. Summary of main findings of studies described within this thesis.

Chapter number and title	Main findings and thesis aims addressed
<p>3. Sleep loss as a trigger of mood episodes in bipolar disorder: Individual differences based on diagnostic subtype and gender.</p>	<p>In 3140 individuals with BD, 20% reported that sleep loss has triggered episodes of mania, and 11% reported that sleep loss has triggered episodes of depression.</p> <p>Individuals with BD-I were more likely than those with BD-II to report that sleep loss had triggered episodes of mania. In addition, women were more likely than men to report that sleep loss had triggered episodes of mania. Comparison of other triggers did not suggest that females consistently over-reported other triggers of mood episodes, although the possibility of female over-reporting cannot be excluded.</p> <p>Being female was associated with an increased likelihood of reporting that sleep loss had triggered depression, however this finding did not persist following adjustment for confounders. Differences between BD-I and BD-II did not reach statistical significance.</p> <p><i>Study design:</i> Retrospective <i>Thesis aims addressed:</i> Aim 1, Aim 4</p>
<p>4. Sleep loss as a trigger of mania and susceptibility to postpartum psychosis.</p>	<p>Parous BD-I women who reported that sleep loss had triggered episodes of mania were more likely to experience postpartum psychosis (PP) compared to BD-I women who did not report sleep loss as a trigger.</p> <p>Reporting sleep loss as a trigger of manic or depressive episodes was not significantly associated with experiencing postpartum depression.</p> <p><i>Study design:</i> Retrospective <i>Thesis aims addressed:</i> Aim 2, Aim 4</p>
<p>5. Trajectories in insomnia prior to episodes of high mood: results from an online mood monitoring system.</p>	<p>Within BD individuals who had used an online mood-monitoring system, latent class analysis revealed that individuals could be grouped into three classes based their trajectories in insomnia prior to episodes of high mood.</p> <p>Individuals could not be split into subgroups based on their insomnia trajectories prior to episodes of depressed mood.</p> <p><i>Study design:</i> Prospective <i>Thesis aims addressed:</i> Aim 1, Aim 4</p>
<p>6. Using actigraphy to measure sleep disturbance in pregnant women at high-risk of postpartum psychosis.</p>	<p>Actigraphy is a challenging methodology to employ in women at high risk of PP, but can procure informative indices of sleep parameters during the perinatal period.</p> <p><i>Study design:</i> Prospective <i>Thesis aims addressed:</i> Aim 3</p>

BD, bipolar disorder; BD-I, bipolar-I disorder, BD-II, bipolar-II disorder; PP, postpartum psychosis

7.2 Thesis Aims

7.2.1 Aim 1

To explore whether there is a subgroup of individuals who experience sleep disruption as a pathway to mania and to examine individual differences associated with this phenotype.

The first aim of this thesis was to explore whether there is a subgroup of individuals with BD who experience sleep disruption as a pathway to mania. The term pathway, in this instance, may refer to a trigger or prodrome of impending illness. This was addressed in Chapter 3 and Chapter 5. In Chapter 3, I examined data from 3,140 participants recruited to the BDRN who were asked about triggers of mood episodes. The results of this chapter revealed that 20% of individuals with BD reported that sleep loss had triggered episodes of high mood, and that a tendency to report this was more likely among individuals with BD-I compared to those with BD-II, and more commonly reported by women. This was consistent with existing estimates of the proportion of individuals who become manic or hypomanic following sleep deprivation therapy (Colombo et al. 1999; Plante and Winkelman 2008), and findings that women may be more susceptible to mood dysregulation following sleep loss than men (Saunders et al. 2015). However, the results were limited by the retrospective nature of data collection and a lack of direct measures of sleep occurring prior to episode onset. Furthermore, it was not possible to account for all possible confounders that may have influenced the results and the results need to be replicated in more representative samples of individuals with BD.

In Chapter 5, I examined data from 692 BDRN participants who had used an online system to monitor their mood. Specifically, I used growth mixture modelling to examine whether individuals who had episodes of high mood when using the system (n=145) could be grouped into latent categories based on their trajectories in insomnia symptoms in the weeks prior to

episode onset. The results indicated that participants could be grouped into three classes based on their insomnia symptom trajectories: those with consistently high levels of insomnia (17%), those with consistently low levels of insomnia (78%) and participants whose symptoms of insomnia were initially low but increased in the weeks preceding episode onset (6%). This suggests that disturbances in sleep are only observed in a subset of individuals with BD prior to episodes of high mood. Subsequent comparisons did not reveal significant differences between the insomnia classes in BD diagnosis, gender, age or other symptoms of mania. However, compared to participants in the low insomnia class, individuals in the high insomnia class had higher levels of depressive symptoms (other than insomnia) and were more likely to be in an episode of low mood. This finding supports a previous hypothesis by Wehr et al. who suggested that insomnia associated with depressive symptoms might trigger mania (Wehr et al. 1987). However, these results require further exploration in a much larger sample, as the subgroups were not large enough to have adequate power to compare differences between the groups. Future research using more robust measures of mood episodes (e.g. clinical observations or interview measures rather than questionnaires) is also required.

In summary, the results described in Chapters 3 and 5 suggest that there is a subgroup of individuals who experience sleep loss as a pathway to mania. Results from the larger study presented in Chapter 3 suggest that gender and BD diagnostic subtype may influence susceptibility to this phenotype, whereas the results of Chapter 5 highlight the importance of considering the role of sleep loss during depression as a potential pathway to mania.

These findings have implications for future research, as studies examining the relationship between sleep and mania in BD should consider the potential effect of gender and BD subtypes on this relationship. If replicated in prospective (Chapter 3) and larger samples (Chapter 5), the results of these studies also have potential implications for clinical practice. For example, the results of Chapter 3 suggest that interventions should focus in particular on

individuals who appear to be at higher risk of relapsing following periods of sleep deprivation (e.g. women with BD-I through childbirth). This could be done by additional efforts to monitor the sleep of these individuals, to encourage healthy sleep behaviours and to offer therapies to improve sleep such as CBT-I. The results of Chapter 5 suggest that clinicians should pay particular attention to symptoms of insomnia, as for some individuals these may herald the onset of (hypo)manic episodes. However, there is a need for more research in larger samples of more representative individuals with BD before it will be possible to gauge clinical utility of these findings.

7.2.2 Aim 2

To determine whether experiencing sleep disruption as a pathway to mania is associated with vulnerability to postpartum psychosis.

The second research aim was to use knowledge of individual differences in response to sleep loss to guide investigations into the role of sleep loss in postpartum psychosis (PP). The role of sleep disruption in PP is of key interest given that the perinatal period is associated with heightened sleep disturbance and high risk of relapse for women with BD (Sharma and Mazmanian 2003; Beebe and Lee 2007).

In Chapter 4, I analysed data from 870 parous women recruited to BDRN and compared the rates of PP among women who reported that sleep loss had triggered episodes of mania and those who did not report this. The main finding of this chapter was that that women who reported that sleep loss had triggered episodes of mania were more likely to experience PP than women who did not report this. This effect remained statistically significant when controlling for potential confounding factors and was of a sufficient magnitude to potentially be clinically significant (OR=2.09, 95% CI=1.43-3.04).

These results have important implications for research on the aetiology of PP. First, few studies have examined the role of sleep loss in PP (Ross et al. 2005; Lawson et al. 2015), and none to date have examined whether sensitivity to the effects of sleep loss increases risk of PP. This study is therefore the first to suggest that women with this phenotype (i.e. with a history of manic episodes triggered by sleep loss) may have a heightened risk of experiencing PP. However, the data analysed in this chapter were retrospective, therefore to estimate risk would require replication in a prospective sample. If replicated, these results may have implications for individualising risk within women at high risk of PP, however these findings need to be explored further using objective, longitudinal measures of sleep (which was explored in Chapter 6 of this thesis) before it will be possible to determine what clinical recommendations (if any) should be made).

7.2.3 Aim 3

To pilot the use of actigraphy to measure perinatal sleep in pregnant women at high risk of PP.

The third thesis aim was to conduct a pilot study using actigraphy to measure the sleep of pregnant women at high risk of PP. In Chapter 6, I present results from a prospective study of pregnant women with BD or a history of PP who monitored their sleep from week 37 of pregnancy until the second postpartum week using actigraphy. This chapter highlighted that recruiting BD participants during pregnancy for actigraphy studies is difficult, with low uptake rates of BD women during pregnancy and issues with user acceptability of actigraphy during pregnancy. Of the ten women who completed the study, technical issues with three of the actigraphs meant that data were available on seven women. Despite these issues, this study revealed that actigraphy can offer detailed insights into perinatal sleep patterns, as there are numerous sleep parameters that can be obtained using this methodology (e.g. sleep fragmentation, intra-individual variability in sleep duration). The data from these women

highlighted that there is significant variation in sleep patterns both within and between women during the perinatal period, and that this relationship is complicated by numerous factors such as medication, mode of delivery, and prophylactic admission or assistance with infant care.

The low uptake during this study highlights that to obtain the sample sizes required for adequately powered analyses would take a substantial amount of time and resources. Recruitment for these studies could be facilitated by: (1) researchers collaborating with other research groups, and (2) including potential participants in the design of research studies to determine barriers to acceptability (e.g. via qualitative studies).

In summary, measuring perinatal sleep using actigraphy in high-risk pregnant populations is compromised by recruitment issues, ensuring that participants are not overburdened, as well as technical issues that may arise. This may explain the lack of published studies to date that have used this methodology. Progress will likely require collaboration across multiple research centres to enable adequately sized (and powered) samples to be collected.

7.2.4 Aim 4

Within aims 1, 2 and 3, to compare results for sleep disruption as a pathway to mania to those examining sleep loss as a pathway to depression.

The relationship between sleep and mania was compared to the relationship between sleep and depression in Chapters 3, 4 and 5. In each of these chapters, the association between sleep and mood differed according to illness polarity. Although there is some evidence implicating sleep loss as a trigger or early warning sign of manic episodes, less is known about the relationship between sleep loss and depression in BD. It is also possible that inconsistencies in research examining sleep and mania in BD (outlined in Chapter 1 section

1.6) are due to including individuals who experience a depressive rather than manic response to sleep loss.

In Chapter 3, fewer participants reported that sleep loss had triggered episodes of depression compared to episodes of (hypo)mania (11% vs. 20%, respectively). In addition, participants who reported that sleep loss had triggered episodes of depression were more likely to have a diagnosis of BD-II, although this finding was not statistically significant. In accordance with the results for mania, women were also more likely than men to report that sleep loss triggered episodes of depression, however this association became non-significant when controlling for potential confounding factors. In Chapter 4, the results for postpartum psychosis differed to those observed for postpartum depression. Specifically, reporting that sleep loss had triggered episodes of depression did not appear to be associated with an increased risk of developing postpartum depression. In Chapter 5, the results suggested that there were no distinct categories in insomnia trajectories prior to episodes of low mood, which was in contrast to the results for high mood (described above). However, it is important to note that the sample size for these analyses was likely underpowered, as only 84 participants were included in the analysis.

These results suggest that the relationship between sleep loss and mood is more likely to present as manic, rather than depressive, mood disturbances for individuals with BD. However, in each of the chapters that examined differences between sleep loss and illness polarity, the sample size for analyses on depression was always smaller than that for mania, which was usually because fewer participants reported an association between sleep loss and depression. An unexplored aspect of the sleep-mood relationship that is worth future consideration is the relationship between hypersomnia and depression. Individuals with BD are more likely than those with major depressive disorder to report hypersomnia during episodes of depression (Bowden 2005; Forty et al. 2008) and BD is characterised by high rates

of hypersomnia during periods of euthymia (Kaplan et al. 2011). Considering this and other factors that may influence the relationship between sleep and depression (e.g. alcohol use) will be important for understanding the factors involved in triggering depressive episodes in BD.

7.3 Strengths and Limitations

The main strength of the studies presented within this thesis was the use of a well-characterised sample of individuals with BD. For each participant, information on diagnosis was obtained using standardised psychiatric assessments and information from case notes. In addition, Chapter 3 and Chapter 4 utilised large sample sizes, which allowed for comparisons between BD-I and BD-II, and between men and women. Furthermore, this thesis used a variety of research methods to explore the relationship between sleep loss and mania in BD, such as using retrospective and prospective data and using interview, questionnaire and actigraphy data to ascertain the relationship between sleep and mania. In contrast to the majority of existing research on the sleep-mania relationship, the studies in this thesis explore individual differences that may affect this relationship as well as the relationship between sleep and depression in BD.

There are also a number of limitations in relation to the studies presented within this thesis. A key issue in Chapter 5 related to the smaller sample size, which meant that analyses were underpowered to detect differences between the insomnia classes identified through growth mixture modelling. This finding therefore needs to be explored in larger samples. Another issue was the low rate of recruitment to the sleep monitoring study in Chapter 6. This precluded analyses comparing the sleep of those women who relapsed in the postpartum period to those women who remained well.

There are three overarching issues that are relevant to all chapters in this thesis: (1) the assessment of sleep; (2) difficulties determining whether sleep acts as a prodrome, early warning sign, or symptom of mania; and (3) the assessment of other variables that may impact on sleep and mood (e.g. medication). These issues are discussed in the following sections.

7.4 The Role of Sleep Loss in the Genesis of Mania: Trigger, Prodrome or Symptom?

A recurring issue with interpreting the results presented in this thesis is the precise role of sleep loss in the genesis of mania, that is, whether sleep loss is a trigger, prodrome or early symptom of manic episodes. For example, in Chapter 3, participants reported whether sleep loss had previously triggered episodes of (hypo)mania. As the data were self-report and retrospective, it is possible that participants thought that sleep loss had been a trigger, when it had actually been a prodromal symptom. Likewise, the analyses in Chapter 4 also used retrospective data on sleep triggering mood episodes. In this instance, it was possible that women with PP thought that sleep loss had triggered episodes of mania due to misattributing the sleep loss that is common in the perinatal period as a cause of the postpartum episode. Chapter 5 tried to disentangle the temporal relationship between sleep and mood, as data were collected prospectively and analyses were conducted only on data from the euthymic period prior to episodes of high mood. Nonetheless, data on sleep loss were subjective and did not specify the source of the sleep loss (i.e. whether participants' insomnia symptoms were due to endogenous or exogenous factors) and it was not possible to determine whether symptoms of sleep disturbance occurring in the 'euthymic' period prior to the onset of (hypo)manic episodes were prodromal, early symptoms, or a trigger. This is also true of the data from Chapter 6; even if changes in sleep occur prior to episode onset recorded by the

clinician or participant, it is not possible to disentangle whether those changes in sleep were a trigger, prodrome or early symptoms of the episode.

Each of the chapters highlights the difficulties of determining whether sleep loss is a trigger or prodrome of manic episodes. However, a broader question is whether sleep disruption is instrumental to the aetiology of BD or an epiphenomenon (e.g. the heat from a light bulb). It is difficult to determine whether changes in sleep observed during mania are part of the manic episodes per se or merely an epiphenomenon of other manic symptoms, such as increased activity (Plante and Winkelman 2008). It was not possible to determine this in this thesis, as the available data were observational, however, as discussed in Chapter 1, sleep deprivation studies provide more compelling evidence that sleep loss can trigger mania, by demonstrating that some bipolar individuals become manic following enforced wakefulness. Nevertheless, as outlined Wehr's sleep reduction model of mania, the relationship between sleep and mood is bidirectional (Wehr et al. 1987). This means that, in theory, a unidirectional relationship between the two is transient.

The clinical implications of distinguishing whether sleep loss is a trigger, prodrome or early symptom of illness will depend on the level of personalised care to which clinicians aspire. For example, in a discussion of detecting prodromal vs. early warning signs of schizophrenia, Bustillo et al. argue that, 'The clinician is concerned not with the conceptual problem of whether the observed change precedes exacerbation or is merely the first indication of this process, but rather with detection and intervention' (Bustillo et al. 1995, p. 555). Therefore, knowing that sleep loss may signal the ascent into mania could alert clinicians to adjust patient care regardless of whether sleep loss did or did not cause (or precede) the episode. However, understanding if sleep loss acts as a trigger versus a prodrome or early symptom could be beneficial, as this would obviate the need for patients to avoid sleep-disrupting scenarios (e.g. night shifts) if these do not trigger their episodes. Therefore, understanding

more about the mechanisms by which sleep loss affects mood may inform more nuanced recommendations and treatments for some patients. For example, some research has suggested that patients who respond to sleep deprivation therapy for depression are also more likely to respond to lithium (Benedetti et al. 2014).

In summary, this thesis is not able to determine whether sleep loss is a trigger, prodrome, or early symptom of mania, but much evidence suggests that disturbances in sleep occur prior to or in the early stages of mania, thus providing an important signal of impending illness. Clinically, therefore, this could be a useful signpost for both clinicians and patients, and understanding more about which patients are more prone to experiencing sleep as a pathway to mania will ultimately improve illness management. This will be discussed in further detail in section 7.8.

7.5 Subjective vs. Objective Measures of Sleep Disruption

Another theme arising in each of the chapters in this thesis surrounds the appropriate measure of sleep. Measures of sleep can be broadly categorised as either subjective or objective. Subjective measures of sleep include interview questions, questionnaires and sleep diaries. The two main 'objective' measures of sleep used in research settings are actigraphy and polysomnography (Sadeh 2015).

Subjective measures of sleep are advantageous as they allow data to be collected on large samples and, if validated and replicated, can provide an affordable and efficient way to impact on clinical practice. However, these measures are limited by reliance on retrospective recall. This was primarily an issue in Chapters 3 and 4, which relied on retrospective data on whether sleep loss had triggered episodes of mania. These chapters attempted to address this issue via other analyses (e.g. controlling for number of mood episodes experienced). In

Chapter 5, the data on sleep prior to episodes of high mood were collected prospectively, however at each time point participants had to recall what their sleep had been like over the preceding week. In contrast, objective measures such as actigraphy and polysomnography (PSG) (described in Chapter 6) are not subject to participant recall biases. However, these techniques also have limitations. For example, although PSG provides the most comprehensive assessment of sleep, it is expensive, intrusive, and usually cannot be administered for more than a few consecutive nights (Sadeh 2015). There is also evidence that PSG can negatively affect sleep (Lee and Gay 2004).

As discussed in Chapter 6, actigraphy is less intrusive and expensive than PSG, and can monitor sleep over extended periods of time (Miller et al. 2012). However, as actigraphy relies on activity to estimate sleep, it cannot distinguish motionless wakefulness from sleep, and thus overestimates sleep durations (Sadeh 2011). Furthermore, at present, PSG and actigraphy data both require researcher input during data processing (e.g. scoring stages of sleep in PSG data currently has to be performed by researchers who are trained in interpreting these data) (Sadeh 2015). Therefore even objective measures of sleep involve an element of subjectivity in their interpretation.

In spite of the limitations outlined above, it is important to recognise that subjective measures of sleep are not always less useful than objective measures of sleep. For example, Bei and colleagues found that the subjective perception of sleep predicted subsequent postpartum depression but did not find a significant association between objectively measured sleep (via actigraphy) and postpartum mood (Bei et al. 2010). Furthermore, subjective measures could be an easier and more cost-effective option to implement in routine clinical practice.

This thesis has also highlighted that utilising 'objective' measures of sleep generates additional challenges, such as interpreting the deluge of data that results from such measures, the necessity to make subjective judgements on the data, and determining which of the many parameters derived are most useful to examine in future research.

In summary, assessing sleep is complex and each measure of sleep has distinct advantages and disadvantages, which have been highlighted in the process of this thesis. The results of this thesis are in line with recommendations to, where possible, triangulate data from a combination of objective and subjective sleep measures (Harvey et al. 2006), therefore this should be a consideration in future research examining the relationship between sleep and mood in BD.

7.6 Additional Influences on Sleep and Mood

As outlined in Chapter 1, the sleep-wake cycle is a product of interactions with the environment and circadian rhythms. A number of authors have highlighted that the relationship between sleep and mood does not operate in isolation, and can be affected by a myriad of factors such as light exposure, atypical patterns of social behaviour, medication, and substance misuse (Wulff et al. 2010; Foster and Kreitzman 2014). It is possible, therefore, that any sleep disturbances that participants observed prior to episodes of mania were an epiphenomenon of other triggers or prodromes of mania, such as stress, alcohol or other substance misuse, and medication. The results of Chapters 3, 4, and 5 were not able to examine medications that were taken during the period of sleep loss, and as shown in Chapter 6, operationalizing medication use in BD for statistical analyses can be complex due to the substantial variation between participants in types and dosages of medication taken. However, one option that has been used in other studies is to quantify medication via rubrics such as the Somatotherapy Index (Bauer et al. 1997). An additional influence on sleep in BD

women is the menstrual cycle, which has also been implicated in disturbed sleep (Parry et al. 1989; Parry et al. 2006; Shechter and Boivin 2010). Therefore, future research into the relationship between sleep and mood must attempt to consider other influences on the sleep-wake cycle, where possible, before we are able to make conclusions on how sleep loss could act as a pathway to mania.

7.7 Future Research

Suggestions for future research have been described in previous sections, however there are a number of additional avenues for future research to explore. Examples include:

1. Determining the extent to which sleep disturbances prior to mood episodes are trait-like or state-like (Harvey 2008b). For example, further analyses could explore whether participants in the 'high insomnia' class described in Chapter 5 always display high levels of sleep disruption or whether this emerges only prior to illness onset.
2. Considering how disruption to the circadian system impacts on sleep and mood – for example, changes in light exposure or social rhythms (Le Strat et al. 2008) – or how circadian preferences (i.e. chronotype) may affect course of illness or risk of developing BD (Etain et al. 2014; Abreu and Bragança 2015).
3. Delineating which characteristics of sleep increase risk of relapse. This could include comparing the effects of chronic vs. acute sleep loss or sleep fragmentation vs. total sleep duration (Montgomery-Downs et al. 2010; Philip et al. 2012).
4. Exploring whether information on genetic variation (e.g. variation in clock genes, or polygenic risk scores) can be used to predict which individuals are most vulnerable to sleep loss. For example, mutations in the gene *CLOCK* have been associated with a manic phenotype in mice (Roybal et al. 2007), and other studies have associated

single nucleotide polymorphisms with how individuals respond to sleep deprivation (Benedetti et al. 2004).

As discussed in the preceding chapters, a limitation of the datasets used in this thesis is that participants recruited to research studies may not be representative of all individuals with BD. Research using more representative samples of individuals with BD is therefore needed. In addition, the results of Chapter 5 and Chapter 6 will require further exploration in larger sample sizes in order to achieve adequate power to detect effects. Another limitation relates to the measures of sleep and mood, which were primarily based on subjective, retrospective accounts. Future work should therefore attempt to use more robust measures of sleep and mood. Finally, future research using methodologies that account for possible confounders of the relationship between sleep and mood regulation outlined above are necessary to delineate the effects (if any) of sleep on subsequent mood.

7.8 Clinical Implications

As outlined above, further research is needed before it will be possible to make definite recommendations for clinical practice. If the results in this thesis are replicated in larger, more methodologically sound studies, they might inform clinical practice via two avenues. First, by advancing understanding of the relationship between sleep and mood in BD, and second, by improving knowledge on which individuals are most likely to experience sleep loss as a pathway to mania.

7.8.1 *The Relationship Between Sleep and Mood in BD*

The results of this thesis may inform current knowledge of how sleep loss can act as a pathway (i.e. trigger or prodrome) of mania in BD. In particular, the results presented in this

thesis suggest that up to 1 in 4 individuals with BD report that sleep loss has triggered episodes of high mood at some point in the course of their illness, and that high or increasing levels of sleep disturbance over a 4-week period may signal the onset of (hypo)manic episodes in some individuals. These results highlight the importance of monitoring sleep for illness management. If sleep loss is a trigger or sign of impending relapse, identifying sleep disruption could allow clinical care teams to intervene by providing additional support, providing closer monitoring, or adjusting medication. However, further replication in larger samples that account for other influences on sleep and mood is required.

In perinatal settings, clinicians might offer additional support in improving sleep for women with BD using cognitive behavioural therapy for insomnia (CBT-I). This has been reported to be preferred by pregnant women as a treatment for insomnia compared to using pharmacotherapy (Sedov et al. 2017) and is associated with improvements in sleep and depression symptoms (Tomfohr-Madsen et al. 2017). However, this would need to be adapted for use in individuals with BD (as described in Harvey et al. 2015), as standard CBT-I includes sleep restriction.

In order for clinicians and patients to be aware of disrupted sleep requires effective monitoring. More recent technological advances could facilitate this, for example via online mood monitoring systems (such as 'True Colours', described in Chapter 5) or smartphone applications (Bhat et al. 2015; Torous and Powell 2015; Bidargaddi et al. 2016). A 2015 systematic review of smartphone apps available for monitoring symptoms in BD revealed that less than 50% provided the option to monitor sleep (Nicholas et al. 2015). However, ethical issues regarding the use of this digital technology (e.g. privacy and validity) must be considered before recommending its use in clinical settings (Bidargaddi et al. 2016; Bauer et al. 2017). Such technology would also need to account for other triggers of mood episodes, such as medication, stressors, and substance use.

7.8.2 Individual Differences in Whether Sleep Loss Acts as a Pathway to Mania

If replicated, the findings of this thesis may also be informative for clinical practice due to highlighting the importance of individual differences in how sleep loss may act as a pathway to mania. Identifying which individuals exhibit sleep disturbances as part of 'relapse signature' could be helpful for illness management and there are a number of ways in which this information could be utilised in clinical settings. For example, there is a version of the online mood monitoring system used in Chapter 5 that is currently used in clinical settings. In theory, clinicians using this system could examine whether some patients display increasing levels of insomnia prior to episodes of high mood, and use this information to modify these patients' care if the system indicates that they are experiencing high or increasing sleep disturbance. Ideally, mood-monitoring systems would automatically learn from an individual's data whether sleep disturbances signalled the onset of mood episodes, and would automatically notify patients and/or their clinicians of this information. However, whether it is possible to use information on sleep to predict and prevent mood episodes will only be ascertained following substantial further research.

In addition, if it is known that some individuals are more prone to relapse following exposure to sleep loss-inducing events (e.g. shift work, long-haul travel), care and medication could be adjusted during these times of increased risk. These individuals could also be a focus for interventions that aim to improve sleep. For example, a pilot randomised control trial found that cognitive behavioural therapy for insomnia that was modified for use in bipolar individuals (CBTI-BP) was associated with a reduced risk of relapse at 6-month follow up (Harvey et al. 2015). For women with BD who are pregnant, clinicians could ask whether sleep loss has previously triggered episodes of mania. If so, perinatal teams could pay particular attention to the sleep loss in pregnancy and postpartum and introduce measures to minimise

this (e.g. help with night time nursing) or utilised other methods of improving sleep outlined above.

7.9 Final Conclusions

In 1609, Thomas Dekker extolled the virtues of sleep for physical and mental health, noting that too little ‘tumbles us into a Church-yard, and to use it but indifferently, throwes[sic] us into Bedlam’ (Dekker 1609 p.10). Over 400 years later, Dekker’s observations have been corroborated in multiple clinical and scientific observations, but there is still much we do not understand about the relationship between sleep loss and mental health. Existing research has established an association between sleep loss and the genesis of mania in BD, but this research also suggested that there are individual differences in this relationship.

This thesis extends previous research by first, providing further confirmation that only a subgroup of individuals with BD will experience sleep loss as a pathway to mania. Second, that this phenotype is potentially associated with female gender and BD-I diagnoses, and could potentially index risk for PP. Third, this thesis highlights the methodological difficulties of measuring perinatal sleep objectively in women at high risk of PP, as well as identifying sleep parameters that may be useful to monitor in larger studies. Finally, the findings of this thesis suggest that sleep loss is less frequently observed as a trigger or early warning sign of depression than mania.

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9 APPENDICES

EPISODES OF DEPRESSION

Depression Triggers

Have you noticed anything that tends to trigger your episodes of depression? (for example sleep loss, physical illness, alcohol, drugs, medication or anything else)

Please record triggers and whether these were 'ever' a trigger or 'usually' a trigger

.....
.....
.....
.....

DEPRESSION TRIGGERS

Sleep loss

Ever

Usually

Physical illness

Ever

Usually

Alcohol

Ever

Usually

Non-presc. drugs

Ever

Usually

Medication

Ever

Usually

Appendix B - Quick Inventory of Depressive Symptomatology (Self-Report)

Please checkmark the one response to each item that is most appropriate to how you have been feeling over the past 7 days.

Q1. Falling asleep	
0	I never take longer than 30 minutes to fall asleep.
1	I take at least 30 minutes to fall asleep, less than half the time (3 days or less out of the past 7 days).
2	I take at least 30 minutes to fall asleep, more than half the time (4 days or more out of the past 7 days).
3	I take more than 60 minutes to fall asleep, more than half the time (4 days or more out of the past 7 days).
Q2. Sleep during the night	
0	I do not wake up at night.
1	I have a restless, light sleep, briefly waking up a few times each night.
2	I wake up at least once a night, but I got back to sleep easily.
3	I wake up more than once a night and stayed awake for 20 minutes or more, more than half the time (4 days or more out of the past 7 days).
Q3. Waking up too early	
0	Most of the time, I woke up no more than 30 minutes before my scheduled time.
1	More than half the time (4 days or more out of the past 7 days), I woke up more than 30 minutes before my scheduled time.
2	I almost always woke up at least one hour or so before my scheduled time, but I got back to sleep eventually.
3	I woke up at least one hour before my scheduled time, and couldn't get back to sleep.
Q4. Sleeping too much:	
0	I slept no longer than 7-8 hours/night, without napping during the day.
1	I slept no longer than 10 hours in a 24-hour period including naps.
2	I slept no longer than 12 hours in a 24-hour period including naps.
3	I slept longer than 12 hours in a 24-hour period including naps.
Q5. Feeling sad:	
0	I didn't feel sad.
1	I felt sad less than half the time (3 days or less out of the past 7 days).
2	I felt sad more than half the time (4 days or more out of the past 7 days).
3	I felt sad nearly all of the time.
Please complete either 6 or 7 (not both)	
Q6. Decreased appetite	
0	There was no change in my usual appetite.
1	I ate somewhat less often or smaller amounts of food than usual.
2	I ate much less than usual and only by forcing myself to eat.
3	I rarely ate within a 24-hour period, and only by really forcing myself to eat or when others persuaded me to eat.
Q7. Increased appetite	
0	There was no change in my usual appetite.
1	I felt a need to eat more frequently than usual.
2	I regularly ate more often and/or greater amounts of food than usual
3	I felt driven to overeat both at mealtime and between meals.
Please complete either 8 or 9 (not both)	
Q8. Decreased weight (within the last 14 days):	
0	My weight has not changed.
1	I feel as if I've had a slight weight loss.
Q9. Increased weight (within the last 14 days):	
0	My weight has not changed.
1	I feel as if I've had a slight weight gain.

2	I've lost 2 pounds (about 1 kilo) or more.	2	I've gained 2 pounds (about 1 kilo) or more.
3	I've lost 5 pounds (about 2 kilos) or more.	3	I've gained 5 pounds (about 2 kilos) or more.
Q10. Concentration/decision-making:			
0	There was no change in my usual ability to concentrate or make decisions.		
1	I occasionally felt indecisive or found that my attention wandered.		
2	Most of the time, I found it hard to focus or to make decisions.		
3	I couldn't concentrate well enough to read or I couldn't make even minor decisions.		
Q11. Perception of myself:			
0	I saw myself as equally worthwhile and deserving as other people.		
1	I put the blame on myself more than usual.		
2	For the most part, I believed that I caused problems for others.		
3	I thought almost constantly about major and minor defects in myself.		
Q12. Thoughts of my own death or suicide:			
0	I didn't think of suicide or death.		
1	I felt that life was empty or wondered if it was worth living.		
2	I thought of suicide or death several times for several minutes over the past 7 days.		
3	I thought of suicide or death several times a day in some detail, or I made specific plans for suicide or actually tried to take my life.		
Q13. General interest:			
0	There was no change from usual in how interested I was in other people or activities.		
1	I noticed that I was less interested in other people or activities.		
2	I found I had interest in only one or two of the activities I used to do.		
3	I had virtually no interest in the activities I used to do.		
Q14. Energy level:			
0	There was no change in my usual level of energy.		
1	I got tired more easily than usual.		
2	I had to make a big effort to start or finish my usual daily activities (for example: shopping, homework, cooking or going to work).		
3	I really couldn't carry out most of my usual daily activities because I just didn't have the energy.		
Q15. Feeling more sluggish than usual:			
0	I thought, spoke, and moved at my usual pace.		
1	I found that my thinking was more sluggish than usual or my voice sounded dull or flat.		
2	It took me several seconds to respond to most questions and I was sure my thinking was more sluggish than usual.		
3	I was often unable to respond to questions without forcing myself.		
Q16. Feeling restless (agitated, not relaxed, fidgety):			
0	I didn't feel restless.		
1	I was often fidgety, wringing my hands, or needed to change my sitting position.		
2	I had sudden urges to move about and was quite restless.		
3	At times, I was unable to stay seated and needed to pace around.		

QIDS Scoring algorithm: The QIDS-SR₁₆ total score is calculated by adding scores obtained for items: Sad mood, concentration/decision-making, outlook (self), suicidal ideation, general interest, energy/fatigability, the highest score on any of the four sleep items (sleep onset insomnia; midnocturnal insomnia; early morning insomnia; hypersomnia); the highest score on any one of the four appetite/weight change items (appetite increase; appetite decrease; weight increase; weight decrease); and the highest score on the two psychomotor agitation/retardation items (psychomotor slowing; psychomotor agitation) (total score range: 0–27) (Rush et al 2000).

Appendix C - Altman Self-Rating Mania Scale

There are 5 groups of statements in this questionnaire, read *each* group of statements carefully. You should choose the statement in each group that best describes the way you have been feeling for the past week.

Please note: The word ‘occasionally’ when used here means once or twice; ‘often’ means several times or more and ‘frequently’ means most of the time.

Q1. Happiness	
0	I do not feel happier or more cheerful than usual.
1	I occasionally feel happier or more cheerful than usual.
2	I often feel happier or more cheerful than usual.
3	I feel happier or more cheerful than usual most of the time.
4	I feel happier or more cheerful than usual all of the time.
Q2. Confidence	
0	I do not feel more self-confident than usual.
1	I occasionally feel more self-confident than usual.
2	I often feel more self-confident than usual.
3	I feel more self-confident than usual.
4	I feel extremely self-confident all of the time.
Q3. Sleep	
0	I do not need less sleep than usual.
1	I occasionally need less sleep than usual.
2	I often need less sleep than usual.
3	I frequently need less sleep than usual.
4	I can go all day and night without any sleep and still not feel tired.
Q4. Talking	
0	I do not talk more than usual.
1	I occasionally talk more than usual.
2	I often talk more than usual.
3	<input type="radio"/> I frequently talk more than usual.
4	I talk constantly and cannot be interrupted.
Q5. Activity	
0	I have not been more active (either socially, sexually, at work, home or school) than usual.
1	I have occasionally been more active than usual.
2	I have often been more active than usual.
3	I have frequently been more active than usual.
4	I am constantly active or on the go all the time.

EG Altman, D Hedeker, JL Peterson, JM Davis. *The Altman Self-Rating Mania Scale*. 42: *Biol Psychiatry* 948-955. 1997.

Appendix D – Comparison of Triggers of Mood Episodes by Gender

It is possible that women were more likely than men in general to report or notice triggers of their mood episodes. However, examining women’s responses to other trigger questions included in the interview did not suggest that they consistently report triggers more often than men. For example, as shown in Table 9-1, women are less likely than men to report that alcohol or non-prescription drugs have triggered episodes of (hypo)mania.

Table 9-1. Comparison between men and women in likelihood of reporting different triggers of mood episodes.

	Female OR (95% CI), p value					
	Sleep Loss	Physical Illness	Medication	Antidepressants	Alcohol	Non-prescription drugs
Triggers of (hypo)mania (n = 3140)	1.43 (1.18-1.75) p <.001	1.94 (1.12-3.37) p =.019	1.14 (0.76-1.72) p =.528	1.16 (0.90-1.49) p =.245	0.78 (0.59-1.04) p =.085	0.61 (0.44-0.83) p =.001
Triggers of depression (n= 3064)	1.37 (1.07-1.77) p =.013	1.92 (1.41-2.62) p <.001	1.68 (0.97-2.88) p =.063	N/A	0.82 (0.62-1.08) p =.158	0.93 (0.60-1.45) p =.756

Appendix E – True Colours Example Participant Summary Graph

Example screenshot of summary graph available to participants using the True Colours mood monitoring system.



Appendix F – Sample Size Calculations for Chapter 5

Sample sizes for future studies were calculated in R using the method outlined in (Noordzij et al. 2011). Specifically, the sample size for a binary outcome is calculated as:

$$n = \frac{[(a + b)2 (p_1 q_1 + p_2 q_2)]}{x^2}$$

Where:

n = the sample size in each group
 p_1 = proportion of participants with the outcome in Group 1
 q_1 = proportion of participants without outcome in Group 1
 p_2 = proportion of participants with the outcome in Group 2
 q_2 = proportion of participants without the outcome in Group 2
 x = the expected difference in the event rate
 a = conventional multiplier for alpha = 0.05
 b = conventional multiplier for power = 0.80

This calculation is based on a binary outcome, therefore the sample sizes required for each of the class comparisons were calculated in pairs (i.e. ‘Increasing’ vs. ‘Low’, ‘Increasing’ vs. ‘High’, and ‘Low’ vs. ‘High’). In addition, the expected difference in event rate (x) was calculated as the observed difference between groups observed in this study. Sample size calculations for key variables of interest (bipolar diagnosis, gender, and presence of a depressive episode) are shown in Table 9-2.

Table 9-2. Sample sizes per group for class comparisons (alpha = 0.05, power = 0.80)

	Class Comparisons		
	‘Increasing’ (1) vs. ‘Low’ (0)	‘Increasing’ (1) vs. ‘High’ (0)	‘Low’ (1) vs. ‘High’ (0)
Bipolar Diagnosis (BD-I vs. BD-II)	62	137	628
Gender	259	1782	679
Depressive Episode	47	311	23

Classes: ‘Increasing’ (n=8), ‘Low’ (n=113), ‘High’ (n=24). BD-I, Bipolar Disorder type I; BD-II, Bipolar

Disorder type II.

Appendix G – Sleep Disorder Screening Questions

1. Narcolepsy

- a. Do you sometimes fall asleep in the daytime completely without warning?
 - b. Is it literally impossible to resist 'sleep attacks' during the day?
 - c. Do you have collapses or extreme muscle weakness triggered by extreme emotion?
 - d. Do you have visual hallucinations, either just as you fall asleep or when you wake in the morning?
 - e. Are you paralyzed and unable to move when you wake up from your sleep?

[Possible narcolepsy: 1a = "TRUE" AND (1b OR 1c OR 1d OR 1e = "TRUE")]

2. Sleep breathing disorder

- a. Are you a very heavy snorer?
 - b. Does your partner say that you sometimes stop breathing?
 - c. Do you often wake up gasping for a breath?
 - d. Are you often excessively sleepy during the day or fall asleep without wanting to?

[Possible sleep breathing disorder: 2a = "TRUE" AND (2b OR 2c OR 2d = "TRUE")]

3. PLMS/ RLS

- a. Do your legs often twitch or jerk or can't keep still in bed?
 - b. Is it very difficult to get to sleep because of repeated muscle jerks?
 - c. Do you frequently wake from sleep with sudden jerky movements or with a compulsion to move your legs?
 - d. Do you simply have to get out of bed and pace around to get rid of these feelings?

[Possible PLMS/ RLS: 3a = "TRUE" AND (3b OR 3c OR 3d = "TRUE")]

4. Circadian Rhythm Sleep Disorder

- a. Do you tend to sleep well but just at the "wrong times"?
 - b. Can you sleep well enough, but only if you stay up very late?
 - c. Are you in a very sound sleep at normal waking time and could sleep on for hours more?
 - d. Can you sleep well enough, but only if you go to bed very early?
 - e. Do you wake very early, bright and alert and no longer sleepy?

[Possible CRSD: 4a = "TRUE" AND EITHER (4b AND 4c = "TRUE") OR (4d AND 4e = "TRUE")]

5. Parasomnia

- a. Do you have unusual behaviours associated with your sleep that trouble you or that are dangerous?
 - b. Do you sleepwalk frequently and run the risk of injuring yourself or others?
 - c. Do you have frequent night terrors when you are extremely distressed but not properly awake?
 - d. Do you act out your dreams and risk injuring yourself or others?
 - e. Do you have terrible recurring nightmares?

[Possible parasomnia: 5a = "TRUE" AND EITHER (5b OR 5c OR 5d OR 5e = "TRUE")]

Appendix H – Sleep Diary and Actigraphy Instructions

(see overleaf)

Actigraphy Instructions:

The Actiwatch

What is an Actiwatch?



The Actiwatch is a medical device that records motion and light. It contains a tiny computer so it should not be dropped or banged.

What will it tell about me?

The Actiwatch provides information about your sleep quantity and quality.



Where and how do I wear it?



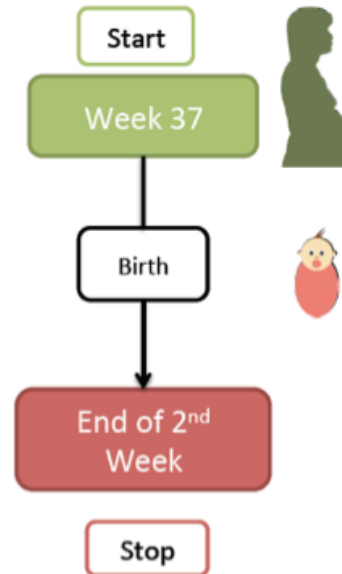
Wear the Actiwatch snugly and securely on your wrist.

If you are **right-handed**, wear it on your **left wrist**. If you are **left-handed**, wear it on your **right wrist**.



When do I wear it?

Wear the Actiwatch from the start of **Week 37** of pregnancy until the **end of the 2nd week after you have given birth**.



If you need to take it off for any reason, keep it in a safe place. Wear it again as soon as you can.

Do I have to take it off for showering or bathing?



The Actiwatch is water resistant up to 1 metre depth so you can wear it while you shower or bathe but should take it off when swimming.



The Actiwatch Screen

The Actiwatch screen will change while you wear it. Below explains what each screen means and lets you know if you need to do anything in particular.

Standby



If you receive the Actiwatch before your 37th week of pregnancy, when you wear it the screen will **only show the time**. This means that the Actiwatch is waiting to collect data.

You do not need to do anything.

Collecting Data



When the Actiwatch starts to collect data, it will show the **time and a black border** that will circle around the edge.

Off Wrist



(Flashing)

If you take the Actiwatch off you will see a **flashing border** (this will also show if the Actiwatch is not fastened properly to your wrist).

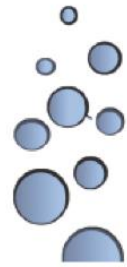
Refasten the watch to your wrist until the flashing stops (it might take up to 45 seconds for the screen to return to normal).

Data Collection Complete



This screen means that data collection is complete. You should now return the Actiwatch in the envelope that will have been sent to you.

Other Questions



Can I clean my Actiwatch?

Yes, you can use a soft cloth moistened in mild detergent and water to remove dirt and stains. Do not use abrasives or alcohol as they may damage the device.

What do I do if my Actiwatch is broken?

If you think the Actiwatch is broken, contact Katie as soon as you can. Her contact details are on the opposite page.

What do the buttons on the Actiwatch do?

Left Button

You do not need to use this.

Do not worry if you accidentally press it.



Right Button

- Press to use the backlight
- Press for 3 seconds to show the data

Questions



If you have any questions, Katie will be happy to help. Her contact details are below:



Sleep Diary Instructions:

Sleep Diary Instructions



Complete your sleep diary **when you get out of bed in the morning**



Fill out the diary **every day** using **pencil**.

1 Each grid **starts in the evening** at 6pm and continues into the **next day** (e.g. **Monday evening** to **Tuesday daytime**)

Draw a line to show the time you **tried to go to sleep**.

This may be different from the time you got into bed.

Draw another line to show the time you **got out of bed for the day**.

3 If you wake up during the night, leave those times **blank**.

Awake between 2:30am and 3:30am

4 Don't forget to shade in any times you **fall asleep in the day**.

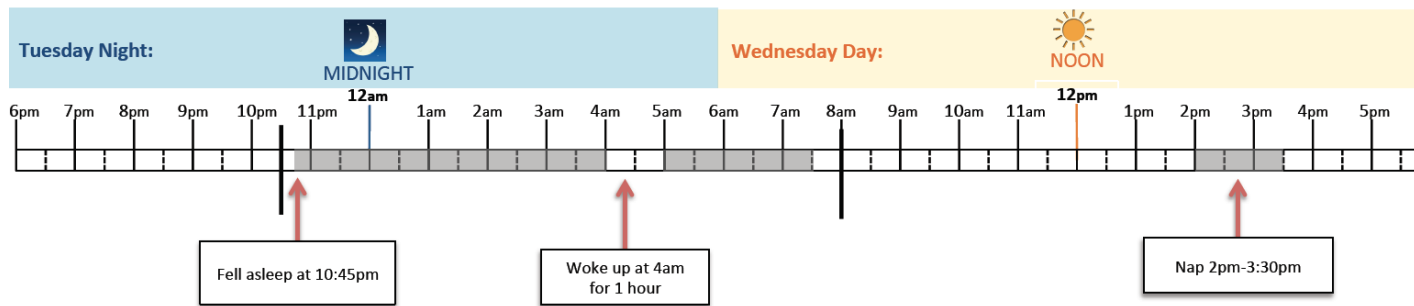
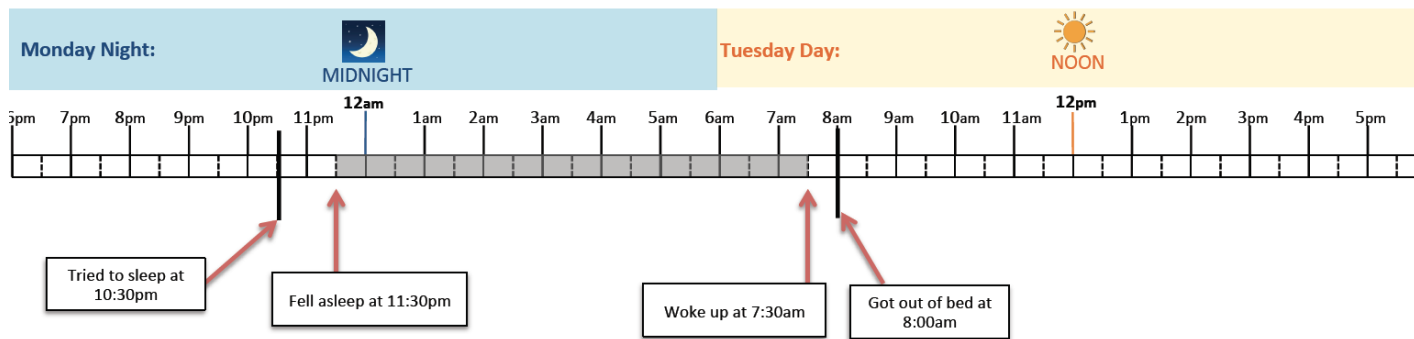
Afternoon nap between 2:00pm and 3:45pm

2 Shade in the times you were asleep to the nearest 15 mins.

Don't worry about exact times, just give your best estimate.

5 Finally, in the circle rate your sleep quality on a scale of 1 "very restless" to 10 "very sound".

Sleep Diary Examples



N.B. You do not have to add notes to your diary.

Appendix I – GP and Psychiatrist Questionnaires

GP Questionnaire:

Pregnancy and Childbirth Questionnaire

Q 1. Date of delivery

Q 2. Pregnancy outcome

Live birth
Stillbirth
Termination
Miscarriage

Q 3. Delivery modality

Normal vaginal delivery
Elective caesarean section
Emergency caesarean section
Forceps / Ventouse

Q. 4 Baby health status:

Healthy
Minor problem
Major problem

Please give brief details of any problems:

Q 5. Has she suffered an episode of psychiatric illness in this pregnancy or post-partum period?

Yes No

If yes please give brief details:

Completed by:

Name

Position

Date

Address

E-mail address

Telephone number

Please send completed questionnaire in the pre-paid envelope provided

Thank you for your time

Pregnancy and Childbirth Questionnaire

Q1. Episodes of psychiatric illness during pregnancy

Did she experience an episode of depression during the pregnancy?

Yes No Unknown

Did she experience an episode of mania, hypomania or a mixed affective episode during the pregnancy?

Yes No Unknown

Did she experience another form of psychiatric episode during the pregnancy?

Yes No Unknown

If yes please give brief details:

If yes to any of the above, was the onset of the episode;

In the first trimester of pregnancy	Yes <input type="checkbox"/>	No <input type="checkbox"/>
In the second trimester of pregnancy	Yes <input type="checkbox"/>	No <input type="checkbox"/>
In the third trimester of pregnancy	Yes <input type="checkbox"/>	No <input type="checkbox"/>
A continuation of an episode from before pregnancy	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Was she admitted to hospital?

Yes No

Q 2. Episodes of psychiatric illness in the postpartum period

Did she experience an episode of depression following this delivery?

Yes No

Did she experience an episode of mania, hypomania or a mixed affective episode following this delivery?

Yes No

Did she experience another form of psychiatric episode following this delivery?

Yes No

If yes please give brief details:

If yes to any of the above, was the onset of the episode:

the continuation of an episode from pregnancy

Yes

No

an onset following delivery

Yes

No

If a postpartum onset, when was the onset in relationship to delivery?

days **Or**

weeks following delivery

Was she admitted to hospital?

Yes No

Q 3. Medication in relationship to the pregnancy

What prescribed medication did she take in the 6 months before pregnancy?
(Please indicate daily doses and say when any changes were made)

What prescribed medication did she take during the pregnancy?
(Please indicate daily doses and say when any changes were made)

What prescribed medication did she take in the postpartum period?
(Please include daily doses and say when any changes made)

Completed by:

Name

Position

Date

Address

E-mail address

Telephone number

Please send completed form in the pre-paid envelope provided

Thank you for your time

Appendix J – Actigraphy Data Processing Protocol

Protocol for processing actigraphy data once uploaded to Actiware software.

1. **Identify bed times (BT) and rise times (RT)** from sleep diary
2. **Calculate automatic rest intervals.**
3. **Increase visibility of actogram:** change max activity level to 500 or 1000 and set actogram to show only 1 or 2 days at a time.
4. If there are diary BTs and RTs, delete the automatic interval. Add diary bed times and rise times as a [custom interval](#) on the software.
5. Add **REST INTERVALS** using the following method:
 - a. **BTs:**
 - i. Using the self-report BT as a guide, check ~30 mins before and after for a drop in activity
 - ii. Set BT to begin 3 mins before drop in activity.
 - b. **RTs:**
 - i. Using the self-report RT as a guide, check ~30 mins before and after for the presence of continuous activity.
 - ii. Set RT 3 minutes into presence of continuous activity
6. If no diary information is available or there are large discrepancies between sleep diary and activity data, examine actogram for periods of inactivity based on:
 - a. the general level of concordance between each participant's diary entries and activity.
 - b. the level and persistence of activity (i.e. high and persistent vs. low and fragmented).
 - c. examination of activity around previously reported bed/rise times to determine whether participants showed a common 'activity signature' during these times.

And apply steps 4-5 and note the decision made.

Appendix K – Participant Correspondence

Participant correspondence 1:

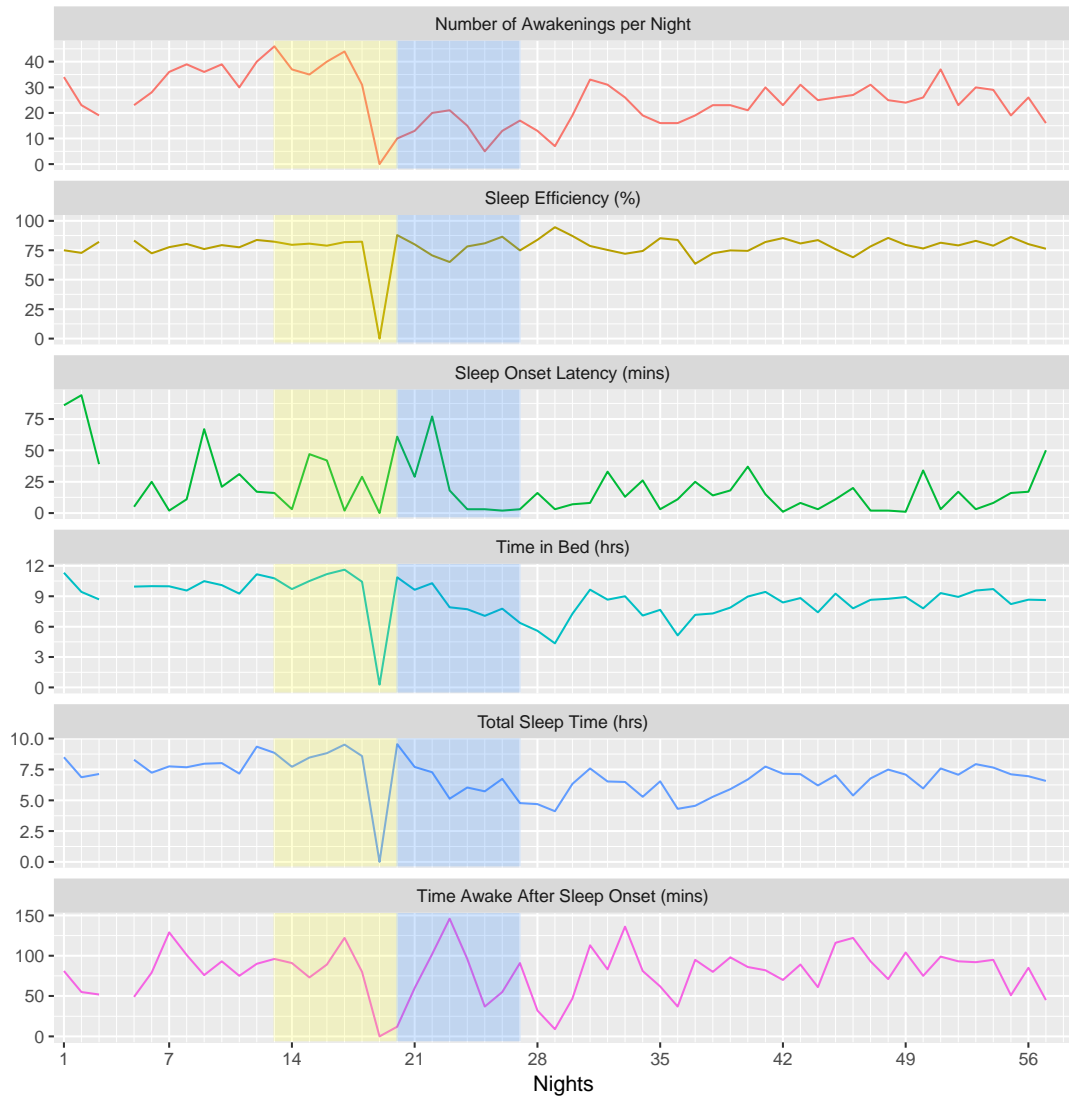
'I really wanted to assist in this research but immediately found wearing the watch [actigraph] and trying to rate when I was awake actually disturbed my ability to go to sleep. Firstly, I don't normally wear a watch and found it hot and uncomfortable; I was very conscious of how it felt on my wrist – preventing me fall[sic] asleep. I was even more conscious of (still) being awake when I knew that I should have been asleep. In the mornings, after having very little sleep, I asked my partner how he would have been able to track whether he was asleep or not – he said that he thought that tracking sleep patterns on the log was reasonable; for me I kept checking my watch through the night or wondering whether I was still truly awake or partially awake or on my way to sleep then wondering whether I would remember the next morning whether it had been half hour or more since I last check the watch. Being this conscious of my sleep patterns 'caused' me to have a very restless night and it reminded me of how my bipolarity is affected by poor sleep as well as how much sleep – or lack of it – is a feature of the days before a manic episode. As a result I decided to not continue wearing the watch as I didn't want to jeopardise my mental health in my last trimester and certainly in the early postnatal weeks. Very sorry not to have helped more.'

Participant correspondence 2:

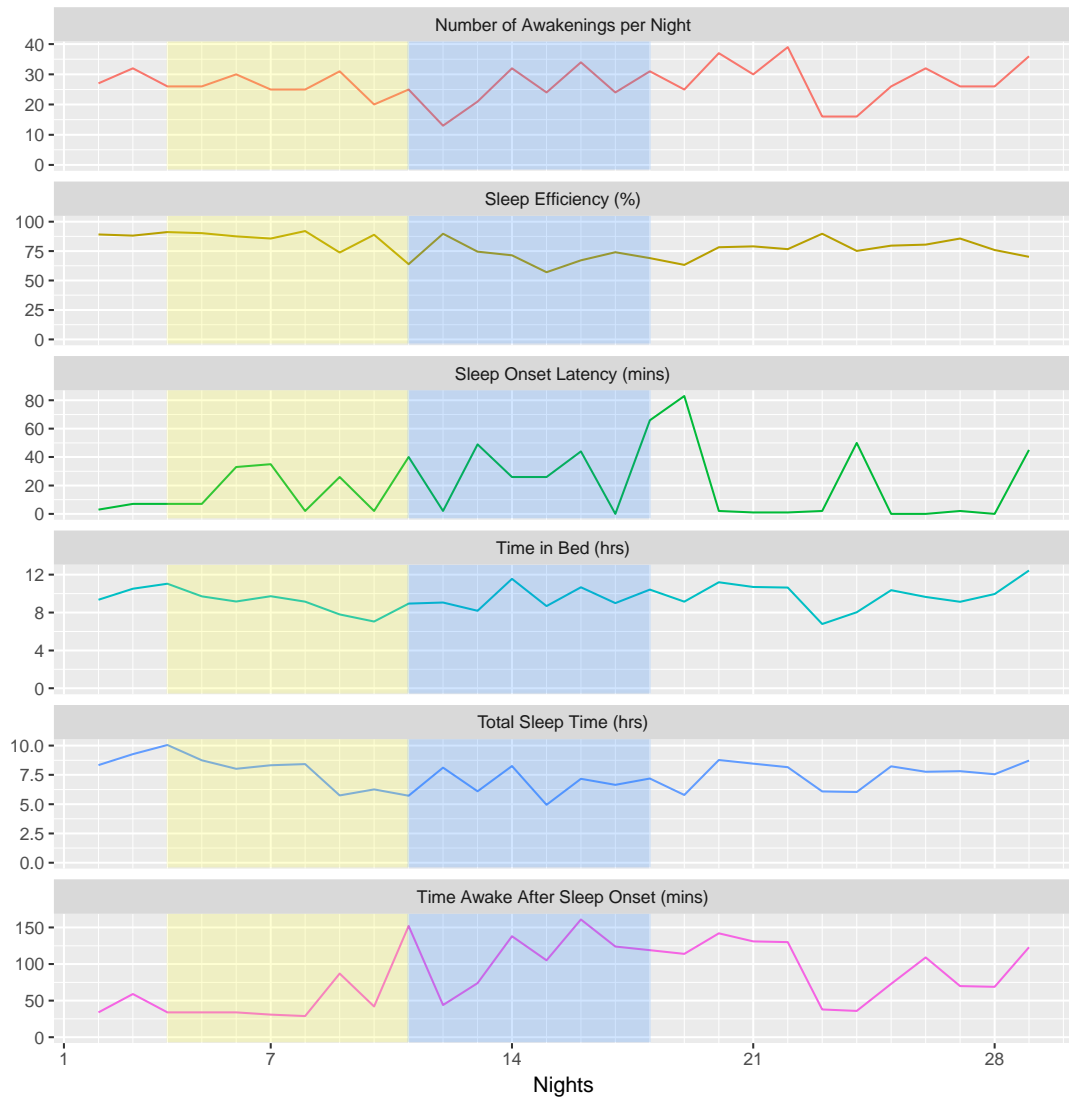
'I apologise wholeheartedly but I am unable to continue with the Actiwatch [actigraph] – I am struggling to find the time to keep an accurate sleep diary and find sleeping whilst wearing it quite uncomfortable. I'm so sorry to have to return it, I really wish you all the best with your study. Good luck!'

Appendix L – Participant Sleep Charts Derived From Actigraphy Data

Participant 1



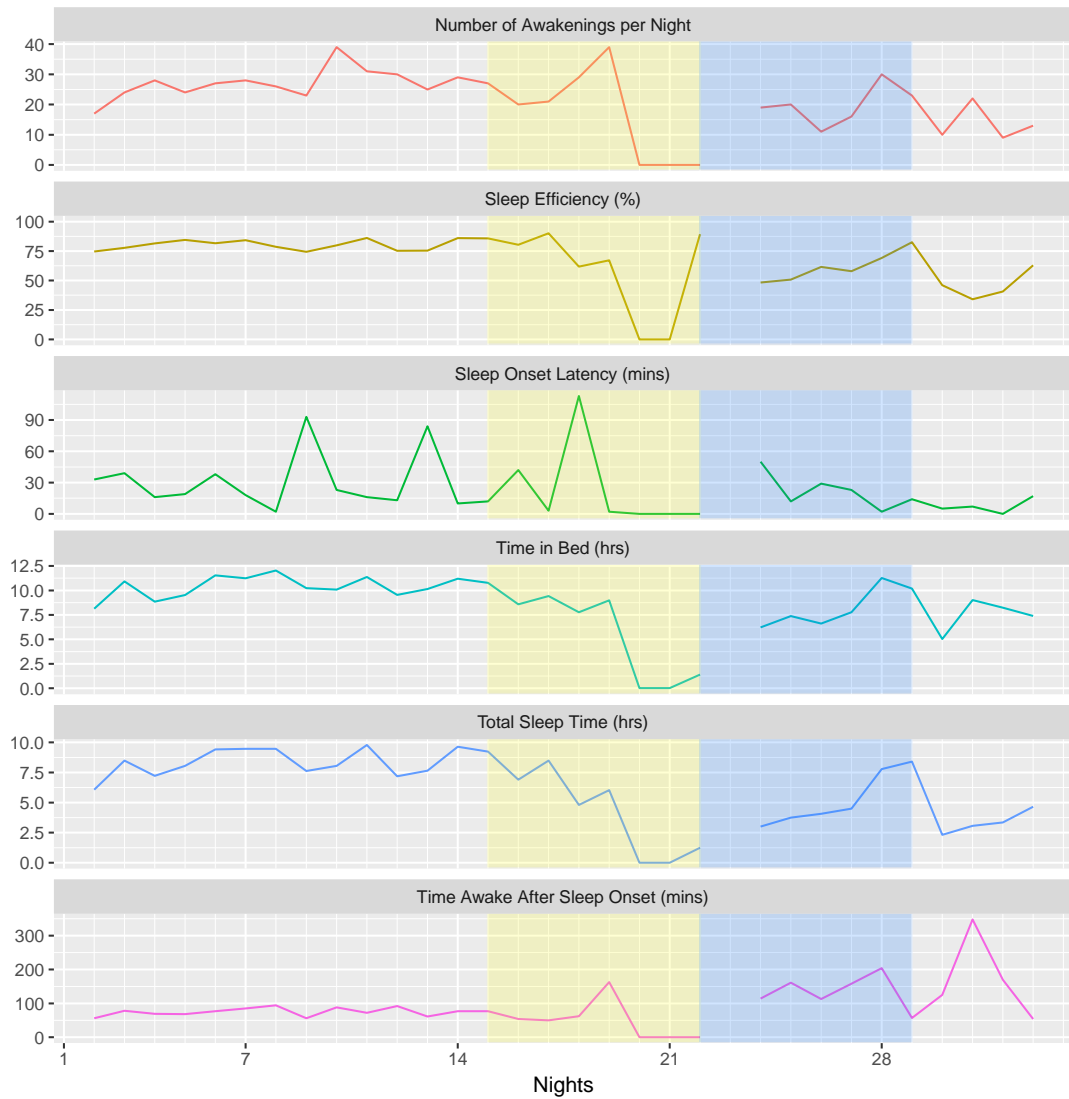
Participant 2



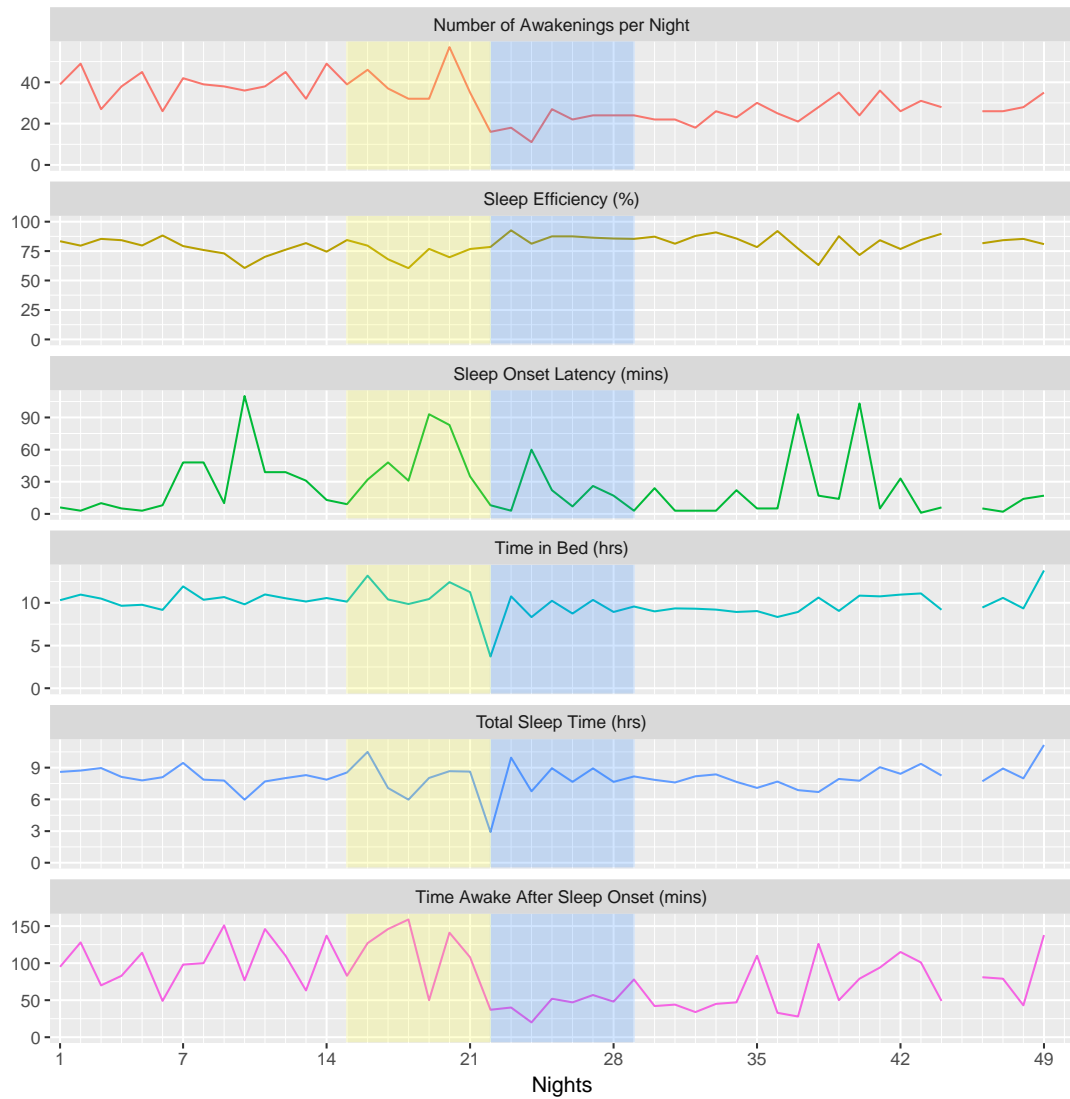
Participant 3



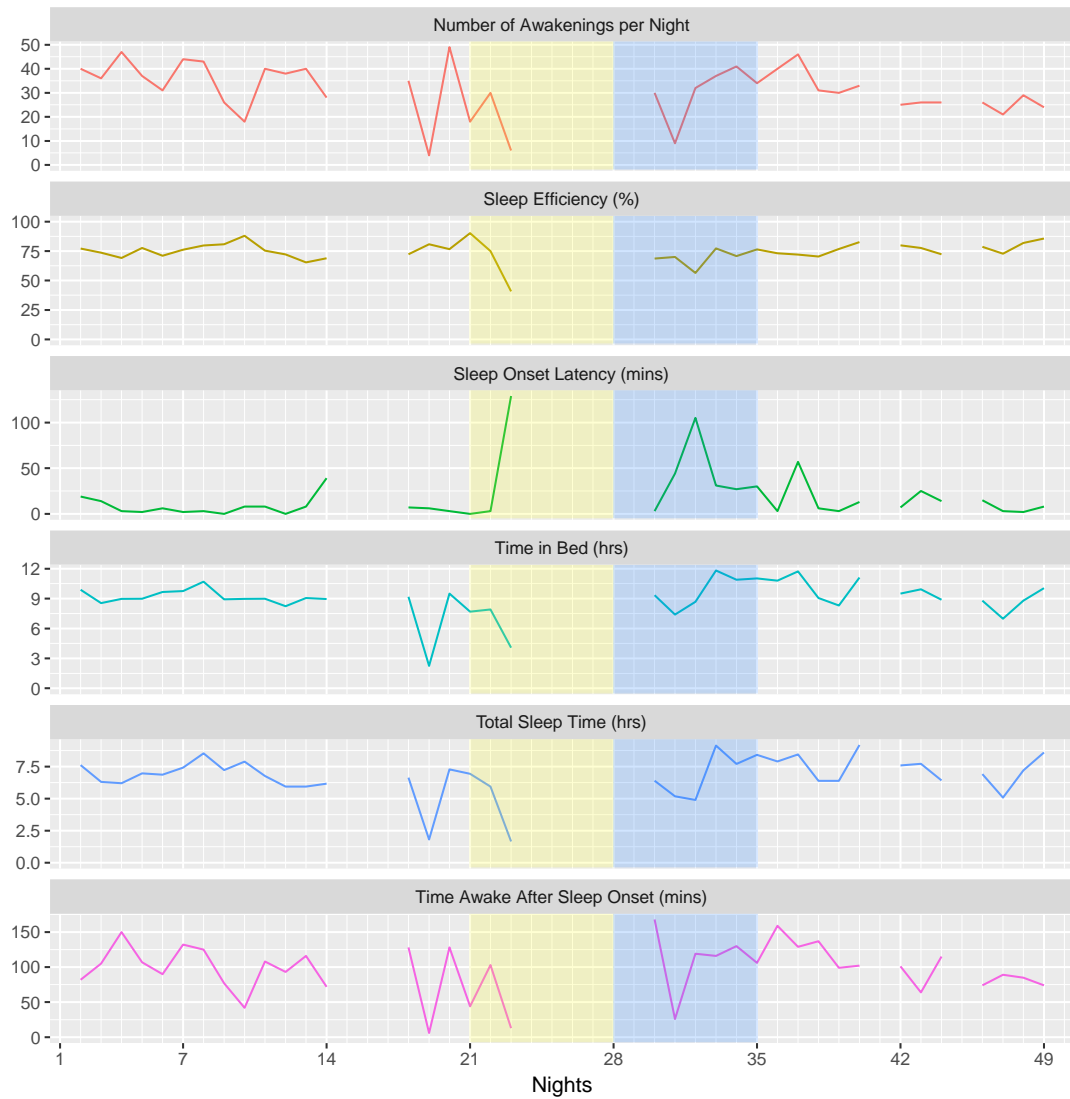
Participant 4



Participant 5



Participant 6



Participant 7

