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The Effect of Poor Sleep Quality on Mood Outcome Differs Between Men and Women: A Longitudinal Study of Bipolar Disorder

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Abstract

Background—Sleep disturbance is bi-directionally related to mood de-stabilization in bipolar disorder (BD), and sleep quality differs in men and women. We aimed to determine whether perception of poor sleep quality would have a different effect on mood outcome in men versus women.

Methods—We assessed association between sleep quality (Pittsburgh Sleep Quality Index (PSQI)) at study intake and mood outcome over 2 years in subjects from the Prechter Longitudinal

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Study of Bipolar Disorder (N=216; 29.6% males). The main outcome measure was the severity, variability, and frequency of mood episodes measured by self-report over 2 years of follow-up. Multivariable linear regression models stratified by sex examined the relationship between PSQI with mood outcomes, while age, stressful life events, mood state and neuroticism at baseline were controlled.

Results—In women, poor sleep quality at baseline predicted increased severity (B=0.28, p<0.001) and frequency of episodes (B=0.32, p<0.001) of depression, and poor sleep quality was a stronger predictor than baseline depression; poor sleep quality predicted increased severity (B=0.19, p<0.05) and variability (B=0.20, p<0.05) of mania, and frequency of mixed episodes (B=0.27, p<0.01). In men, baseline depression and neuroticism were stronger predictors of mood outcome compared to poor sleep quality.

Limitations—We measured perception of sleep quality, but not objective changes in sleep.

Conclusions—In a longitudinal study of BD, women reported poorer perceived sleep quality than men, and poor sleep quality predicted worse mood outcome in BD. Clinicians should be sensitive to addressing sleep complaints in women with BD early in treatment to improve outcome in BD.

Keywords

bipolar disorder; sleep; mood; depression; mania; sex

Introduction

Bipolar disorder (BD) is a recurrent, disabling illness. Though BD is an episodic illness, individuals with BD suffer from depressive symptoms up to 32% of the time, and manic symptoms about 9% of the time (Judd, Akiskal et al. 2002). Subsyndromal and mixed symptoms are prevalent, and contribute to restricting the effort of individuals with BD to achieve life goals in areas such as education, occupation, and personal relationships (Judd, Akiskal et al. 2005).

Poor sleep quality is a state marker and symptom of depressive and manic episodes (Goodwin and Jamison 2007). Lack of sleep can incite mania, and sleep deprivation has been shown since the 1970s to treat depressions (Wu and Bunney 1990, Jackson, Cavanagh et al. 2003), especially in bipolar disorder (Barbini, Colombo et al. 1998, Colombo, Benedetti et al. 1999). Insomnia and poor sleep quality has been linked to worse symptom severity and poor outcome in bipolar disorder (Wu and Bunney 1990, Colombo, Benedetti et al. 1999, Bauer, Grof et al. 2006, Perlman, Johnson et al. 2006, Gruber, Harvey et al. 2009, Gruber, Miklowitz et al. 2011). Also, sleep-disordered breathing, primary insomnia and sleep phase disorders are often comorbid with bipolar disorder, begging the question of these pathologies being related to the underlying mood pathology (Kripke, Mullaney et al. 1978, Wehr 1992, Harvey 2008, Soehner, Kaplan et al. 2013, Naqvi, Wang et al. 2014).

Rates and phenotypes of mood disorders differ between men and women. Women of reproductive age were more prone to depression in the Stanley Foundation bipolar disorder cohort (Altshuler, Kupka et al. 2010), but not in the STEP-BD study (Baldassano, Marangell

et al. 2005). In addition, the comorbidity of BD with illnesses that present with gender differences (including anxiety disorders (Baldassano, Marangell et al. 2005, Baldassano 2006, Altshuler, Kupka et al. 2010, Saunders, Fitzgerald et al. 2012), migraine (Fasmer 2001, Low, Cui et al. 2007, Baptista, Uzcategui et al. 2012, Saunders, Nazir et al. 2014), and eating disorders (Baldassano, Marangell et al. 2005, Baldassano 2006, Jen 2013)) has been shown to cause more depression and worse course of illness in BD. Women in the general population report more insomnia than men during the reproductive years at a ratio of 1.4:1.0, (Ohayon 2002, Zhang and Wing 2006, Phillips, Collop et al. 2008, Fernandez-Mendoza, Vgontzas et al. 2012, Singareddy, Vgontzas et al. 2012, Vgontzas, Fernandez-Mendoza et al. 2012), and persistence of insomnia has been associated with depressive disorders, as well as sleep misperception (Fernandez-Mendoza, Calhoun et al. 2011, Fernandez-Mendoza, Vgontzas et al. 2012).

Sleep and gender are both important factors in influencing course of illness in bipolar disorder (Baldassano 2006, Gruber, Harvey et al. 2009, Eidelman, Talbot et al. 2010, Gruber, Miklowitz et al. 2011, Saunders, Fitzgerald et al. 2012, Saunders, Nazir et al. 2014). Women in the general population have more insomnia than men and women are also more prone to mood disorders and different courses of illness in BD. We investigated the relationship between perceived sleep quality and mood outcome in a cohort of patients with BD that were deeply-phenotyped and followed prospectively for two years. We hypothesized women would be more sensitive to the effect of poor sleep quality on mood outcome, and that sleep would differentially affect mood outcome in men and women with bipolar disorder.

Methods

Participants

The Prechter Longitudinal Study of Bipolar Disorder at the University of Michigan (UM) is an IRB approved observational study of outcomes in bipolar disorder (IRBMED HUM000606). Participants in the Prechter Longitudinal Study were evaluated initially for a baseline and study intake assessment described below and followed long-term with self-reported questionnaires and yearly visits. Patients with BD (bipolar disorder type I, bipolar disorder type II, schizoaffective disorder, bipolar type or bipolar disorder NOS, Table 1) and healthy controls (HC) with no personal or family history of mood or psychotic disorders were included.

Analytic cohort

The clinical sample for this investigation included participants recruited at the University of Michigan between 2005 and 2010, and data were extracted in 2/2012. Inclusion criteria include: diagnosis of BD; exclusion criteria include: mental retardation, active substance dependence, head injury or medical illness causing BD. The cohort selected for analysis included patients with DSM-IV TR BD I, II, NOS or Schizoaffective disorder, bipolar type (n=216) who completed the Pittsburgh Sleep Quality Index (PSQI) at baseline. Participants were excluded in the current analysis if they did not have complete data on the PSQI (n=75).

Process—At baseline, clinicians administered the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger, Blehar et al. 1994), Hamilton Depression Rating Scale – 21 with Atypical (HDRS) (Hamilton 1960) and Young Mania Rating Scale (YMRS) (Young, Biggs et al. 1978), and recorded height and weight. The DIGS is a clinician-administered diagnostic interview that collects self-reported demographic data including race and ethnicity, and includes the ability to assess the lifetime course of mood disorder as well as associated features of mood illness of the individual, and a comprehensive assessment of psychiatric and medical illnesses. Physicians, psychologists, and masters-level mental health professionals completed standardized training in the study instruments, and a best-estimate procedure was used to verify diagnoses (Leckman, Sholomskas et al. 1982). A baseline set of self-rating questionnaires was completed. Follow-up questionnaires including the Patient Health Questionnaire (PHQ-9) and the Altman Self-Rating Mania Scale (ASRM) were sent to participants every two months. Median number of follow-up questionnaires completed in the 24-month period was 9.0 for both PHQ-9 and ASRM (minimum=2, maximum=13).

Main Outcomes—Our dependent variable of interest was mood outcome over time, characterized by severity, variability, and frequency of clinically significant symptoms of depression or mania through the duration of a two-year follow-up period. Severity of depression was defined for each individual by the maximum PHQ-9 score over the follow up period (maximum = 27.00, minimum = 0); severity of mania was defined for each individual by the maximum ASRM score during follow up (maximum = 20.00, minimum = 0). Variability of depression was defined for each individual by the standard deviation in PHQ-9 scores over the duration of follow up (maximum = 12.73, minimum = 0); variability of mania was defined by the standard deviation in ASRM scores over the duration of follow-up (maximum = 10.31, minimum = 0). The proportion of the follow-up period that the individual had a PHQ-9 or ASRM score over 5 defined the frequency of clinically significant depressive, manic or mixed symptoms (maximum = 1.00, minimum = 0).

We assessed sleep quality with the Pittsburgh Sleep Quality Inventory (PSQI)(Buysse, Reynolds et al. 1989). The PSQI obtains a general measure of sleep quality and the total score is derived from seven subscales: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medication, and daytime dysfunction. The Life Events Occurrence Survey (LEOS) assesses for stressful life events in the past 6-month period (McKee SA 2005). The NEO PI is a dimensional measure of personality, which includes Neuroticism, defined as the tendency to experience negative valence emotions including depression and anxiety (Costa and McCrae 1992, McCrae and Costa 2003).

Data and statistical analysis

Values of continuous variables were compared between males and females using two-sample t-tests, and categorical variables were compared using the Pearson chi-square test. All independent variables were standardized, and standardized regression coefficients are reported. Initial models were created to include only PSQI score, gender and the interaction term, which was not significant for any model. Linear multivariate regression models stratified by sex were created to determine the influence of PSQI on mood outcome, accounting for covariates of interest including age, baseline mood symptoms, and recent

stressful events and neuroticism. Stress and neuroticism were included because they have been found at baseline to correlate with poor sleep quality independent of mood (Saunders 2013). Models were run on all women, and repeated for all women reported to not be in menopause.

Results

Demographic description of the sample (Table 1)

We followed 216 individuals with BD for 2 years. The majority of the patients were female (152/216, 70%), the average age was 40 years old with a BMI of 29. Age and BMI did not differ between males and females. The majority of both men and women had BPI disorder and were Caucasian. The rates of marriage differed between men and women. About one-quarter of the women had undergone menopause. During the two-year follow-up period, women had greater severity and frequency of depression, and severity and variability of mania. Males and females did not differ by age, sleep quality, stressful life events, baseline depression, baseline mania, or neuroticism.

Gender and Outcome

Because we were interested in the differential impact of outcome by gender, we tested the interaction term for each outcome variable. No interaction terms were significant (data not shown).

We then tested three clinically-relevant dimensions of the course of mood illness for depression and mania, including severity of symptoms, frequency of symptoms and variability of symptoms each for mania and depression As covariates, we included factors known to effect mood outcome, including age, baseline depressive and manic symptoms. In addition, we included a measure of stress and neuroticism, both factors that were shown to predict poor sleep quality at baseline (Saunders 2013). We ran each model in men and women separately to identify the effect of poor sleep in each group (Figure 1).

Depression (Table 2 & 3; Supplemental Table 1)

Depression severity and frequency were predicted by poor sleep in women but not in men. In men, depression severity was predicted by poor sleep until baseline mood symptoms were included, which had a stronger effect than sleep. The most significant predictors of depression frequency in men were baseline depression, baseline mania, and age. In women, the effect of poor sleep remained significant despite inclusion of baseline depression and neuroticism, which each accounted for some of the variance in depression frequency. Depression variability had no gender differential, and poor sleep predicted depression variability until Neuroticism was included, which has a stronger effect.

Mania (Table 4; Supplemental Tables 2 & 3)

For women, poor sleep predicted mania severity; however baseline mania and age were stronger factors. Poor sleep was not a predictor of mania severity in men, and the only significant predictors were baseline depression and neuroticism. For women, poor sleep was a predictor of variability manic symptoms, however for men, the only predictors of mania

variability were lower baseline depression and neuroticism. Poor sleep was not a predictor of mania frequency, however lower baseline depression scores, baseline mania, and age were predictors.

Mixed (Supplemental Table 4)

The frequency of having clinically-significant mixed symptoms was predicted by poor sleep and baseline manic symptoms in women, but not in men.

Exclusion of women who have completed menopause leads to similar findings in depression outcome variables, however PSQI was no longer a significant predictor of mania variability and frequency.

Discussion

We found that poor sleep quality at baseline prospectively predicted poor mood outcome in bipolar disorder above and beyond baseline depression in women, but not in men. Women had increased depression severity and frequency, increased mania severity and variability, and increased frequency of mixed episodes if, at the intake baseline, sleep was of poor quality. Why would we see an effect of sex in the relationship of quality of sleep to outcome in bipolar disorder? Sleep abnormalities have been linked to poor outcome in bipolar disorder: in a one-year follow-up study from the STEP-BD cohort, Gruber et al. found lower total sleep time was associated with higher mania scores, but a relationship of total sleep time to depression scores was not found, however sleep variability was associated with depression scores over time (Gruber, Miklowitz et al. 2011). Sex differences, including an increased prevalence of BPII in women, has been shown in the STEP-BD (Baldassano, Marangell et al., 2005). A study in the Stanley Foundation Bipolar Treatment Outcome Network showed women spent a higher proportion of visits in a depressive episode than men (Altshuler, Kupka et al., 2010). Findings from our study corroborate the findings from the Altshuler et al. study and suggest that poor sleep quality may influence longitudinal depressive symptoms in women.

Women in the general population are more likely to report insomnia than men, and the subjective sleep complaints have been suggested to be more associated with psychological distress than with physiological consequences of objective sleep loss (Ohayon 2002, Zhang and Wing 2006, Phillips, Collop et al. 2008, Fernandez-Mendoza, Calhoun et al. 2011, Fernandez-Mendoza, Vgontzas et al. 2012, Singareddy, Vgontzas et al. 2012, Vgontzas, Fernandez-Mendoza et al. 2012). In adolescents, insomnia and daytime sleepiness were associated with anxiety and depression and not with objective sleep disturbance (Calhoun, Vgontzas et al. 2011). While subjective sleep is poor in BD as noted above, BD is also associated with objective sleep disturbance. Studies in euthymic BP subjects using actigraphy, an objective measurement of sleep disturbance, have shown decreased sleep efficiency (Harvey, Schmidt et al. 2005), more variability in circadian activity (Jones, Hare et al. 2005), longer sleep onset latency, longer sleep duration and variability of sleep duration and less day-to-day stability relative to comparison subjects (Millar, Espie et al. 2004), demonstrating that sleep abnormalities are present not only in mood episodes, but at baseline euthymia as well.

While women in general report more subjective sleep complaints than men, studies suggest healthy women of reproductive age without sleep complaints objectively sleep better than men and have more resilience to effect of sleep-loss induced cytokines (Vgontzas, Zoumakis et al. 2004). Healthy women of reproductive age have been shown to sleep physiologically better (Redline, Kirchner et al. 2004, Walsleben, Kapur et al. 2004, Bixler, Papaliaga et al. 2009), and have some protection against disruption of sleep by external awakenings (Bixler, Papaliaga et al. 2009). A robust ability to survive sleep interruption and deprivation during the phase of life in which a woman may care for an infant may be a result of evolutionary adaption. If a hormonal influence on sleep is protective and adaptive, we would hypothesize that disruption of the sleep-wake regulation system in women would require a stronger stimulus than to disrupt the sleep-wake system in men. Therefore, if mood disorder is disrupting sleep in women, and we are detecting mood disorder outcome, we would expect to detect worse outcome in women because the threshold for disrupting the sleep regulation system is higher. However, unipolar depression is more prevalent in reproductive-aged women than in men (Kessler, McGonagle et al. 1993, Kessler, Berglund et al. 2005), which may counter this hypothesis or indicate that systems other than the interaction with sleep are at play.

These objective sleep differences in BD between men and women are likely to have several driving biological mechanisms. The circadian clock has long been hypothesized to be altered in bipolar disorder (Georgi 1947, Kripke, Mullaney et al. 1978, Wehr, Goodwin et al. 1982, Nievergelt, Kripke et al. 2005, Nievergelt, Kripke et al. 2006, Roybal, Theobold et al. 2007), and may be altered by ovarian hormones (Murphy, Pezuk et al. 2013, Bailey and Silver 2014). Alterations in the sleep-wake system as a part of the genetic and neurobiological differences that predispose to bipolar disorder may alter the way in which ovarian hormones interact with the circadian system, thus altering the phenotype of sleep in bipolar disorder. The sex differences and altered sleep provide powerful opportunities to study dynamic patterns in related biological mechanisms asking specific questions aimed towards understanding perturbations of the circadian patterns.

Limitations

The measurements used in this study are self-report of sleep quality. The PSQI is a well-validated, reliable instrument for measuring self-reported quality of sleep, and is valid for capturing accurate reports of sleep for up to one month (Buysse, Reynolds et al. 1989, Broderick, Junghaenel et al. 2013). However, we do not have objective sleep data to correlate with subjective report. Thus the sex difference in sleep quality may be due to a difference in perception of sleep quality rather than underlying differences in sleep architecture. Women with BD may perceive poor sleep quality due to higher sensitivity to negative internal states (Fernandez-Mendoza, Calhoun et al. 2011). Objective measures of sleep and activity levels such as actigraphy or polysomnography will quantify these parameters but require substantial resources. Detailed and repetitive sleep studies in variable mood states would be ideal.

Conclusion

Sleep quality differentially affected mood outcome in bipolar disorder by sex. Baseline sleep quality predicted worse mood outcome in women. These data suggest that particular attention to sleep quality in BD women during clinical treatment would be beneficial. Subjective and biological factors may be involved, and further studies of the hormonal influence on the sleep-wake cycle may elucidate the relationship between sex differences in sleep and mood in BD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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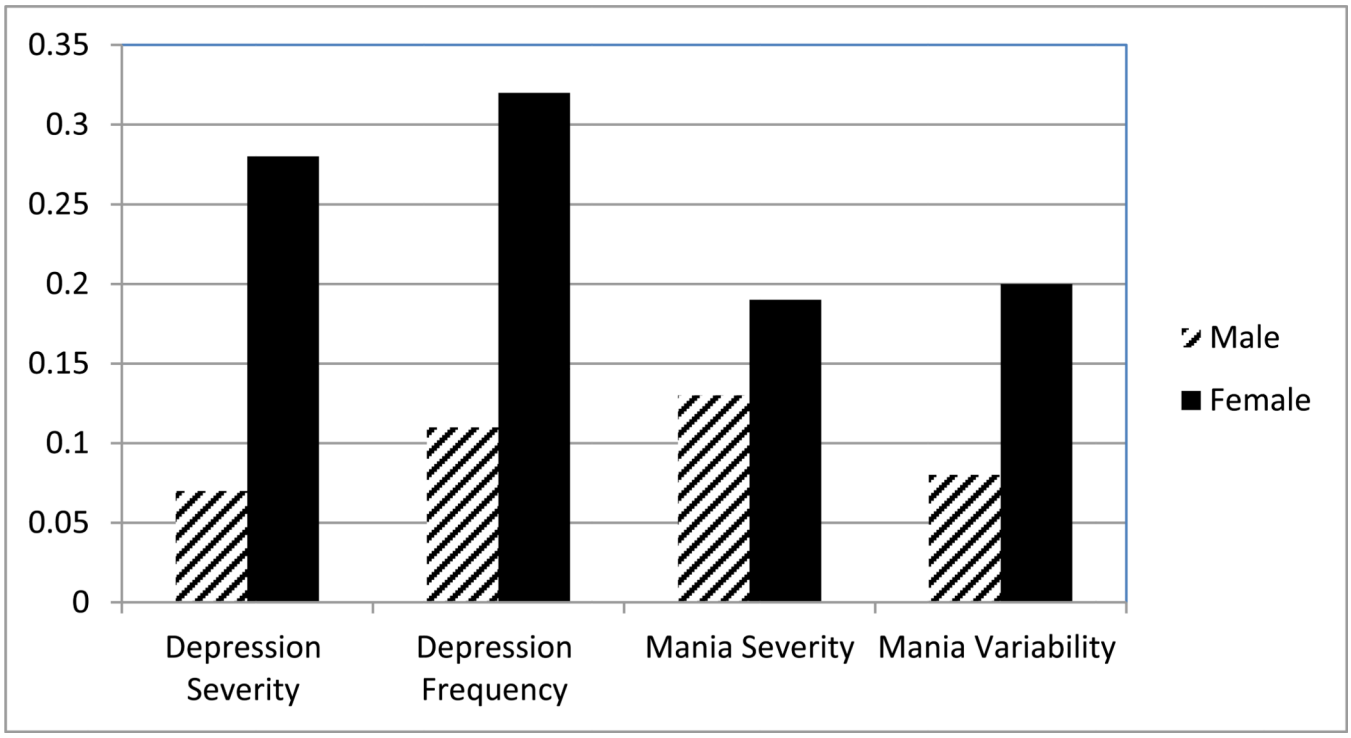

Figure 1.

The Effect of Poor Sleep Quality on Mood Outcome over 2 years Differs in Men and Women. Standardize betas presented for multivariable models including sex, age, stressful events, baseline mania, baseline depression, and neuroticism.

Table 1

Description of the sample

	ALL (N=216) Mean (SD)	Male (N=64) Mean (SD)	Female (N=152) Mean (SD)	P
Age	40.25 (12.47)	41.61 (11.80)	39.67 (12.74)	0.30
Body Mass Index	29.17 (6.90)	29.43 (5.47)	29.06 (7.46)	0.69
BPI	152 (70%)	50 (78%)	102 (67%)	0.34
BPII	44 (20%)	11 (17%)	33 (22%)	
BP NOS	15 (7%)	2 (3%)	13 (9%)	
Schizoaffective, BP	5 (3%)	1 (2%)	4 (3%)	
Caucasian	179 (83%)	57 (90%)	122 (80%)	0.42
African-American	10 (5%)	3 (5%)	7 (5%)	
Asian	3 (1%)	1 (2%)	2 (1%)	
More than one race	11 (5%)	1 (2%)	10 (7%)	
Missing		2 (3%)	11 (7%)	
Hispanic or Latino	5 (2%)	1 (2%)	4 (3%)	0.10
Not Hispanic or Latino	196 (91%)	59 (92%)	137 (90%)	
Missing	15 (7%)	4 (6%)	11 (7%)	
Married	87 (40%)	34 (53%)	53 (35%)	0.02
Never married	76 (35%)	21 (33%)	55 (36%)	
Divorced	45 (21%)	7 (11%)	38 (25%)	
Separated	5 (2%)	0 (0)	5 (3%)	
Widowed	3 (1%)	2 (3%)	1 (1%)	
Employed/student	129 (60%)	44 (69%)	85 (56%)	0.08
Not employed/disabled	68 (30%)	15 (23%)	53 (35%)	
Menopause	N/A		41 (27%)	
Sleep Quality (PSQI)	8.45 (4.24)	8.08 (4.04)	8.61 (4.32)	0.40
Stressful events (LEOS)	1.93 (2.34)	1.84 (2.51)	1.98 (2.27)	0.70
Baseline Depression (HDRS-21 with AT)	13.62 (11.77)	11.61 (10.51)	14.46 (12.19)	0.10
Baseline Mania (YMRS)	2.82 (4.13)	2.72 (4.05)	2.87 (4.17)	0.81
Neuroticism	63.28 (14.41)	62.97 (13.94)	63.41 (14.65)	0.84
Follow-up Depression severity (PHQ-9)	15.63 (7.23)	13.77 (7.23)	16.42 (7.11)	0.01
Follow-up Depression variability (PHQ-9)	4.25 (2.42)	3.99 (2.54)	4.36 (2.37)	0.30
Follow-up Depression frequency (PHQ-9)	0.63 (0.35)	0.53 (0.37)	0.68 (0.33)	5×10^{-2}
Follow-up Mania severity (ASRM)	7.94 (4.45)	7.16 (4.20)	8.27 (4.53)	0.09
Follow-up Mania variability (ASRM)	2.56 (1.53)	2.24 (1.36)	2.70 (1.58)	0.04
Follow-up Mania frequency (ASRM)	0.25 (0.27)	0.26 (0.29)	0.24 (0.26)	0.58
Follow-up Mixed frequency (ASRM)	0.47 (0.50)	0.14 (0.22)	0.15 (0.20)	0.61

Table 2

Depression Severity Outcome

Model	Sex	Age	Poor sleep	Stressful Events	Baseline Mania	Baseline Depression	Neuroticism	Adj R^2
ALL								
1	0.17*							0.024
2	0.17*	0.06						0.023
3	0.14*	0.06	0.48***					0.252
4	0.14*	0.06	0.47***	0.06				0.252
5	0.14*	0.06	0.45***	0.04	0.15*			0.270
6	0.12*	0.05	0.31***	0.06	0.12*	0.27***		0.319
7	0.13*	0.09	0.23***	0.29	0.12*	0.18**	0.29***	0.380
Male								
1		<0.01						−0.016
2		−0.01	0.46***					0.182
3		>−0.01	0.46***	−0.02				0.169
4		−0.01	0.43**	−0.03	0.17			0.184
5		0.06	0.15	−0.3	0.23*	0.50***		0.347
6		0.09	0.07	0.01	0.22*	0.40**	0.23	0.369
Female								
1		0.09						0.001
2		0.08	0.50***					0.247
3		0.09	0.48***	0.10				0.265
4		0.09	0.46***	0.07	0.14			0.285
5		0.07	0.36***	0.08	0.10	0.21*		0.315
6		0.10	0.28***	0.08	0.11	0.13	0.30***	0.384

*p=<0.05

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** p=<0.01

*** p=<0.001

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Table 3

Depression Frequency

Model	Sex	Age	Poor sleep	Stressful Events	Baseline Mania	Baseline Depression	Neuroticism	Adj R^2
ALL								
1	0.19**							0.031
2	0.19**	0.05						0.030
3	0.16**	0.05	0.51***					0.291
4	0.16**	0.05	0.51***	−<0.01				0.287
5	0.16**	0.05	0.50***	−0.02	0.09			0.292
6	0.14*	0.04	0.37***	−0.01	0.06	0.27***		0.344
7	0.15*	0.07	0.28***	−0.01	0.06	0.19*	0.31***	0.412
Male								
1		0.21						0.028
2		0.20	0.42***					0.196
3		0.19	0.45***	−0.08				0.188
4		0.19	0.42**	−0.09	0.17			0.204
5		0.25*	0.19	−0.09	0.22*	0.40*		0.306
6		0.27*	0.11	0.05	0.21	0.30*	0.23	0.327
Female								
1		−0.01						−0.01
2		−0.02	0.57***					0.311
3		−0.01	0.56***	0.03				0.307
4		−0.01	0.55***	0.02	0.05			0.305
5		−0.04	0.41***	0.05	−0.01	0.30***		0.365
6		−0.01	0.32***	0.04	0.004	0.21**	0.33***	0.449

Table 4

Mania Severity

Model	Sex	Age	Poor sleep	Stressful Events	Baseline Mania	Baseline Depression	Neuroticism	Adj R^2
ALL								
1	0.11							0.008
2	0.13	0.15*						0.025
3	0.11	0.15*	0.21*					0.064
4	0.11	0.16*	0.18*	0.11				0.070
5	0.11	0.16*	0.16*	0.08	0.19*			0.101
6	0.12	0.16*	0.22*	0.07	0.21*	−0.14		0.110
7	0.13	0.18*	0.17*	0.08	0.21*	−0.18*	0.16*	0.126
Male								
1		0.10						−0.007
2		0.10	0.21					0.023
3		0.10	0.21	0.003				0.006
4		0.09	0.19	−0.003	0.10			0.000
5		0.07	0.30	−0.01	0.08	−0.18		0.007
6		0.12	0.13	0.07	0.04	−0.39*	0.48*	0.135
Female								
1		0.17*						0.021
2		0.16*	0.21*					0.057
3		0.18*	0.18*	0.15				0.072
4		0.18*	0.15	0.11	0.22*			0.114
5		0.20*	0.22*	0.10	0.25*	−0.15		0.124
6		0.21*	0.19*	0.10	0.26*	−0.17	0.09	0.124

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