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Sleep disturbances precede depressive symptomatology following traumatic brain injury

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Abstract

The purpose of the present study was to evaluate the impact of sleep disturbances on subsequent depressive symptomatology among a representative sample of patients following traumatic brain injury (TBI). Within a retrospective cohort design, our sample included 305 individuals from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot (TRACK-TBI Pilot; NINDS-OD09-004) database. At 3-months post-TBI, symptoms of insomnia were reported by 34% of patients, and symptoms of hypersomnia were reported by 39% of patients. For the vast majority of individuals, sleep complaints were likely to persist through 6-month follow-up. Symptoms of hypersomnia but not insomnia at three months were associated with worsened depressive symptomatology at six months. These results highlight the importance of sleep disturbances in recovery from TBI and suggest targeted sleep treatments as a pathway to improve outcomes and quality of life following TBI.

Introduction

Disturbed sleep is among the most frequent complaints following traumatic brain injury (TBI), with 30 to 75% of TBI patients reporting poor sleep quality [1-4]. Although most

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sleep complaints resolve over time without intervention, approximately 25% of individuals report sleep complaints that persist for months or years following injury [1-4]. Among TBI patients, poor sleep is associated with worsened outcomes, including depression, pain, and cognitive impairment, which can prolong or exacerbate many common sequelae of TBI [1-4]. Further, the neurologic mechanisms underlying disturbed sleep are directly relevant to recovery from TBI [1-4]. As a result, there has been a dramatic increase in examining the role of sleep and sleep disorders following TBI, as sleep represents a modifiable target to enhance treatment outcomes.

In addition to disturbed sleep, psychological distress and depression increase after TBI and are associated with poorer functional and cognitive recovery [5-14]. Although disturbed sleep is a well-known antecedent and diagnostic criterion for many mood disorders [15], the temporal relationships between sleep disturbances and other TBI sequelae remain unclear. Several studies have suggested that sleep disturbances and comorbid psychological distress create a “vicious cycle,” with the effects of one of the comorbidities perpetuating and potentially exacerbating the others [15]. Understanding the temporal and mechanistic relationships between sleep and mood disturbances can help guide targeted treatment development efforts among patients with TBI.

We examined the temporal relationship between sleep disturbances and subsequent depressive symptomatology following TBI. We hypothesized that sleep disturbances would be positively related to subsequent depressive symptomatology. Specifically, we sought to evaluate whether difficulty sleeping at night (i.e., insomnia symptoms) as well as difficulty staying awake during the day (i.e., hypersomnia symptoms) would predict future depressive symptoms following TBI.

Methods

Participants

We conducted a retrospective cohort study using data from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot (TRACK-TBI Pilot; NINDS-OD09-004) study database. TRACK-TBI Pilot was a prospective, multicenter study that enrolled participants with TBI from 2010-2012 [16]. Participants were recruited from emergency departments of three Level 1 trauma centers (University Medical Center Brackenridge, Austin, TX; University of Pittsburgh Medical Center; San Francisco General Hospital) within 24 hours of injury. Inclusion criteria were external force trauma to the head requiring a clinically indicated head computed tomography (CT) scan within 24 hours of injury and ability to understand and speak English. Exclusion criteria included pregnancy, incarceration, nonsurvivable physical trauma, debilitating mental health disorders or neurological disease, MRI contraindications (e.g., cardiac pacemakers, aneurism clips, insulin pumps), and pre-existing medical conditions which could interfere with neuropsychological assessments. Because we were interested in estimating the association between sleep disturbances at three months and depressive symptomology at six months, we excluded individuals <18 years old, those who died at discharge or within six months of injury, those with missing exposure information at three months, and those with missing outcome information at six months. This research was approved by multiple institutional

review boards, including University of Maryland, Baltimore; University Medical Center Brackenridge, Austin, TX; University of Pittsburgh Medical Center; and San Francisco General Hospital. Data is available through the TRACK-TBI Consortium.

Measures

Patients were assessed at baseline, three months, and six months.

Demographics: Demographic, clinical, and injury-related variables were obtained at baseline from the patient or proxy.

TBI Injury severity: The Glasgow Coma Scale (GCS) score was used as a measure of TBI severity [17]. The GCS is a measure of neurologic deficit and is typically categorized as 13-15 (mild TBI), 9-12 (moderate TBI), and 3-8 (severe TBI).

Sleep complaints: Sleep disturbances were measured at three and six months using four questions from the cognitive assessment [18]. We combined responses to two questions ("Do you have trouble falling asleep?" and "Are you sleeping less than usual?") to form a face valid insomnia composite measure consisting of three independent scores (range 0-2). Similarly, we combined responses to two other questions ("Are you sleeping more than usual?" and "Are you feeling drowsier than usual?") to form a face valid hypersomnia composite score (range 0-2).

Depressive symptomatology: Sadness was measured at three months and six months using a single yes/no item. Depressive symptomology was measured at six months using the raw score from the depression subscale of the brief symptom inventory (BSI) assessed at six months (range 0-24) [18,19].

Analytic plan

We first examined the distribution and frequencies of all variables. Then, we compared all variables between participants who reported a positive response to at least one insomnia symptom and participants who reported no insomnia symptoms. Similar analyses were conducted for hypersomnia. Differences between categories were evaluated using chi square goodness of fit, Student's t, or Wilcoxon rank sum tests.

The depression subscale at six months was highly skewed with numerous zero values. To accommodate over-dispersion of our outcome, we employed a zero-inflated negative binomial regression model, using study-site as the inflation factor to account for clustering. First, we ran unadjusted models. Next, potential confounders identified in bivariate analysis ($p<0.05$) were added simultaneously to the model. These were systematically removed if not significant ($p<0.05$) and the effect estimate was not changed by more than 10%. Two separate models were built for the hypersomnia and insomnia composite independent variables. Rate ratios (RR) and 95% confidence intervals (CI) are reported.

Sadness at three months was associated with depressive symptomology at six months, but technically could not be a confounder because it was measured at the same time as the

exposures (insomnia and hypersomnia) [20,21]. Thus, we ran the regressions with and without the sadness variable.

Results

We initially identified 599 participants with TBI. After excluding those age <18 years (n=27), discharged dead (n=18), dead by six months (n=10), missing exposure at three months (n=129), or missing outcome at six months (n=110), we were left with 305 participants in our study sample. Average age was 42.7 ± 17.7 years (Table 1). The sample was predominantly male (70.5%) and white (82.5%). The majority had a GCS score of 13-15 (88.9%), suggesting mild TBI.

Prevalence of sleep complaints

At three months post-TBI, 104 (34.1%) participants reported at least one symptom of insomnia (Table 1). Of these, 55 (52.9%) reported one symptom and 49 (47.1%) reported two symptoms. These individuals were more likely to be Hispanic (18.3% vs 10.0%, X^2 = 4.3, p=0.04) and to be less educated (X^2 = 19.3, p<0.001 for all education levels). Individuals reporting at least one insomnia symptom were also more likely to report a history of anxiety (25.0% vs. 10.5%, X^2 = 11.1, p=0.001), depression (34.6% vs. 19.9%, X^2 = 7.9, p=0.01), and prior TBI (31.7% vs. 15.9%, X^2 = 10.2, p=0.001). Among those reporting at least one symptom of insomnia at three months, 90 (86.5%) also reported at least one symptom of insomnia at six months, and 46 (61.5%) reported at least one symptom of hypersomnia at six months.

At three months post-TBI, 119 (39.0%) individuals reported at least one symptom of hypersomnia (Table 2). Of these, 83 (69.8%) reported one symptom and 36 (30.5%) reported two symptoms. Individuals with at least one symptom of hypersomnia were more likely to be women (36.1% vs 25.3%, X^2 = 4.1, p=0.04) and to be less educated (X^2 = 10.5, p=0.02 for all education levels). Individuals reporting at least one hypersomnia symptom were also more likely to report history of anxiety (23.5% vs. 10.2%, X^2 = 9.9, p=0.002) and depression (35.3% vs. 18.3%, X^2 = 11.2, p=0.001). Among those reporting at least one symptom of hypersomnia at three months, 89 (74.8%) also reported at least one symptom of hypersomnia at six months, and 71 (59.7%) reported at least one symptom of insomnia at six months.

Depressive symptomatology

The mean raw score on the BSI depression subscale at 6 months was 4.4 ± 5.1.

Sleep complaints and future depression

Compared with individuals not reporting insomnia complaints, those who reported at least one insomnia symptom at three months scored significantly higher on the BSI at six months (6.5±5.6 vs. 3.2±3.9, p<0.001). Similarly, compared with individuals not reporting hypersomnia complaints, those who reported at least one hypersomnia symptom at three months scored significantly higher on the BSI at six months (6.4±5.5 vs. 3.1±4.3, p<0.001).

In an unadjusted model, insomnia symptoms at three months were significantly associated with increased depressive symptoms at six months (Table 3). This association was attenuated after adjusting for history of depression, prior TBI, and sadness at three months. When sadness was removed from the model, we once again observed a significant association between one symptom of insomnia at three months and depressive symptoms at six months (RR 1.33; 95% CI 1.00, 1.78). A similar association was also observed between two symptoms of insomnia at three months and depressive symptoms at six months (RR 1.45; 95% CI 1.10, 1.92).

In an unadjusted model, hypersomnia symptoms at three months were significantly associated with increased depressive symptoms at six months (Table 4). After adjusting for female sex, marital status, history of depression and sadness at three months, we observed a significant association between one symptom of hypersomnia at three months and depressive symptoms at six months (RR 1.57; 95% CI 1.16, 2.12). We also observed a significant association between two symptoms of hypersomnia at three months and depressive symptoms at six months (RR 1.73; 95% CI 1.21, 2.48). Removing sadness at three months from the model did not significantly change the effect estimates.

Discussion

In our sample of TRACK-TBI Pilot participants primarily with mild TBI (GCS 13-15), the prevalence of sleep disturbances was high among both men and women and increased over time. Further, the vast majority of individuals reporting symptoms of insomnia and hypersomnia at three months post-injury continued to report these difficulties at six-month follow-up, suggesting that sleep disturbances develop early post-injury and persist into the chronic phase. After adjusting for potential confounding variables, symptoms of hypersomnia but not insomnia at three months were predictive of depression at six months. These results add to a growing body of evidence regarding the role of sleep in recovery from TBI and highlight that disturbed sleep is an important precursor to worsened outcomes [1,2] .

In the broader TBI literature, insufficient and disturbed sleep are reported by between 30 to 75% of patients [1-4]. Insomnia, characterized by difficulty initiating or maintaining sleep with an associated daytime complaint, is the most common sleep disorder in this population and reported by up to 65% of individuals following TBI [1-4]. Further, in both healthy controls as well as non-TBI clinical samples, insomnia frequently persists for months or years and has been shown to be unlikely to remit on its own [22]. Results of the present study are consistent with these previous findings. Thirty-four percent of participants reported at least one symptom of insomnia at the three-month follow-up, and 86.5% of these individuals continued to report at least one symptom of insomnia at six months. However, our hypothesis regarding insomnia and depression was not supported. Although previous studies have demonstrated that insomnia is frequently prodromal for depression [13], insomnia at three months was not significantly associated with depression at six months, after adjusting for potential confounding variables. It is unclear whether this surprising finding is due to a unique characteristic of our sample or some other reason. The two items in our insomnia composite were scored yes/no, and neither item assessed

difficulty maintaining sleep, a common symptom of insomnia. Certainly, our two-item insomnia scale cannot be considered a comprehensive assessment of sleep, and the screening accuracy and psychometric properties of our insomnia measure are thus unknown.

In addition to excessive wakefulness, excessive sleepiness is a common sequela of TBI [1-4]. In the present study, an even greater number (39%) of participants reported at least one symptom of hypersomnia at three months than reported insomnia, and nearly 75% of these individuals continued to report at least one symptom of hypersomnia at six months. Thus, like insomnia, hypersomnolence appears to develop early and persist for a minimum of six months following TBI. Further, hypersomnia at the three-month follow-up was associated with increased depressive symptomatology at six months, even after controlling for sex, marital status, history of depression, and self-reported sadness. Finally, it is also important to note that although TBI severity as measured by the GCS was not a significant predictor of depressive symptomatology in multivariate analyses, individuals reporting hypersomnolence were more likely to score in the moderate to severe TBI range on the GCS. Although studies of well-characterized TBI samples are generally lacking in the literature, extant data suggests increased rates of sleepiness following moderate and severe TBI [23]. This increase in somnolence post-TBI is likely multifactorial, involving not only more severe injury to sleep-related neural pathways but also extended hospital stays, which increased risk for sequelae related to delirium.

From a clinical perspective, it is important to understand the trajectory of post-TBI hypersomnolence; in this vein our results provide valuable insight into the role of sleepiness in the development of depressive symptoms post-TBI. At the same time, it is also necessary to understand the etiology of hypersomnia to enable targeted treatment development and delivery. Daytime sleepiness is a common consequence of many sleep disorders, including insomnia (prevalence in TBI: 29% [24]), obstructive sleep apnea (OSA; prevalence in TBI: 25% [24]), excessive sleep need (i.e., pleisomnia; prevalence in TBI: 22% [23]), post-traumatic narcolepsy (prevalence in TBI: 4% [24]), and post-traumatic hypersomnia (prevalence in TBI: 28% [24]). Compared with non-TBI controls, patients with TBI demonstrate elevated rates of each of these conditions. In addition to sleep disorders, Baumann and colleagues have observed low levels of CSF hypocretin-1 levels within four days of injury, which was associated with increased daytime sleepiness and which tended to normalize within six months [25]. Regardless, although the mechanisms for post-TBI sleepiness remain poorly understood, our results suggest that clinicians should be encouraged to screen proactively for sleep disturbances following TBI. In non-TBI samples, early sleep interventions have been shown to reduce subsequent depressive symptomatology, prevent relapse to clinical depression, and improve health-related quality of life.

Our study possesses several strengths. First, whereas prior studies examined TBI patients at a single time point or across relatively short intervals, our longitudinal design enabled assessment of baseline (i.e., less than four days) and post-acute (i.e., three month) factors influencing chronic (i.e., six month) TBI outcomes. Second, our TBI sample represents the full distribution of injury severity. Third, our sleep assessment measured both nighttime and daytime complaints and thus advances understanding of TBI sequelae across the 24-hour day.

Study Limitations

At the same time, several limitations must be noted. Most important, our assessment of sleep disturbances was limited, relying on four non-validated self-report items. Both subjective and objective measures of sleep are recommended when studying sleep in TBI populations [1,2]. Further, although the BSI was administered at six-month follow-up, no validated measure of depressive symptomatology was administered at three months. Thus, although we controlled for self-reported sadness at three months, we were unable to evaluate other markers of depressive onset during the transition from the post-acute to chronic phase. Finally, although the serial assessment of the TRACK-TBI Pilot is a strength, our six-month follow-up period is nonetheless relatively brief, and longer follow-up periods will enable greater understanding into the natural history and outcomes associated with sleep disturbances post-TBI. Finally, in part due to the multi-site nature of our study, a larger than expected number of patients were lost to follow-up and not included in the final sample. However, we compared individuals included and excluded from the study, and no differences were observed.

Conclusions

In this TRACK-TBI Pilot study analysis, sleep disturbances following traumatic brain injury were noted in more than threefourths of subjects, and sleep disturbances persisted through at least six months post-injury. Given the incidence and public health impact of TBI [1,2], targeted interventions for posttraumatic sleep disturbances represent a major opportunity to improve outcomes and improve quality of life following traumatic brain injury. Multimethod assessment [1,2] of post-TBI sleep and sleep complaints are likely to provide helpful guidance in initiating extant sleep interventions with potential to improve HrQOL and patient-centered outcomes post TBI.

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Conflicts of Interest

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Table 1.

Characteristics of TRACK-TBI Pilot Study Participants Aged 18 and Older Who Survived to 6 Months Without Missing Exposure or Outcome Information, by Insomnia Status at 3 Months, N=305.

	Total Sample, n=305	No insomnia, n=201	Insomnia, n=104	p-value[1]
Age, mean (SD)	42.7 (17.7)	43.1 (18.4)	42.1 (16.1)	0.64
Sex, n(%)				
Female	90 (29.5)	58 (28.9)	32 (30.8)	0.73
Male	215 (70.5)	143 (71.1)	72 (69.2)	
Race, n(%)				0.31
White	241(82.5)	164 (85.4)	77 (77.0)	
Black	25(8.6)	13 (6.8)	12 (12.0)	
Asian	13(4.5)	8 (4.2)	5 (5.0)	
AI/AN/Hawaiian/Pacific	13(4.4)	7 (3.7)	6 (6.0)	
Hispanic, n(%)	39(12.8)	20 (10.0)	19 (18.3)	0.04
Education, n(%)				<0.001
Less than HS	16(5.5)	4 (2.1)	12 (11.9)	
High School	148(50.5)	90 (46.9)	58 (57.4)	
Some College/Graduate	93(31.7)	71 (37.0)	22 (21.8)	
Post Graduate	36(12.3)	27 (14.1)	9 (8.9)	
Employment Status, n(%)				0.43
Full time	130(44.1)	90 (46.6)	40 (39.2)	
Part time	43(14.6)	28 (14.5)	15 (14.7)	
Unemployed	122(41.4)	75 (38.9)	47 (46.1)	
Married, n(%)	103(34.3)	74 (37.8)	29 (27.9)	0.09
Study Site, n(%)				0.44
UCSF	196(64.3)	126 (62.7)	70 (67.3)	
UMC Brackenridge	20(6.6)	12 (6.0)	8 (7.7)	
University of Pittsburgh	89(29.2)	63 (31.3)	26 (25.0)	
Arrival GCS categories, n(%)				0.23
13-15	271(88.9)	183 (91.0)	88 (84.6)	
9-12	14(4.6)	7 (3.5)	7 (6.7)	
3-8	20(6.6)	11 (5.5)	9 (8.7)	
Medical History, n(%)				
Anxiety	47(15.4)	21 (10.5)	26 (25.0)	0.001
Depression	76(24.9)	40 (19.9)	36 (34.6)	0.01
Sleep Disorder	26(8.5)	14 (7.0)	12 (11.5)	0.18
Alcohol and/or Drug Use	177(58.0)	113 (56.2)	64 (61.5)	0.37
Cardiovascular disease	95(32.2)	65 (32.3)	30 (28.8)	0.53
Renal Disease	26(8.5)	18 (9.0)	8 (7.7)	0.71

	Total Sample, n=305	No insomnia, n=201	Insomnia, n=104	p-value[1]
Diabetes	21(6.9)	15 (7.5)	6 (5.8)	0.58
Seizures	33(10.8)	18 (9.0)	15 (14.4)	0.14
Prior TBI	65(21.3)	32 (15.9)	33 (31.7)	0.001
Pulmonary Disease	68(22.3)	48 (23.9)	20 (19.2)	0.36
Sadness at 3 months, n(%)				<0.001
Yes	63(20.7)	23 (11.5)	40 (38.5)	
No	241 (79.3)	177 (88.5)	64 (61.5)	
Hypersomnia at 6 months, n(%)	149 (48.9)	85 (42.3)	64 (61.5)	0.001
Insomnia at 6 months, n(%)	142 (42.6)	52 (25.9)	90 (86.5)	<0.001
BSI[2] Depression at 6 months, mean (SD)	4.4 (5.1)	3.2 (3.9)	6.5 (5.6)	<0.001
BSI[2] Depression at 6 months, median (interquartile range)	3 (0, 7)	2 (0, 5)	5 (1, 10)	<0.001

[1]P-value reflects significance test between insomnia and no insomnia, using Chi Square Goodness of Fit, Student's t-test, or Wilcoxon rank sum.

[2]BSI – Brief Symptom Inventory

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Table 2.

Characteristics of TRACK-TBI Pilot Study Participants Aged 18 and Older Who Survived to 6 Months Without Missing Exposure or Outcome Information, by Hypersomnia Status at 3 Months, N=305.

	No Hypersomnia, n=186	**Hypersomnia, n=119**	**p-value**[1]
Age, mean (SD)	43.2 (17.9)	42.0 (17.3)	0.57
Sex, n(%)			
Female	47 (25.3)	43 (36.1)	0.04
Male	139 (74.7)	76 (63.9)	
Race, n(%)			0.40
White	146 (84.4)	95 (79.8)	
Black	12 (6.9)	13 (10.9)	
Asian	9 (5.2)	4 (3.4)	
AI/AN/Hawaiian/Pacific	6 (3.5)	7 (5.9)	
Hispanic, n(%)	23 (12.4)	16 (13.5)	0.78
Education, n(%)			0.02
Less than HS	8(4.4)	8(7.1)	
High School	80(44.2)	68(60.7)	
Some College/Graduate	68(37.0)	26(23.2)	
Post Graduate	26(14.4)	10(8.9)	
Employment Status, n(%)			0.42
Full time	85(46.7)	45(39.8)	
Part time	27(14.8)	16(14.2)	
Unemployed	70(38.5)	52(46.0)	
Married, n(%)	71(39.2)	32(26.9)	0.03
Study Site, n(%)			0.15
UCSF	123(66.1)	73(61.3)	
UMC Brackenridge	15(8.1)	5(4.2)	
University of Pittsburgh	48(25.8)	41(34.5)	
Arrival GCS categories, n(%)			0.19

	No Hypersomnia, n=186	Hypersomnia, n=119	p-value[1]
13-15	170 (91.4)	101 (84.9)	
9-12	6 (3.2)	8 (6.7)	
<9	10 (5.4)	10 (8.4)	
Medical History, n(%)			
Anxiety	19(10.2)	28(23.5)	0.002
Depression	34(18.3)	42(35.3)	0.001
Sleep Disorder	14(7.5)	12(10.1)	0.44
Alcohol and/or Drug Use	107(57.5)	70(58.8)	0.82
Arrhythmia	121(65.1)	96(80.7)	0.003
Cardiovascular disease	58(31.2)	37(31.1)	0.99
Renal Disease	16(8.6)	10(8.4)	0.95
Diabetes	10(5.4)	11(9.2)	0.19
Seizures	15(8.1)	18(15.1)	0.05
Prior TBI	33(17.7)	32(26.9)	0.06
Pulmonary Disease	45(24.2)	23(19.3)	0.32
Sadness at 3 months, n(%)			<0.001
Yes	25(13.5)	38(31.9)	
No	160(86.5)	81(68.1)	
Hypersomnia at 6 months, n(%)	60 (32.3)	89 (74.8)	<0.001
Insomnia at 6 months, n(%)	71 (38.2)	71 (59.7)	<0.001
BSI[2] Depression at 6 months, mean (SD)	3.1 (4.3)	6.4 (5.5)	<0.001

[1] P-value reflects significance test between hypersomnia and no hypersomnia, using Chi Square Goodness of Fit, Student's t-test, or Wilcoxon rank sum;

[2] BSI – Brief Symptom Inventory

Table 3.

Adjusted Rate Ratio (RR) Between Insomnia at Three Months and Raw Score on the Brief Symptom Inventory Depression Sub-Scale at Six Months.

	RR (95% CI)
Unadjusted	
Insomnia at 3 months	
No positive response	reference
One positive response	1.54 (1.15, 2.07)
Two positive responses	1.84 (1.37, 2.47)
Adjusted	
Insomnia at 3 months	
No positive response	reference
One positive response	1.21 (0.91, 1.60)
Two positive responses	1.25 (0.91, 1.72)
History of depression	1.78 (1.42, 2.23)
Prior TBI	1.36 (1.06, 1.75)
Sadness at 3 months	1.58 (1.24, 2.01)
Remove Sadness at 3 Months	
Insomnia at 3 months	
No positive response	reference
One positive response	1.33 (1.00, 1.78)
Two positive responses	1.45 (1.10, 1.91)

Table 4.

Adjusted Rate Ratio (RR) Between Hypersomnia at Three Months and Raw Score on the Brief Symptom Inventory Depression Sub-Scale at Six Months.

	RR (95% CI)
Unadjusted	
Hypersomnia at 3 months	
No positive response	reference
One positive response	1.73 (1.27, 2.36)
Two positive responses	2.05 (1.44, 2.92)
Adjusted	
Hypersomnia at 3 months	
No positive response	reference
One positive response	1.57 (1.16, 2.12)
Two positive responses	1.73 (1.21, 2.48)
Female	0.72 (0.56, 0.92)
Married	0.68 (0.52, 0.89)
History of depression	1.87 (1.47, 2.39)
Sadness at 3 months	1.78 (1.40, 2.28)
Remove Sadness at 3 Months	
Hypersomnia at 3 months	
No positive response	reference
One positive response	1.58 (1.18, 2.12)
Two positive responses	1.80 (1.28, 2.52)