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Factors Associated with the Remission of Insomnia After Traumatic Brain Injury: A Traumatic Brain Injury Model Systems Study

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Abstract

Objective: To examine the factors associated with the remission of insomnia by examining a sample of individuals who had insomnia within the first two years after traumatic brain injury (TBI) and assessing their status at a secondary time point.

Design and Methods: Secondary data analysis from a multicenter longitudinal cohort study. A sample of 40 individuals meeting inclusion criteria completed a number of self-report scales measuring sleep/wake characteristics (Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, Insomnia Severity Index, Sleep Hygiene Index), fatigue and depression (Multidimensional Assessment of Fatigue, Patient Health Questionnaire-9), and community participation (Participation Assessment with Recombined Tools-Objective). One cohort was followed at 1 and 2 years post-injury (n=19) while a second cohort was followed at 2 and 5 years post-injury (n=21).

Results: Remission of insomnia was noted in 60% of the sample. Those with persistent insomnia had significantly higher levels of fatigue and depression at their final follow-up and poorer sleep

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hygiene across both follow-up time-points. A trend toward reduced community participation among those with persistent insomnia was also found.

Conclusion: Individuals with persistent post-TBI insomnia had poorer psychosocial outcomes. The chronicity of post-TBI insomnia may be associated with sleep-related behaviors that serve as perpetuating factors.

Keywords

Traumatic Brain Injury; Sleep Disturbance; Insomnia

Introduction

Traumatic Brain Injury (TBI) annually impacts more than 2.8 million people across the US [1], of whom about 15% incur a moderate or severe injury, necessitating acute hospitalization, sometimes followed by rehabilitation hospitalization [2]. With ongoing improvements in the treatment of acute moderate and severe TBI, more individuals are surviving and are often left with chronic cognitive and physical impairments that affect various aspects of functioning [3, 4]. Sleep/wake cycle disturbances (SWCDs) are particularly common after moderate or severe TBI, with as many as 50 to 70 percent of individuals reporting some type of SWCD [5–7]. Among individuals with TBI, sleep disturbance has been associated with a number of cognitive [8], emotional [9], and functional [10] problems, leading to considerable restrictions in social and occupational functioning [11, 12]. The most common SWCD noted after TBI has consistently been insomnia which is the inability to fall asleep or stay asleep [5, 13].

There is a need for longitudinal studies to better understand whether severity of insomnia changes over time in the years following TBI, and the factors associated with that change. A better understanding of the natural course of SWCDs after TBI will inform the extent of need for, and appropriate timing of, treatments for this high-risk population. The purpose of the present study was to examine the factors associated with the remission of insomnia by examining a sample of individuals who had insomnia within the first two years after TBI. This analysis utilized an existing dataset from a longitudinal study examining the relationship between insomnia and fatigue after TBI inpatient rehabilitation. It was hypothesized that those who experienced remission of insomnia by the second follow-up time point would show more favorable outcomes than individuals with persistent insomnia, on a number of key factors in the domains of sleep quality, sleep hygiene, depression, fatigue, and community participation.

Methods

Participants

Participants were consecutive enrollees into the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR)-funded TBI Model Systems (TBIMS) National Database (NDB) at five participating centers: Icahn School of Medicine at Mount Sinai, Kessler Foundation, JFK-Johnson Rehabilitation Institute, Carolinas Rehabilitation, and Santa Clara Valley Medical Center. The TBIMS NDB inclusion criteria are: brain

damage caused by an external force meeting criteria for moderate or severe TBI (post-traumatic amnesia (PTA) greater than 24 hours, loss of consciousness greater than 30 minutes, emergency department admission Glasgow Coma Scale score less than 13, or intracranial neuroimaging abnormalities); age 16 or older at time of injury; presenting to a TBIMS center's acute care hospital within 72 hours of injury; receiving both acute hospital care and comprehensive rehabilitation at the TBIMS center; and informed consent provided by patient or proxy. For this study, all individuals participating in the TBIMS NDB's standard 1 or 2 year post TBI-onset interview were approached for enrollment. Further enrollment criteria specific to the current study included: sufficient knowledge of English; being free from PTA and able to independently complete study measures; and meeting criteria for insomnia as described below. All centers received Institutional Review Board approval, and all subjects provided verbal informed consent.

Two cohorts were followed: one with interviews at 1 and 2 years post-injury and another with interviews at 2 and 5 years post-injury. Of the 237 individuals with two waves of data who were screened for inclusion in this analysis, 40 met criteria for insomnia at their first of two follow-up interviews (T1). Insomnia was operationally defined as meeting a combination of diagnostic criteria previously used in TBI research by Ouellet et al. [14] that was derived from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [15] and the International Classification of Sleep Disorders (ICSD) [16], or obtaining a score of 15 or greater on the Insomnia Severity Index (ISI) at the time of the interview. The criteria developed by Ouellet and colleagues are presented in Appendix A.

Within the sample of 40 individuals with insomnia at T1, ages ranged from 16 to 88 years. 73% of the sample had at least a high school education. Two Insomnia Outcome Groups were formed. The Persistent group met criteria for insomnia at both time points, whereas the Remission group was operationally defined as individuals who met criteria for insomnia at T1 but no longer met criteria at their second interview (T2). Demographics and descriptive statistics appear in Table 1.

Measures:

The Epworth Sleepiness Scale (ESS) [17] is a 8-item measure of daytime sleepiness that has been widely used by clinicians and researchers to assess the probability of dozing or sleeping during daytime activities. Scores ≥ 11 indicate significant daytime sleepiness [18]. The ESS has been shown to have acceptable reliability [19]. Scores correlate well with objective measures of daytime sleep onset latency, particularly the Multiple Sleep Latency Test [18, 20].

The Insomnia Severity Index (ISI) [21] is a 7-item self-administered questionnaire designed to assess the severity of insomnia symptoms (e.g., sleep onset, distress related to insomnia) on a five-point Likert scale. A cut-off score of 14 has demonstrated validity in identifying individuals meeting diagnostic criteria for an insomnia disorder based on the DSM and ICSD [22]. For studies examining treatment response, a reduction of 8 points on the ISI was associated with moderate improvement [23] and a reduction of 6 points was identified as a minimal clinically important difference [24].

The Multidimensional Assessment of Fatigue (MAF) is a self-report measure of fatigue severity and timing, distress caused by fatigue, and fatigue's impact on activity [25]. The first 15 questions are used to calculate a Global Fatigue Index (GFI), with scores that range from 0: no fatigue to 50: severe fatigue. Abnormal or excessive fatigue has been defined as scores over 21 to 28 [26–28]. The MAF has good concurrent and divergent validity and it has been used in research with individuals with TBI [29].

The Participation Assessment with Recombined Tools – Objective (PART-O) is a 24-item self-report scale that measures participation in the community and social relationships after TBI [30]. The three subscales (Productivity, Social Relations, and Out and About in the Community) allow clinicians and researchers to describe community integration and participation after brain injury. The PART-O has been shown to have good construct and concurrent validity and reliability [31].

The Patient Health Questionnaire-9 (PHQ-9) [32], a measure derived from PRIME-MD [33], is a 9-item screening tool to assess the frequency of symptoms associated with depression. It has been shown to be a valid and reliable tool for detecting major depressive disorder in people with TBI [34].

The Pittsburgh Sleep Quality Index (PSQI) [35] is a validated, 9-item measure of sleep characteristics previously demonstrated to be sensitive to TBI-related sleep problems [36]. In a number of studies across a variety of samples it has been shown to have strong reliability and validity [37]. Scores ≥8 are consistent with a sleep disorder in individuals with TBI of varying severities (sensitivity = 83%; specificity = 100%) [36].

The Sleep Hygiene Index (SHI) [38] is a 13-item self-administered questionnaire designed to assess the presence of temporal, environmental, and habitual factors theorized to negatively impact sleep, and was derived from the diagnostic criteria for inadequate sleep hygiene in the International Classification of Sleep Disorders [16]. Items are rated on a 5-point Likert scale indicating how frequently the respondent engages in each behavior (i.e., always, frequently, sometimes, rarely, never), with higher individual scores (and summed total) indicating worse sleep hygiene. This instrument has demonstrated satisfactory reliability and validity [38, 39].

Additional Survey Questions were included in the interviews. These items required yes/no responses and inquired about a history of ever having been diagnosed with sleep apnea, restless leg syndrome, a sleep schedule disorder, or narcolepsy. Participants were also asked about the use of medications and other non-pharmacological interventions for the treatment of sleep disturbance (e.g., "Have you received treatment other than medication to help you sleep (e.g., psychotherapy to help with sleep problems, acupuncture to help with sleep problems, doctor recommended changes in sleep routines)?"). Those who endorsed having received these treatments were asked whether they found the treatments helpful.

Analysis

Data were screened to ensure that appropriate statistical assumptions were met. Where necessary, variables were transformed to improve normality [40]. Descriptive statistics were

generated to characterize the sample. Chi-square analyses, Fisher exact tests and t-tests were used to determine whether there were any differences between Insomnia Outcome Groups on demographics or injury characteristics. A series of repeated measures ANCOVAs was conducted with the Insomnia Outcome Group as the between-subjects variable. Cohort (1–2 year or 2–5 year) was entered as a covariate.

Results

Of the 40 individuals who met inclusion criteria, 16 had persistent insomnia at T2 (Persistent group) and 24 no longer met insomnia criteria at T2 (Remission group). All but 4 of the individuals in the Remission group achieved a reduction of 8 points on the ISI, suggesting a moderate improvement. The groups were comparable, with no significant differences with regard to demographics. Because of the small sample size, effect sizes for demographic characteristics were examined, and all found to be small for age (η^2=0.003), education (η^2=0.016), sex (φ=0.183), and injury severity (φ=0.200).

Nine of the participants (23%) in the sample reported having had insomnia at some time in their life prior to their TBI. The following rates of sleep disorders other than insomnia were reported and remained stable at both time points: sleep apnea (10%), restless leg syndrome (8%), sleep-schedule disorder (5%), and narcolepsy (0%). There were no striking differences between Insomnia Outcome Groups in the reporting of sleep disorders or in the prevalence of insomnia prior to TBI.

Sleep Quality –

For the PSQI, a significant Time × Insomnia Outcome Group interaction was found. Further analysis of the interaction revealed a significant group difference only at T2, with a large effect size as indicated by partial eta squared, $F(1,37)=27.4$, $p<0.001$, $\eta_p^2=0.43$. This is illustrated in Figure 1a.

Sleep Hygiene –

For the SHI, there were no significant within-group effects or interactions. However, there was a group main effect, with the Remission group having better sleep hygiene as indicated by lower scores (See table 2). As can be seen in Figure 1b, this difference became more pronounced at T2.

Daytime Sleepiness –

As can be seen in Figure 1c, ESS scores were slightly higher (indicating more daytime sleepiness) in the Persistent group at both time points, with a marginally significant between-groups effect and medium effect size. To examine sleepiness using established cut-offs for excessive sleepiness on the ESS (total score ≥ 11), chi-square analysis or Fisher's exact test was performed at each of the time points. Fifty percent of the Persistent group scored in the excessive sleepiness range at T1 compared with only 21% of the Remission group, $\chi^2=3.7$, $df=1$, $p=0.054$. At T2, 44% of the Persistent group scored in the excessive sleepiness range compared with only 17% of the Remission group. Because the

expected count fell below 5 in this cell for the Remission group, Fisher's exact test was used (p=0.080).

Fatigue –

For the GFI, a significant Time × Insomnia Outcome Group interaction can be seen in Table 2. Further breakdown of the interaction revealed a significant difference between groups only at T2 with a large effect size, $F(1,37)=22.8$, p<0.001, $\eta_p^2=0.38$. The divergence of scores across time points resulted in a significantly lower GFI at T2, as shown in Figure 1d.

Depression –

A significant Time × Insomnia Outcome Group interaction was noted for scores on the PHQ-9. Further analysis showed significantly lower PHQ-9 scores for the Remission group only at T2 with a medium effect size, $F(1,37)=4.6$, p=0.038 $\eta_p^2=0.11$. As can be seen in Figure 1e, a decline in PHQ-9 scores was only observed in the Remission group.

Community Participation –

For the PART-O, there was a marginally significant between-groups main effect with a medium effect size. As can be seen in Figure 1f, higher scores were observed for the Remission group across time points.

Treatment Questions

To explore whether remission of insomnia may have been associated with engagement in various treatments, the use of pharmacological and non-pharmacological treatments for insomnia was examined. It should be noted that data were missing for 6 participants on these questions.

At T1, 50% of participants reported taking medication for the treatment of insomnia. There were no significant differences between Insomnia Outcome Groups in the percentage of individuals who tried medication at this time (Persistent: 54% Remission: 48%), $\chi^2=0.1$, df=1, p=0.724. Of those reporting treatment with medication, 13 (77%) found it to be effective. Fisher's exact test showed no significant difference between Insomnia Outcome Groups at T1 with 6 out of 7 in the Persistent group and 7 out of 10 in the Remission group reporting medication to be effective (p=0.441). Only 2 individuals reported trying a non-pharmacological treatment. Both of them were in the Remission Group and both reported the treatments ("medicinal marijuana" and "chiropractor") to be helpful.

At T2, 53% reported having tried medication for the treatment of insomnia. There was no significant difference between Insomnia Outcome Groups in the percentage of individuals who had tried medication (Persistent: 63%, Remission: 61%), $\chi^2=0.01$, df=1, p=0.934. Of those reporting treatment with medication, 10 (46%) found it to be effective. Fisher's exact test showed a significant difference between Insomnia Outcome Groups with 1 out of 10 in the Persistent group and 9 out of 11 in the Remission group reporting medication to be effective (p=0.002).

Only 4 (12%) of the people who responded to the T2 treatment questions reported receiving a non-pharmacological treatment (2 in the Remission group and 2 in the Persistent group). Three out of the 4 individuals who received such treatment reported it to be helpful (2 in the Remission group and 1 in the Persistent group).

Discussion

In this small sample of TBI survivors with insomnia, there were clear differences between those with persistent insomnia compared with those who experienced a remission of insomnia in reports of sleep quality, depression, and fatigue. These differences were evident between 1–2 and 2–5 years post-injury, where significant Time × Insomnia Outcome interactions were noted, with the Remission group showing better sleep quality and reductions in fatigue and depression by T2. Results extend previously documented findings that insomnia is associated with impaired mood and participation, [11, 12] indicating that prolonged persistent insomnia is associated with worsening of depression symptoms over time after TBI. The relationship between fatigue, depression, and sleep disturbance has been shown previously [41]. Cognitive-behavioral interventions targeting sleep disturbance have also been shown to result in reduced depression and fatigue [42, 43]. This highlights the importance of inquiring about sleep among individuals who present with symptoms of depression after TBI so that a treating clinician can consider treating symptoms in tandem.

The two Insomnia Outcome Groups also showed some differences in sleep hygiene, with the Persistent group showing poorer sleep hygiene overall. While a causal relationship cannot be established, there appears to be a significant association. The fact that the remission group had better sleep hygiene compared with the persistent group even at T1 may reflect a protective factor that placed them in a position to more effectively manage their symptoms over time. These findings are consistent with the behavioral models of chronic insomnia such as the Spielman 3P Model [44]. Spielman's theory suggests that following emergent events (such as TBI) that may precipitate a period of insomnia, the condition may become chronic due to perpetuating factors such as maladaptive cognitive and behavioral coping strategies (e.g., staying in bed longer to attempt to increase amount of sleep). These strategies often have the unintended consequence of disrupting healthy sleep patterns and increasing physical and mental arousal during the intended sleep period [45]. While sleep hygiene interventions in isolation have little support in the research literature, the SHI contains items describing maladaptive behaviors and aspects of chronic insomnia that are the target of Cognitive Behavioral Therapy for Insomnia (CBT-I). Targeting the specific perpetuating factors, through cognitive behavioral treatments, has led to improved sleep across a number of conditions including osteoarthritis [46, 47], cancer [48], fibromyalgia [49], chronic pain [50], and cardiopulmonary disease [47]. To date, there have been no large-scale studies of CBT-I in TBI, but a number of smaller scale studies have shown promising results [42, 43, 51]. Other studies have demonstrated improvement in subjective sleep quality using non-pharmacological interventions including sleep hygiene related practices combined with more potent cognitive-behavioral therapeutic techniques [43, 52, 53]. While there is little support for sleep hygiene education as a stand-alone treatment for chronic insomnia, [52] it may be worthwhile to incorporate sleep hygiene education into TBI rehabilitation programs as a potential preventative measure for those who may be at risk for

developing the maladaptive behaviors to compensate for disturbed sleep [54]. This education can also include some guidance as to when it would be important to seek the help of a sleep specialist to address problematic issues in a more timely fashion before they become chronic.

Over half of our respondents tried treatment with medication, with similar rates of use in the Remission and Persistent groups. Of subjects reporting use of medication, 82% of those in the Remission group found it to be effective in treating their insomnia, compared with only 10% of those in the Persistent group. However, it is unclear whether medication usage directly contributed to the remission of insomnia in this group or whether this represents attribution bias. Only 12% of respondents reported receiving treatment that did not involve medication. These findings suggest that non-pharmacological interventions are under-utilized in the treatment of post-TBI insomnia, which is surprising given the demonstrated efficacy of such treatments in other clinical populations [46–50]. This may be due to a shortage of individuals trained in the delivery of behavioral treatments [55].

Daytime sleepiness showed a marginally significant main effect, with the Persistent group reporting greater sleepiness across time points. Within the Persistent group, a trend toward higher percentages of individuals with excessive sleepiness was noted. While excessive daytime sleepiness is not typical among individuals with primary insomnia who tend to be prone to hyperarousal [56, 57], it is possible that the daytime effects of chronic insomnia may be different for individuals with TBI. Previous research has shown a tendency for daytime sleepiness among this group, with the symptom becoming chronic in 25% and 67% of two samples studied [58, 59]. Individuals with chronic insomnia after TBI may experience an exacerbation of an already existing excessive daytime sleepiness phenomenon. It should be noted that excessive daytime sleepiness may be the result of an undiagnosed sleep disorder such as obstructive sleep apnea [60].

The marginally significant main effect found for community participation showed a medium effect size. Increased community participation may result from a reduction of insomnia symptoms and reduced fatigue. However, it is also possible that among individuals with insomnia at T1, those with greater community participation may have been engaging in activities that contributed to improvement in their sleep over time. For example, in population-based studies, physical activity has been shown to be a protective factor against insomnia [61, 62]. Increased physical activity has also been shown to be an effective intervention for insomnia [63].

Those with persistent insomnia were less likely to be male and to have sustained a severe TBI. Although the latter is counterintuitive, research has shown a higher reporting of sleep disturbance among TBI survivors with less severe injuries [64]. This may be a function of decreased self-awareness in more severely injured individuals.

Limitations

The study sample consisted of individuals with moderate to severe TBI who received acute hospitalization followed by inpatient rehabilitation at specialized rehabilitation centers. As such, the findings may not represent those with milder injuries or those who do not receive

access to specialized rehabilitation care. Insomnia, fatigue, depression and participation were characterized using self-report measures and retrospective assessment which may be limited by recall and self-awareness biases.

The proportion of individuals with insomnia after TBI who were included in this analysis (17% of the 237 with 2 waves of data) is much smaller than what has been reported in the literature. Having two separate cohorts with one assessed at 1 and 2 years post-injury and the other at 2 and 5 years post-injury was an additional limitation. The small sample size precluded separate analyses for each cohort and prohibited the drawing of conclusions regarding rate of change and other granular aspects of recovery over a 5-year period after TBI. For example, the 2–5 year cohort did not capture individuals who may have met insomnia criteria at 1 year post-injury, and it is possible that remission actually occurred in years 3 or 4. Future longitudinal studies should consider following individuals from the point of rehabilitation discharge, possibly with yearly follow-up interviews, to determine the course of sleep disturbance over the years after injury, with a potential for objective measurements using more widely available biosensors. Future research should consider including three or more measurement time points across all participants to allow for the use of statistical techniques such as growth curve modelling to more finely characterize trajectories of change over time.

A self-reported history of sleep apnea was reported by 10% of the sample, which may be an under-representation There may be additional cases of undiagnosed sleep apnea within this sample, contributing to sleep disruption that is masquerading as primary insomnia. Although it is entirely possible for sleep apnea and insomnia to be comorbid conditions, screening for the presence of sleep apnea is essential as a first step to determine the role of sleep disordered breathing in sleep disruption. In addition, behavioral treatments such as CBT-I are unlikely to be effective in the face of untreated sleep apnea. Future studies should include more detailed questions to screen for sleep-related breathing disorders.

In summary, results from the current study underscore the detrimental impact of chronic insomnia on the lives of individuals with TBI, and highlight the need for more effective interventions for post-TBI insomnia. While use of sleep medications occurred in both the Remission and Persistent groups, individuals who experienced a remission of their insomnia tended to report medication to be successful. This may be associated with attribution bias in the sample based on the respective experiences of the participants. Pharmacological treatments alone cannot account for the remission of insomnia. Use of non-pharmacological interventions was surprisingly low among participants in this study, despite abundant research suggesting that low-risk activities like CBT [65–67] and engaging in physical activity [63] can improve symptoms in clinical populations. More prospective research into the onset and chronicity of post-TBI insomnia is needed to better understand the most appropriate timing of non-pharmacological (as a low-risk first-line treatment) and pharmacological interventions for this high-risk group.

Conflicts of Interest and Sources of Funding

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Appendix A

Criteria for Insomnia Syndrome as presented by Ouellett et al. (2006)[14].

- **A.** The patient must present with a significant sleep complaint (i.e., dissatisfaction with sleep or significant distress)
- **B.** The patient must report insomnia symptoms defined as either (or both) of the following:
  1. difficulty initiating sleep operationalized as taking more than 30 min to fall asleep
  2. difficulty maintaining sleep operationalized as spending more than 30 min awake during the night
- **C.** The sleep disturbance occurs at least 3 nights per week
- **D.** The sleep disturbance causes significant negative daytime effects in at least 2 domains of functioning (e.g., mood, mental capacities, social activities, occupation) or significant distress or preoccupation
- **E.** The sleep disturbance has been present for at least 1 month

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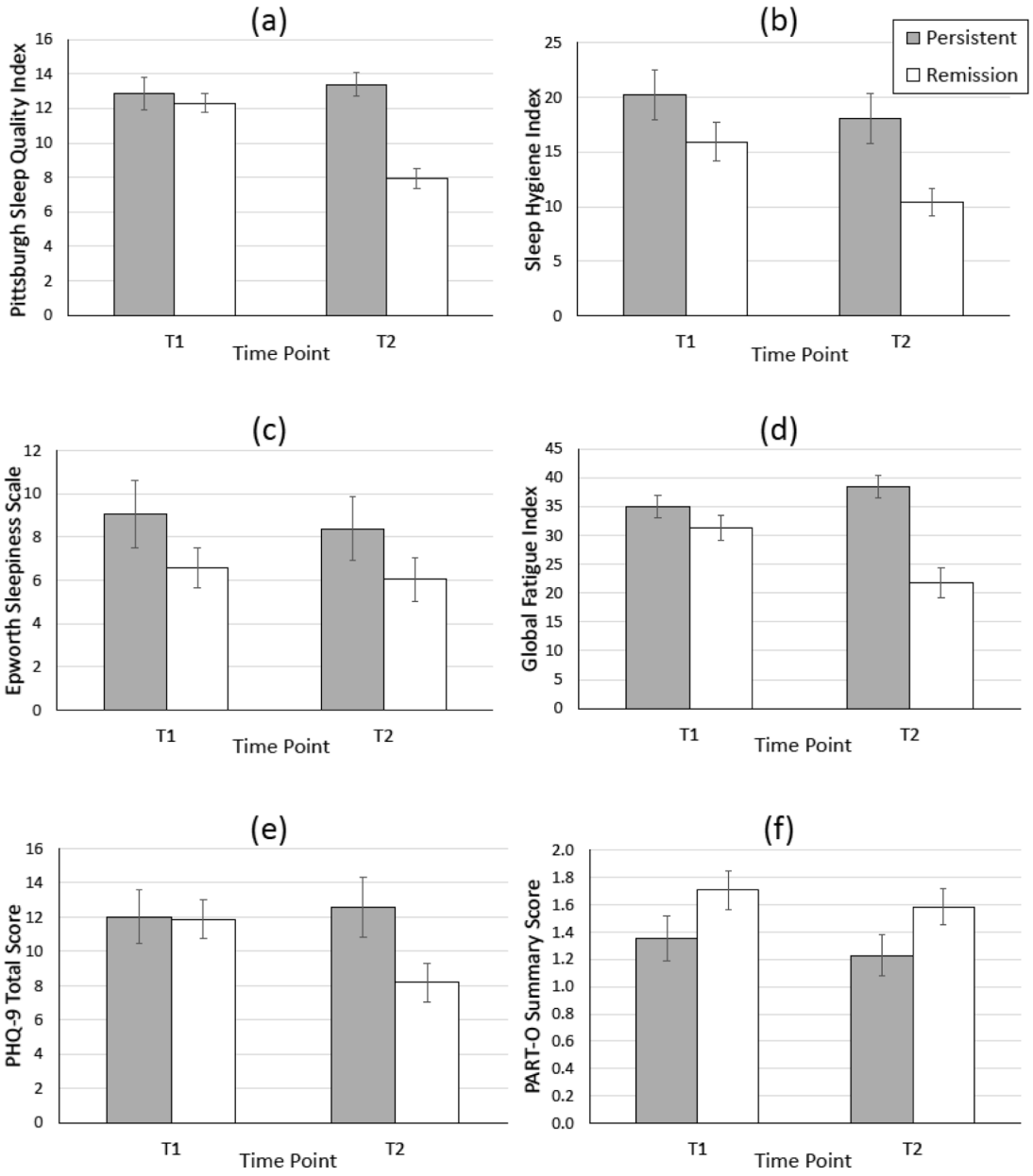

Figure 1 (a-f).
Relationships between the remission of insomnia and outcome variables.

Table 1.

Demographics and Sample Characteristics

Variables	Persistent		Remission		Total	
	n	%	n	%	n	%
Sex						
Female	6	37.5	5	20.8	11	27.5
Male	10	62.5	19	79.2	29	72.5
Race/Ethnicity						
White	11	68.7	13	54.2	24	60.0
Black	1	6.3	1	4.2	2	5.0
Hispanic	2	12.5	9	37.5	11	27.5
Other	2	12.5	1	4.2	3	7.5
Cause of Injury						
Vehicular	11	68.7	15	62.5	26	65.0
Fall	2	12.5	5	20.8	7	17.5
Assault	2	12.5	2	8.3	4	10.0
Sports or Other	1	6.3	2	8.3	3	7.5
Injury Severity						
Moderate	13	81.3	15	62.5	28	70.0
Severe	3	18.8	9	37.5	12	30.0
Cohort						
1–2 Years	8	50.0	11	45.8	19	47.5
2–5 Years	8	50.0	13	54.2	21	52.5
Age at Injury (Mean, SD)	35.8	19.0	34.0	16.2	34.6	17.1
Years of Education (Mean, SD)	12.4	2.7	11.8	2.1	12.0	2.3

Table 2.

Repeated Measure ANCOVAs for Outcomes by group.

Outcome Variables*	Group Main Effect			Time Main Effect			Time × Group Interaction		
	F(1,37)	*p*	η_p^2	*F(1,37)*	*p*	η_p^2	*F(1,37)*	*p*	η_p^2
PSQI	7.7	0.009	0.17	0.5	0.489	0.01	21.0	<0.001	0.36
SHI	8.2	0.007	0.18	<0.01	0.988	<0.01	1.0	0.320	0.03
ESS	2.9	0.097	0.07	0.4	0.513	0.01	0.0	0.910	<0.01
GFI	14.5	0.001	0.28	0.8	0.366	0.02	11.6	0.002	0.24
PHQ-9	1.8	0.190	0.05	0.3	0.560	0.01	4.2	0.049	0.10
PART-O	3.7	0.061	0.09	<0.01	0.935	<0.01	0.0	0.990	<0.01

*PSQI = Pittsburgh Sleep Quality Index; SHI = Sleep Hygiene Index; ESS = Epworth Sleepiness Scale; GFI = Global Fatigue Index; PHQ-9 = Patient Health Questionnaire-9; PART-O = Participation Assessment with Recombined Tools.