Recovery from Sleep Disturbance Precedes that of Depression and Anxiety Following Mild Traumatic Brain Injury: A Six-Week Follow-up Study

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Recovery from Sleep Disturbance Precedes that of Depression and Anxiety Following Mild Traumatic Brain Injury: A Six-Week Follow-up Study

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ABSTRACT

Introduction: Previous studies of recovery after mild traumatic brain injury (mTBI) have focused on chronic mental disorders. The detailed course of these disorders at the acute and subacute stages, especially with regard to recovery from sleep disturbances, have not been well characterized. The aim of our study was to determine the course of mental disorders, including depression, anxiety, and sleep disturbance, following mTBI.

Methods: We recruited 250 mTBI patients and 100 healthy participants (control group) for our observational study between January 2011 to July 2012. The mTBI and control participants were assessed at baseline and 6 weeks after mTBI using the Beck Anxiety Inventory (BAI), the Beck Depression Inventory II (BDI), the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI).

Results: The ESS scores were not significantly different between the 2 groups at baseline or at 6 weeks after mTBI. Although the BAI, BDI, and PSQI scores of the mTBI group were significantly different than those of the control group at baseline, all had improved significantly 6 weeks later. However, only the PSQI score improved to a level that was not significantly different from that of the control group.

Conclusions: Daytime sleepiness is not affected by mTBI. However, mTBI causes depression and anxiety and diminishes sleep quality. Although all these conditions improve significantly within 6 weeks post-mTBI, only sleep quality improves to a pre-mTBI level. Thus, recovery from mTBI-induced sleep disturbance occurs more rapidly than that of mTBI-induced depression and anxiety.

Article summary

- 100 mTBI patients and the 137 control participants who completed the questionnaires.
- The number of women is more than the number of men that jointed our study
- Sleep disturbance, depression, anxiety improved after 6 weeks post-injury.
- Recovery from sleep disturbance occurred more rapidly

Strengths and limitations of this study

Previous reports of the incidence of insomnia among post-acute TBI patients have ranged from 2% to 56%. In our study, 90% of the mTBI patients and 44% of the control participants reported sleep disturbances. Our data showed that recovery from sleep disturbance occurred more rapidly among the mTBI patients than did recovery from post-injury depression and anxiety. Previous studies have demonstrated significant changes in anxiety- and depression-related symptoms between 1 week and 3 months following mTBI. We observed improvement in the depression and anxiety assessment scores in our mTBI cohort at 6 weeks post-injury. Nonetheless, the BDI and the BAI scores differed significantly between the mTBI and control groups at the 6-week post-injury assessment.

Some of our mTBI patients may have used medications before or after suffering mTBI that may have influenced their assessment scores. It is also possible that some of our mTBI patients may have had unrelated diseases or pre-injury conditions that were not identified before or during their participation in our study. In addition, we investigated only the subacute stages of depression, anxiety, and diminished sleep quality, rather than the chronic stages of these diseases.

INTRODUCTION

Traumatic brain injury (TMI) and mild traumatic brain injury (mTBI) are major public health problems. Studies in Australia have estimated lifetime costs of over $2.5 million per TMI survivor [1]. Headache, blurred vision, fatigue, and sleep disturbance are the most common physical symptoms following brain injury [2]. Previous studies have reported that the symptom scores following mTBI were equal to that of control patients within 7 days post-injury [3].

However, increasing evidence suggests that the risk of developing a psychiatric disorder increases following mTBI [4]. Although multiple studies have investigated post-traumatic stress disorder (PTSD), the risk of other disorders, such as depression, have also been found to increase following mTBI [5]. The most common psychiatric disorders during the first 12 months following injury are depression, anxiety disorder, and agoraphobia [4].

Diminished sleep quality is one of the most commonly reported symptoms following mTBI [6], and depression and anxiety are also prevalent. However, these conditions are often under-reported, and may become chronic in the absence of treatment. The objectives of our study were to characterize the course of post-mTBI depression, anxiety, and diminished sleep quality during a 6-week follow up, and to compare the baseline and 6-week clinical assessments of mTBI patients with those of healthy participants.

METHODS

Participants and Study Design

Our prospective study was approved by the Joint Institutional Review Board of Taipei Medical University. Eligible patients aged ≥20 years who were treated in an emergency room within 24 hours after closed head trauma were recruited from 3 hospitals in Taiwan between January 2011 and July 2012. The definition of mTBI was based on the diagnostic criteria established by the American Congress of Rehabilitation Medicine, which consist of a Glasgow Coma Scale (GCS) score of 13 to 15 at presentation and loss of consciousness for < 30 min. Patients with a history of cerebrovascular disease, mental retardation, previous TBI, epilepsy, or severe systemic medical illness were excluded from our study. The inclusion of the healthy control participants were no brain injury history and older than 20 years old.

Patients were initially contacted by phone. A total of 607 mTBI patients were recruited for our study, among whom 250 (41.19%) provided informed consent, and completed a baseline assessment during an initial evaluation within 1 month after experiencing an mTBI. Six weeks after completing the baseline assessment, 100 (40%) of the mTBI patients completed the final assessment. The baseline and 6-week assessments consisted of 4 investigator-administered questionnaires, namely, the Beck Anxiety Inventory (BAI) [7], the Beck Depression Inventory-II (BDI) [8], the Epworth Sleepiness Scale (ESS) [9], and the Pittsburgh Sleep Quality Index (PSQI) [10].

Outcome Measures

The patients' demographic information, injury-related data, and smoking and drinking history were recorded at the baseline evaluation. Chinese versions of the BDI, the BAI, the ESS, and the PSQI were used in our study [11-13]. Depression was assessed using the BDI, which scored the patient's selection of 1 of 4 possible responses to 21 multiple-choice items on a scale of 0 to 3 based on their response. The severity of anxiety symptoms was assessed using the BAI, which also scored the patient's selection of 1 of 4 possible responses to 21 multiple-choice items on a scale of 0 to 3 based on their response. A high score on the BAI indicates a high level of anxiety. Daytime sleepiness was subjectively assessed using the ESS, which asked the patient to rate their risk of falling asleep on a 4-point Likert scale (0-3) in 8 different situations. Overall sleep quality was assessed using the PSQI, which evaluated 7 aspects of sleep quality. A high overall score on the PSQI indicates poor sleep quality.

Statistical methods

Associations between the categorical variables were evaluated using a chi-squared analysis, and the Fisher exact test was used when at least one of the values was <5. Associations between the normally distributed continuous variables were evaluated using *t* tests, and the Mann-Whitney U test was used to evaluate the continuous variables with an asymmetrical distribution. Paired *t* tests and a paired Mann-Whitney U test were used to evaluate the intragroup differences between the baseline and 6-week assessments for normally and asymmetrically distributed data, respectively. In addition, linear regression analyses were conducted for outcomes with or without adjustment for age and sex. All the statistical analyses were performed using the R statistical software, version 3.0.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria). The level of statistical significance was set at $P < .05$.

RESULTS

The demographic information and clinical data of all the mTBI and control participants who were initially enrolled in the study are shown in Table 1. Six weeks following their baseline assessment, 150 patients could not be contacted, or declined to participant further in our study. The age; sex; education level; smoking status; alcohol use; proportion reporting depression; mechanism of injury; and GCS, BDI, ESS scores of patients who completed the study did not differ significantly from those of patients who did not complete the study. The patients who did not complete the study had lower mean scores for the BAI and the PSQI than the patients who completed the study.

The demographic information and clinical data of the 100 mTBI patients and the 137 control participants who completed the study are shown in Table 2. The mean age of the mTBI group

was significantly higher than the mean age of the control group. The proportions reporting alcohol use, headache, and depression were significantly different between the mTBI and control groups. The percentages of mTBI patients who reported headache or depression were higher than those of the control group. Transportation accidents and falls caused 39% and 34% of the mTBI cases, respectively. Considering the clinical cut-off for each questionnaire, most control patients did not have depression, anxiety, daytime sleepiness, or diminished sleep quality, whereas most of mTBI patients had high PSQI scores.

The mean scores of the 4 outcome measures are shown in Figure 1. The average scores for the mTBI patients at baseline were the highest. After 6 weeks, the average scores for the mTBI patients decreased. The differences between the outcomes of the mTBI and control groups are shown in Table 3. The average baseline and 6-week BAI scores for mTBI group were 10.74 and 7.23, respectively. The BAI scores of the patients in the mTBI group significantly improved at 6 weeks post-injury. However, the mean BAI scores for the mTBI group for both the baseline and 6 week assessments were significantly different from those of the control groupat the baseline assessment. The mean BDI scores of the mTBI group were 9.8 and 7.99 at the baseline and 6-week assessments, respectively. The mean BDI score for mTBI group significantly decreased to 1.81 at 6 weeks post-injury. The mean BDI score of the control group was 5.72. The mean BDI scores of the mTBI group were significantly different from those of the control group.

No significant difference was observed between the baseline and 6-week ESS scores for the mTBI group. The mean daytime sleepiness score for the control group was 6.62, which was not significantly different from that of the mTBI group. The mean baseline PSQI score for the mTBI group was greater than 9, which was higher than the clinical cut-off point of 5. In addition, the mean PSQI score of mTBI at baseline assessment was higher than the mean score of 5.7 for the control group. The mean 6-week PSQI score for the mTBI group improved significantly to 6.4. The sleep quality of the mTBI group at 6 weeks post-injury was not significantly different from that of the control group.

Because of the significant difference in mean age between the mTBI and control groups and the predominance of women in both groups, we performed linear regression analysis of the outcome measures with and without adjusting for age and sex (Table 4). The differences in depression, anxiety, and sleep quality between the mTBI and control patients did not vary significantly before or after adjusting for age or sex. However, sex was found to be a significant predictor of sleep quality, anxiety, and depression in the baseline and 6-week assessments. After adjusting for age and sex, the ESS score was significantly different between the control and mTBI groups at the baseline and 6-week assessments, and age was determined to be a significant predictor of daytime sleepiness. In addition, the scores for all 4 outcome measures were higher among women than among men.

DISCUSSION

Previous studies have shown that 85% of mTBI patients demonstrate improvement in psychiatric-related symptoms, whereas the remainder develop chronic psychosocial problems [14-16]. Often presenting with anxiety, depression, or sleep disturbances, TBI patients are at an increased risk of developing a psychiatric disorder within 3 months to 1 year post-injury [4]. It is unclear whether post-mTBI sleep disturbances are related to depression or anxiety. Thus, sleep disturbance may be a risk factor of subsequent depression. A meta-analysis of 21 studies demonstrated that insomnia patients have a 2-fold risk of developing depression [17]. The detailed course of post-mTBI depression, anxiety, and diminished sleep quality, especially during the early stages of recovery, have not been well characterized.

We examined the early stages of recovery from mTBI by using self-reported measures of depression, anxiety, sleep quality, and daytime sleepiness. We determined that daytime sleepiness is not significantly affected by mTBI. Both the anxiety and depression symptoms in the mTBI group improved by the sixth week of recovery, but remained more severe than those of the control participants. However, sleep quality significantly improved within 6 weeks of experiencing mTBI, returning to a level that did not differ significantly from that of the control group. These results indicate that recovery from diminished sleep quality occurred more rapidly than did recovery from depression and anxiety.

Our prospective cohorts contained more women than men, and the mean ages of the mTBI and control groups differed significantly. Thus, we adjusted our analysis for effects of age and sex. The BAI, BDI, PSQI, and ESS scores were influenced by sex. However, our results demonstrated that the BAI, BDI, and PSQI scores were significantly affected by mTBI, whereas the ESS scores were not. We found the women in the mTBI group reported more severe symptoms for depression, anxiety, and diminished sleep quality at baseline. After 6 weeks of recovery, although the depression- and anxiety-related symptoms of both male and female mTBI patients improved, those of the female mTBI patients remained more severe than those of the male mTBI patients. Female mTBI patients also reported more severe symptoms related to diminished sleep quality and daytime sleepiness than did male mTBI patients.

Previous reports of the incidence of insomnia among post-acute TBI patients have ranged from 2% to 56% [18, 19]. Bryan found that sleep disturbance increases in patients who suffer repetitive TBI [20]. In our study, 90% of the mTBI patients and 44% of the control participants reported sleep disturbances. Our data showed that recovery from sleep disturbance occurred more rapidly among the mTBI patients than did recovery from post-injury depression and anxiety. There are 2 possible reasons for this finding. Sleep disturbance may be an independent symptom of mTBI that alters the circadian rhythm through injury-related changes in gene expression [21]. Alternatively, sleep disturbance may simply be a symptom of depression or anxiety that improves early during recovery [22].

Previous studies have demonstrated significant changes in anxiety- and depression-related symptoms between 1 week and 3 months following mTBI [23]. We observed improvement in the depression and anxiety assessment scores in our mTBI cohort at 6 weeks post-injury. Nonetheless, the BDI and the BAI scores differed significantly between the mTBI and control groups at the 6-week post-injury assessment.

Depression and PTSD have been shown to be critical mediators of the recovery of physical health following mTBI [24]. Multiple studies have investigated the incidence of PTSD following TBI [25]. Psychiatric comorbidities have been associated with PTSD following TBI, and depression was shown to be a predictor of the post-TBI chronicity of PTSD [26, 27]. We did not explore the role of PTSD in recovery from depression, anxiety, and diminished sleep quality, but we speculate that PTSD is associated with all of these mental disorders in mTBI patients.

Certain limitations to our findings should be considered. First, some of our mTBI patients may have used medications before or after suffering mTBI that may have influenced their assessment scores. Second, it is possible that some of our mTBI patients may have had unrelated diseases or pre-injury conditions that were not identified before or during their participation in our study. Third, we investigated only the subacute stages of depression, anxiety, and diminished sleep quality, rather than the chronic stages of these diseases. Although long-term observational studies are required to confirm our findings, our results provide valuable information for understanding the development and recovery of mental disorders following mTBI.

Table 1. The demographic and clinical data of all mTBI patients initially enrolled in our study

	Lost to follow up	Completed 6-wk follow up	*P* value
Age (y)	38.88	39.53	NS
Male / Female (n)	56/94	35/65	NS
Education (y)	15.04	15.46	NS
Smoker (N/Y)	113 / 37	82 / 18	NS
Drink alcohol (N/Y)	94/56	58/ 42	NS
Headache (N/Y)	50/100	25/75	.02
Depression (N/Y)	91 / 59	51 / 49	NS
GCS	14.80	14.98	NS
Mechanism of Injury			
Transportation accident	77	39	NS
Falls	40	34	
Other	33	27	
BAI	7.85	10.74	.03
BDI	8.19	9.80	NS
ESS	6.89	7.95	NS
PSQI	6.27	9.51	<.01

mTBI: mild traumatic brain injury; NS: $P > .05$; GCS: Glasgow Coma Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

Table 2. The demographic and clinical data of the mTBI patients and the control participants who completed the 6-week follow up

	mTBI	Control	*P* value
Sample size (n)	100	137	
Age (y)	39.53	29.86	<.001
Male / Female (n)	35/65	47/90	NS
Education (y)	15.46	14.91	.045
Smoker (N/Y)	82/18	115/22	NS
Drink (N/Y)	58/42	51/82	<.01
Headache (N/Y)	25/75	98/39	<.01
Depression (N/Y)	51 / 49	103/ 34	<.01
GCS	14.98	-	-
Questionnaires			
BAI >7 (N/Y)	57 / 43	125 / 12	<.01
BDI >9 (N/Y)	53 / 47	111 / 26	<.01
ESS >9 (N/Y)	66 / 34	108 / 29	<.01
PSQI >5 (N/Y)	10 / 90	77 / 60	<.01
Mechanisms of Injury			
Transportation accident	39	-	-
Falls	34	-	-
Other	27	-	-

mTBI: mild traumatic brain injury; NS: *P* >.05; GCS: Glasgow Coma Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

Table 3. Differences between control participants and mTBI patients at baseline and 6 weeks post-injury

	BAI	BDI	ESS	PSQI
mTBI Baseline vs Control	8.02*	4.08*	1.33	3.81*
mTBI 6 wk vs Control	4.51*	2.27*	0.87	0.7
mTBI Baseline vs mTBI 6 wk[+]	3.51*	1.81*	0.46	3.11*

mTBI: mild traumatic brain injury; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

*$P < .05$

[+]paired *t* test

Table 4. Adjusted differences between control participants and mTBI patients at baseline and 6 weeks post-injury

	Control vs mTBI (baseline)				Control vs mTBI (6-wk)			
	BAI	BDI	ESS	PSQI	BAI	BDI	ESS	PSQI
mTBI	8.079*	4.331*	1.808*	3.609*	4.701*	2.632*	1.309*	0.557
Age	0.004	-0.023	-0.049*	0.021	-0.009	-0.035	-0.045*	0.016
Women	2.450*	3.457*	0.973	0.972*	2.324*	2.945*	1.263*	1.170*

mTBI: mild traumatic brain injury; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

*$P < .05$

Conflict of interest

None declared.

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Data sharing

There is no additional data available.

Contributorship statement

The six authors are justifiably credited with authorship, according to the authorship criteria. In detail: Hon-Ping Ma – conception, design and interpretation of data, drafting of the manuscript, final approval given; Ju-Chi Ou–analysis and interpretation of data, drafting of the manuscript, final approval given; Chun-Ting Yeh – acquisition of data, final approval given; Dean Wu – final approval given; Shin-Han Tsai – final approval given; Wen-Ta Chiu – Conception, design, final approval given; Chaur-Jong Hu – Conception, design, analysis and interpretation of data, drafting of the manuscript, final approval given.

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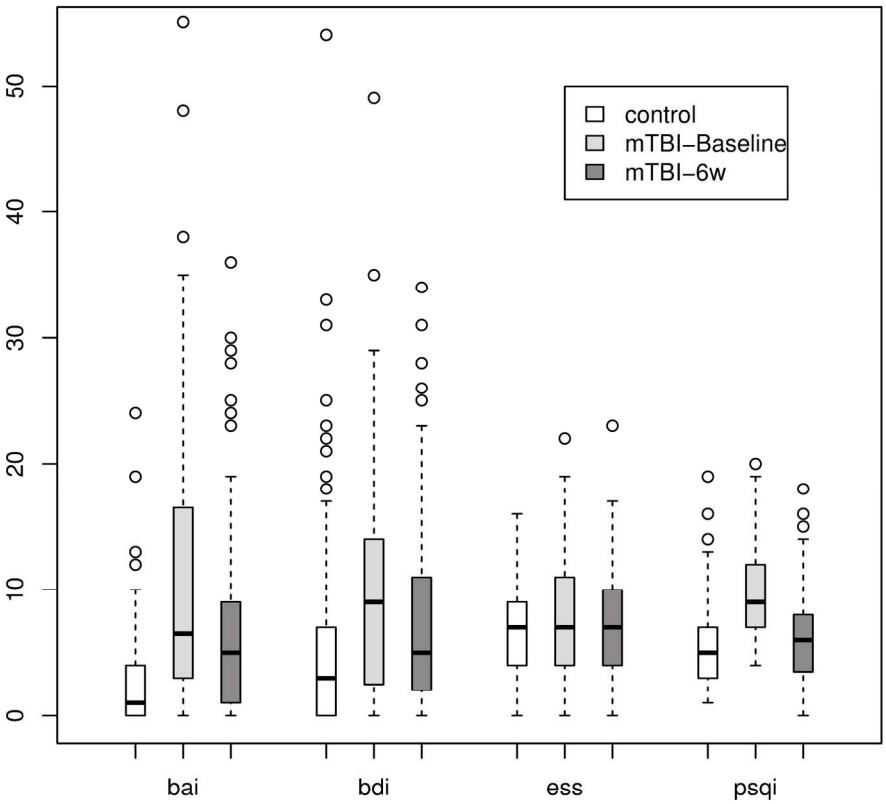

Figure 1. Box plot of the baseline and 6-wk post-injury assessments of the clinical outcomes. White bars represent the data for the control group. Light gray and dark gray bars represent the mild traumatic brain injury (mTBI) patients at baseline and 6 weeks post-injury, respectively. From left to right, the data for the Beck Anxiety Inventory (BAI), the Beck Depression Inventory-II (BDI), the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI) scores are represented.
177x177mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		Page 2 – observational study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
		Page 2 – results and conclusions
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
		Page 3
Objectives	3	State specific objectives, including any prespecified hypotheses
		Page 3
Methods		
Study design	4	Present key elements of study design early in the paper
		Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
		Page 3
Participants	6	(*a*) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		Page 3
		(*b*) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
		Not matched study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
		Page 3 & 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
		Page 4
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
		Page 4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		Page 4
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		Not applicable
		(*e*) Describe any sensitivity analyses
		Not applicable
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		Page 4
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		Page 4 & 5, table2
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
		Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Page 4 & 5
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		Page 5
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
		Not applicable
Discussion		
Key results	18	Summarise key results with reference to study objectives
		Page 6

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
		Page 6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
		Page 6 & 7
Generalisability	21	Discuss the generalisability (external validity) of the study results
		Page 6 & 7
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
		Page 11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Recovery from Sleep Disturbance Precedes that of Depression and Anxiety Following Mild Traumatic Brain Injury: A Six-Week Follow-up Study

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Recovery from Sleep Disturbance Precedes that of Depression and Anxiety Following Mild Traumatic Brain Injury: A Six-Week Follow-up Study

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ABSTRACT

Introduction: Previous studies of recovery after mild traumatic brain injury (mTBI) have focused on chronic mental disorders. The detailed course of these disorders at the acute and subacute stages, especially with regard to recovery from sleep disturbances, has not been well characterized. The aim of our study was to determine the course of mental disorders, including depression, anxiety, and sleep disturbance, following mTBI.

Methods: We recruited 250 mTBI patients and 100 healthy participants (control group) for our observational study between January 2011 to July 2012. The mTBI and control participants were assessed at baseline and 6 weeks after mTBI using the Beck Anxiety Inventory (BAI), the Beck Depression Inventory II (BDI), the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI).

Results: The ESS scores were not significantly different between the 2 groups at baseline or at 6 weeks after mTBI. Although the BAI, BDI, and PSQI scores of the mTBI group were significantly different than those of the control group at baseline, all had improved significantly 6 weeks later. However, only the PSQI score improved to a level that was not significantly different from that of the control group.

Conclusions: Daytime sleepiness is not affected by mTBI. However, mTBI causes depression and anxiety and diminished sleep quality. Although all these conditions improve significantly within 6 weeks post-mTBI, only sleep quality improves to a pre-mTBI level. Thus, recovery from mTBI-induced sleep disturbance occurs more rapidly than that of mTBI-induced depression and anxiety.

Article summary

- 100 mTBI patients and the 137 control participants who completed the questionnaires.
- The number of women is more than the number of men that jointed our study
- Sleep disturbance, depression, anxiety improved after 6 weeks post-injury.
- Recovery from sleep disturbance occurred more rapidly

Strengths and limitations of this study

Previous reports of the incidence of insomnia among post-acute TBI patients have ranged from 2% to 56%. In our study, 90% of the mTBI patients and 44% of the control participants reported sleep disturbances. Our data showed that recovery from sleep disturbance occurred more rapidly among the mTBI patients than did recovery from post-injury depression and anxiety. Previous studies have demonstrated significant changes in anxiety- and depression-related symptoms between 1 week and 3 months following mTBI. We observed improvement in the depression and anxiety assessment scores in our mTBI cohort at 6 weeks post-injury. Nonetheless, the BDI and the BAI scores differed significantly between the mTBI and control groups at the 6-week post-injury assessment.

Some of our mTBI patients may have used medications before or after suffering mTBI that may have influenced their assessment scores. It is also possible that some of our mTBI patients may have had unrelated diseases or pre-injury conditions that were not identified before or during their participation in our study. In addition, we investigated only the subacute stages of depression, anxiety, and diminished sleep quality, rather than the chronic stages of these diseases.

INTRODUCTION

Traumatic brain injury (TMI) and mild traumatic brain injury (mTBI) are major public health problems. Studies in Australia have estimated lifetime costs of over $2.5 million per TMI survivor [1]. Headache, blurred vision, fatigue, and sleep disturbance are the most common physical symptoms following brain injury [2]. Previous studies have reported that the symptom scores following mTBI were equal to that of control patients within 7 days post-injury [3].

However, increasing evidence suggests that the risk of developing a psychiatric disorder increases following mTBI [4]. Although multiple studies have investigated post-traumatic stress disorder (PTSD), the risk of other disorders, such as depression, have also been found to increase following mTBI [5]. The most common psychiatric disorders during the first 12 months following injury are depression, anxiety disorder, and agoraphobia [4].

Diminished sleep quality is one of the most commonly reported symptoms following mTBI [6], and depression and anxiety are also prevalent. However, these conditions are often under-reported, and may become chronic in the absence of treatment. The objectives of our study were to characterize the course of post-mTBI depression, anxiety, and diminished sleep quality during a 6-week follow up, and to compare the baseline and 6-week clinical assessments of mTBI patients with those of healthy participants.

METHODS

Participants and Study Design

Our prospective study was approved by the Joint Institutional Review Board of Taipei Medical University. Eligible patients aged ≥20 years who were treated in an emergency room within 24 hours after closed head trauma were recruited from 3 hospitals in Taiwan between January 2011 and July 2012. The definition of mTBI was based on the diagnostic criteria established by the American Congress of Rehabilitation Medicine, which consist of a Glasgow Coma Scale (GCS) score of 13 to 15 at presentation and loss of consciousness for < 30 min. Patients with a history of cerebrovascular disease, mental retardation, previous TBI, epilepsy, or severe systemic medical illness were excluded from our study. The inclusion of the healthy control participants were no brain injury history and older than 20 years old.

Patients were initially contacted by phone. A total of 607 mTBI patients were recruited for our study, among whom 250 (41.19%) provided informed consent, and completed a baseline assessment during an initial evaluation within 1 month after experiencing an mTBI. Six weeks after completing the baseline assessment, 100 (40%) of the mTBI patients completed the final assessment. The baseline and 6-week assessments consisted of 4 investigator-administered questionnaires, namely, the Beck Anxiety Inventory (BAI) [7], the Beck Depression Inventory-II (BDI) [8], the Epworth Sleepiness Scale (ESS) [9], and the Pittsburgh Sleep Quality Index (PSQI) [10].

Outcome Measures

The patients' demographic information, injury-related data, and smoking and drinking history were recorded at the baseline evaluation. Chinese versions of the BDI, the BAI, the ESS, and the PSQI were used in our study [11-13]. Depression was assessed using the BDI, which scored the patient's selection of 1 of 4 possible responses to 21 multiple-choice items on a scale of 0 to 3 based on their response. The severity of anxiety symptoms was assessed using the BAI, which also scored the patient's selection of 1 of 4 possible responses to 21 multiple-choice items on a scale of 0 to 3 based on their response. A high score on the BAI indicates a high level of anxiety. Daytime sleepiness was subjectively assessed using the ESS, which asked the patient to rate their risk of falling asleep on a 4-point Likert scale (0-3) in 8 different situations. Overall sleep quality was assessed using the PSQI, which evaluated 7 aspects of sleep quality. A high overall score on the PSQI indicates poor sleep quality.

Statistical methods

Associations between the categorical variables were evaluated using a chi-squared analysis, and the Fisher exact test was used when at least one of the values was <5. Associations between the normally distributed continuous variables were evaluated using *t* tests, and the Mann-Whitney U test was used to evaluate the continuous variables with an asymmetrical distribution. Paired *t* tests and a paired Mann-Whitney U test were used to evaluate the intragroup differences between the baseline and 6-week assessments for normally and asymmetrically distributed data, respectively. In this study, all outcome were abnormally distributed thus the non-parametric method was used. In addition, Generalized linear regression analyses were conducted for outcomes with or without adjustment for age and sex. All the statistical analyses were performed using the R statistical software, version 3.0.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria). The level of statistical significance was set at $P<.05$.

RESULTS

The demographic information and clinical data of all the mTBI and control participates who were initially enrolled in the study are shown in Table 1. Six weeks following their baseline assessment, 150 patients could not be contacted, or declined to participant further in our study. The age; sex; education level; smoking status; alcohol use; proportion reporting depression; mechanism of injury; and GCS, BDI, ESS scores of patients who completed the study did not differ significantly from those of patients who did not complete the study. The patients who did not complete the study had lower mean scores for the BAI and the PSQI than the patients who completed the study.

The demographic information and clinical data of the 100 mTBI patients and the 137 control

participants who completed the study are shown in Table 2. The mean age of the mTBI group was significantly higher than the mean age of the control group. The proportions reporting alcohol use, headache, and depression were significantly different between the mTBI and control groups. The percentages of mTBI patients who reported headache or depression were higher than those of the control group. Transportation accidents and falls caused 39% and 34% of the mTBI cases, respectively. Considering the clinical cut-off for each questionnaire, most control patients did not have depression, anxiety, daytime sleepiness, or diminished sleep quality, whereas most of mTBI patients had high PSQI scores.

The mean scores of the 4 outcome measures are shown in Figure 1. The average scores for the mTBI patients at baseline were the highest. After 6 weeks, the average scores for the mTBI patients decreased. The differences between the outcomes of the mTBI and control groups are shown in Table 3. The average baseline and 6-week BAI scores for mTBI group were 10.74 and 7.23, respectively. The BAI scores of the patients in the mTBI group significantly improved at 6 weeks post-injury. However, the mean BAI scores for the mTBI group for both the baseline and 6 week assessments were significantly different from those of the control groupat the baseline assessment. The mean BDI scores of the mTBI group were 9.8 and 7.99 at the baseline and 6-week assessments, respectively. The mean BDI score for mTBI group significantly decreased to the value of 1.81 at 6 weeks post-injury. The mean BDI score of the control group was 5.72. The mean BDI scores of the mTBI group were significantly different from those of the control group.

No significant difference was observed between the baseline and 6-week ESS scores for the mTBI group. The mean daytime sleepiness score for the control group was 6.62, which was not significantly different from that of the mTBI group. The mean baseline PSQI score for the mTBI group was greater than 9, which was higher than the clinical cut-off point of 5. In addition, the mean PSQI score of mTBI at baseline assessment was higher than the mean score of 5.7 for the control group. The mean 6-week PSQI score for the mTBI group improved significantly to 6.4. The sleep quality of the mTBI group at 6 weeks post-injury was not significantly different from that of the control group. Because of the significant difference in mean age between the mTBI and control groups and the predominance of women in both groups, we performed generalized linear regression analysis of the outcome measures with adjusting for age and sex (Table 4). The differences in depression, anxiety, and sleep quality between the mTBI and control patients kept significance after adjusting for age or sex. However, sex was found to be a significant predictor of sleep quality, anxiety, and depression in the baseline and 6-week assessments. After adjusting for age and sex, the ESS score was significantly different between the control and mTBI groups at the baseline and 6-week assessments, and age was determined to be a significant predictor of daytime sleepiness. In addition, the scores for all 4 outcome measures were higher among women than among men.

DISCUSSION

Previous studies have shown that 85% of mTBI patients demonstrate improvement in psychiatric-related symptoms, whereas the remainder develop chronic psychosocial problems [14-16]. Often presenting with anxiety, depression, or sleep disturbances, TBI patients are at an increased risk of developing a psychiatric disorder within 3 months to 1 year post-injury [4]. It is unclear whether post-mTBI sleep disturbances are related to depression or anxiety. Thus, sleep disturbance may be a risk factor of subsequent depression. A meta-analysis of 21 studies demonstrated that insomnia patients have a 2-fold risk of developing depression [17]. The detailed course of post-mTBI depression, anxiety, and diminished sleep quality, especially during the early stages of recovery, have not been well characterized.

We examined the early stages of recovery from mTBI by using self-reported measures of depression, anxiety, sleep quality, and daytime sleepiness. Most of them injured by transportation accident and falls. Other mechanism of injury included hit by something, and sport injury. There was no participant who injured by an industrial accident. We determined that daytime sleepiness is not significantly affected by mTBI. Both the anxiety and depression symptoms in the mTBI group improved by the sixth week of recovery, but remained more severe than those of the control participants. However, sleep quality significantly improved within 6 weeks of experiencing mTBI, returning to a level that did not differ significantly from that of the control group. These results indicate that recovery from diminished sleep quality occurred more rapidly than did recovery from depression and anxiety.

Our prospective cohorts contained more women than men, and the mean ages of the mTBI and control groups differed significantly. Thus, we adjusted our analysis for effects of age and sex. The BAI, BDI, PSQI, and ESS scores were influenced by sex. However, our results demonstrated that the BAI, BDI, and PSQI scores were significantly affected by mTBI, whereas the ESS scores were not. We found the women in the mTBI group reported more severe symptoms for depression, anxiety, and diminished sleep quality at baseline. After 6 weeks of recovery, although the depression- and anxiety-related symptoms of both male and female mTBI patients improved, those of the female mTBI patients remained more severe than those of the male mTBI patients. Female mTBI patients also reported more severe symptoms related to diminished sleep quality and daytime sleepiness than did male mTBI patients.

Previous reports of the incidence of insomnia among post-acute TBI patients have ranged from 2% to 56% [18, 19]. Bryan found that sleep disturbance increases in patients who suffer repetitive TBI [20]. In our study, 90% of the mTBI patients and 44% of the control participants reported sleep disturbances. The average score of PSQI in the control group (5.7) is higher than previously published values (2.7) [10], but it is close to the result of

another study in Taiwan also by use of the Chinese PSQI study in healthy group (5.7) [13]. It may result from the different versions of questionnaire (English and Chinese) or other uncertain reasons. Our data showed that recovery from sleep disturbance occurred more rapidly among the mTBI patients than did recovery from post-injury depression and anxiety. There are 2 possible reasons for this finding. Sleep disturbance may be an independent symptom of mTBI that alters the circadian rhythm through injury-related changes in gene expression [21]. Alternatively, sleep disturbance may simply be a symptom of depression or anxiety that improves early during recovery [22].

Previous studies have demonstrated significant changes in anxiety- and depression-related symptoms between 1 week and 3 months following mTBI [23]. We observed improvement in the depression and anxiety assessment scores in our mTBI cohort at 6 weeks post-injury. Nonetheless, the BDI and the BAI scores differed significantly between the mTBI and control groups at the 6-week post-injury assessment.

Depression and PTSD have been shown to be critical mediators of the recovery of physical health following mTBI [24]. Multiple studies have investigated the incidence of PTSD following TBI [25]. Psychiatric comorbidities have been associated with PTSD following TBI, and depression was shown to be a predictor of the post-TBI chronicity of PTSD [26, 27]. We did not explore the role of PTSD in recovery from depression, anxiety, and diminished sleep quality, but we speculate that PTSD is associated with all of these mental disorders in mTBI patients.

Certain limitations to our findings should be considered. First, some of our mTBI patients may have used medications before or after suffering mTBI that may have influenced their assessment scores. Second, it is possible that some of our mTBI patients may have had unrelated diseases or pre-injury conditions that were not identified before or during their participation in our study. Third, we investigated only the subacute stages of depression, anxiety, and diminished sleep quality, rather than the chronic stages of these diseases. In addition, REM sleep plays an important role in mood disorders. The changes of REM sleep after mTBI are still controversial[28, 29]. This is certainly a major issue for study. However, sleep architecture was not measured in our study. Although long-term observational studies are required to confirm our findings, our results provide valuable information for understanding the development and recovery of mental disorders following mTBI.

Table 1. The demographic and clinical data of all mTBI patients initially enrolled in our study

	Lost to follow up	Completed 6-wk follow up	*P* value
Age (y)	38.88	39.53	NS
Male / Female (n)	56/94	35/65	NS
Education (y)	15.04	15.46	NS
Smoker (N/Y)	113 / 37	82 / 18	NS
Drink alcohol (N/Y)	94/56	58/ 42	NS
Headache (N/Y)	50/100	25/75	.02
Depression (N/Y)	91 / 59	51 / 49	NS
GCS	14.80	14.98	NS
Mechanism of Injury			
Transportation accident	77	39	NS
Falls	40	34	
Other	33	27	
BAI	7.85	10.74	.03
BDI	8.19	9.80	NS
ESS	6.89	7.95	NS
PSQI	6.27	9.51	<.01

mTBI: mild traumatic brain injury; NS: $P > .05$; GCS: Glasgow Coma Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

Table 2. The demographic and clinical data of the mTBI patients and the control participants who completed the 6-week follow up

	mTBI	Control	*P* value
Sample size (n)	100	137	
Age (y)	39.53	29.86	<.001
Male / Female (n)	35/65	47/90	NS
Education (y)	15.46	14.91	.045
Smoker (N/Y)	82/18	115/22	NS
Drink (N/Y)	58/42	51/82	<.01
Headache (N/Y)	25/75	98/39	<.01
Depression (N/Y)	51 / 49	103/ 34	<.01
GCS	14.98	-	-
Questionnaires			
BAI >7 (N/Y)	57 / 43	125 / 12	<.01
BDI >9 (N/Y)	53 / 47	111 / 26	<.01
ESS >9 (N/Y)	66 / 34	108 / 29	<.01
PSQI >5 (N/Y)	10 / 90	77 / 60	<.01
Mechanisms of Injury			
Transportation accident	39	-	-
Falls	34	-	-
Other	27	-	-

mTBI: mild traumatic brain injury; NS: *P* >.05; GCS: Glasgow Coma Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

Table 3. Differences between control participants and mTBI patients at baseline and 6 weeks post-injury

	BAI	BDI	ESS	PSQI
mTBI Baseline vs Control	8.02*	4.08*	1.33	3.81*
mTBI 6 wk vs Control	4.51*	2.27*	0.87	0.7
mTBI Baseline vs mTBI 6 wk[+]	3.51*	1.81*	0.46	3.11*

mTBI: mild traumatic brain injury; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

*$P < .05$

[+]paired *t* test

Table 4. Coefficients of generalized linear model between control participants and mTBI patients at baseline and 6 weeks post-injury

	Control vs mTBI (baseline)				Control vs mTBI (6-week)			
	BAI	BDI	ESS	PSQI	BAI	BDI	ESS	PSQI
mTBI	1.4*	0.567*	0.245*	0.487*	1.026*	2.632*	1.309*	0.557
Age	0.0007	-0.003	-0.007*	0.003	-0.001	-0.035	-0.045*	0.016
Women	0.437*	0.056*	0.137*	0.137*	0.562*	2.945*	1.263*	1.170*

mTBI: mild traumatic brain injury; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

*$P < .05$

Conflict of interest

None declared.

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Data sharing

There is no additional data available.

Contributorship statement

The six authors are justifiably credited with authorship, according to the authorship criteria. In detail: Hon-Ping Ma – conception, design and interpretation of data, drafting of the manuscript, final approval given; Ju-Chi Ou–analysis and interpretation of data, drafting of the manuscript, final approval given; Chun-Ting Yeh – acquisition of data, final approval given; Dean Wu – final approval given; Shin-Han Tsai – final approval given; Wen-Ta Chiu – Conception, design, final approval given; Chaur-Jong Hu – Conception, design, analysis and interpretation of data, drafting of the manuscript, final approval given.

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ABSTRACT

Introduction: Previous studies of recovery after mild traumatic brain injury (mTBI) have focused on chronic mental disorders. The detailed course of these disorders at the acute and subacute stages, especially with regard to recovery from sleep disturbances, has not been well characterized. The aim of our study was to determine the course of mental disorders, including depression, anxiety, and sleep disturbance, following mTBI.

Methods: We recruited 250 mTBI patients and 100 healthy participants (control group) for our observational study between January 2011 to July 2012. The mTBI and control participants were assessed at baseline and 6 weeks after mTBI using the Beck Anxiety Inventory (BAI), the Beck Depression Inventory II (BDI), the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI).

Results: The ESS scores were not significantly different between the 2 groups at baseline or at 6 weeks after mTBI. Although the BAI, BDI, and PSQI scores of the mTBI group were significantly different than those of the control group at baseline, all had improved significantly 6 weeks later. However, only the PSQI score improved to a level that was not significantly different from that of the control group.

Conclusions: Daytime sleepiness is not affected by mTBI. However, mTBI causes depression and anxiety and diminished sleep quality. Although all these conditions improve significantly within 6 weeks post-mTBI, only sleep quality improves to a pre-mTBI level. Thus, recovery from mTBI-induced sleep disturbance occurs more rapidly than that of mTBI-induced depression and anxiety.

Article summary

- 100 mTBI patients and the 137 control participants who completed the questionnaires.
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- Sleep disturbance, depression, anxiety improved after 6 weeks post-injury.
- Recovery from sleep disturbance occurred more rapidly

Strengths and limitations of this study

Previous reports of the incidence of insomnia among post-acute TBI patients have ranged from 2% to 56%. In our study, 90% of the mTBI patients and 44% of the control participants reported sleep disturbances. Our data showed that recovery from sleep disturbance occurred more rapidly among the mTBI patients than did recovery from post-injury depression and anxiety. Previous studies have demonstrated significant changes in anxiety- and depression-related symptoms between 1 week and 3 months following mTBI. We observed improvement in the depression and anxiety assessment scores in our mTBI cohort at 6 weeks post-injury. Nonetheless, the BDI and the BAI scores differed significantly between the mTBI and control groups at the 6-week post-injury assessment.

Some of our mTBI patients may have used medications before or after suffering mTBI that may have influenced their assessment scores. It is also possible that some of our mTBI patients may have had unrelated diseases or pre-injury conditions that were not identified before or during their participation in our study. In addition, we investigated only the subacute stages of depression, anxiety, and diminished sleep quality, rather than the chronic stages of these diseases.

INTRODUCTION

Traumatic brain injury (TMI) and mild traumatic brain injury (mTBI) are major public health problems. Studies in Australia have estimated lifetime costs of over $2.5 million per TMI survivor [1]. Headache, blurred vision, fatigue, and sleep disturbance are the most common physical symptoms following brain injury [2]. Previous studies have reported that the symptom scores following mTBI were equal to that of control patients within 7 days post-injury [3].

However, increasing evidence suggests that the risk of developing a psychiatric disorder increases following mTBI [4]. Although multiple studies have investigated post-traumatic stress disorder (PTSD), the risk of other disorders, such as depression, have also been found to increase following mTBI [5]. The most common psychiatric disorders during the first 12 months following injury are depression, anxiety disorder, and agoraphobia [4].

Diminished sleep quality is one of the most commonly reported symptoms following mTBI [6], and depression and anxiety are also prevalent. However, these conditions are often under-reported, and may become chronic in the absence of treatment. The objectives of our study were to characterize the course of post-mTBI depression, anxiety, and diminished sleep quality during a 6-week follow up, and to compare the baseline and 6-week clinical assessments of mTBI patients with those of healthy participants.

METHODS

Participants and Study Design

Our prospective study was approved by the Joint Institutional Review Board of Taipei Medical University. Eligible patients aged ≥20 years who were treated in an emergency room within 24 hours after closed head trauma were recruited from 3 hospitals in Taiwan between January 2011 and July 2012. The definition of mTBI was based on the diagnostic criteria established by the American Congress of Rehabilitation Medicine, which consist of a Glasgow Coma Scale (GCS) score of 13 to 15 at presentation and loss of consciousness for < 30 min. Patients with a history of cerebrovascular disease, mental retardation, previous TBI, epilepsy, or severe systemic medical illness were excluded from our study. The inclusion of the healthy control participants were no brain injury history and older than 20 years old.

Patients were initially contacted by phone. A total of 607 mTBI patients were recruited for our study, among whom 250 (41.19%) provided informed consent, and completed a baseline assessment during an initial evaluation within 1 month after experiencing an mTBI. Six weeks after completing the baseline assessment, 100 (40%) of the mTBI patients completed the final assessment. The baseline and 6-week assessments consisted of 4 investigator-administered questionnaires, namely, the Beck Anxiety Inventory (BAI) [7], the Beck Depression Inventory-II (BDI) [8], the Epworth Sleepiness Scale (ESS) [9], and the Pittsburgh Sleep Quality Index (PSQI) [10].

Outcome Measures

The patients' demographic information, injury-related data, and smoking and drinking history were recorded at the baseline evaluation. Chinese versions of the BDI, the BAI, the ESS, and the PSQI were used in our study [11-13]. Depression was assessed using the BDI, which scored the patient's selection of 1 of 4 possible responses to 21 multiple-choice items on a scale of 0 to 3 based on their response. The severity of anxiety symptoms was assessed using the BAI, which also scored the patient's selection of 1 of 4 possible responses to 21 multiple-choice items on a scale of 0 to 3 based on their response. A high score on the BAI indicates a high level of anxiety. Daytime sleepiness was subjectively assessed using the ESS, which asked the patient to rate their risk of falling asleep on a 4-point Likert scale (0-3) in 8 different situations. Overall sleep quality was assessed using the PSQI, which evaluated 7 aspects of sleep quality. A high overall score on the PSQI indicates poor sleep quality.

Statistical methods

Associations between the categorical variables were evaluated using a chi-squared analysis, and the Fisher exact test was used when at least one of the values was <5. Associations between the normally distributed continuous variables were evaluated using *t* tests, and the Mann-Whitney U test was used to evaluate the continuous variables with an asymmetrical distribution. Paired *t* tests and a paired Mann-Whitney U test were used to evaluate the intragroup differences between the baseline and 6-week assessments for normally and asymmetrically distributed data, respectively. In this study, all outcome were abnormally distributed thus the non-parametric method was used. In addition, Generalized linear regression analyses were conducted for outcomes with or without adjustment for age and sex. All the statistical analyses were performed using the R statistical software, version 3.0.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria). The level of statistical significance was set at $P < .05$.

RESULTS

The demographic information and clinical data of all the mTBI and control participates who were initially enrolled in the study are shown in Table 1. Six weeks following their baseline assessment, 150 patients could not be contacted, or declined to participant further in our study. The age; sex; education level; smoking status; alcohol use; proportion reporting depression; mechanism of injury; and GCS, BDI, ESS scores of patients who completed the study did not differ significantly from those of patients who did not complete the study. The patients who did not complete the study had lower mean scores for the BAI and the PSQI than the patients who completed the study.

The demographic information and clinical data of the 100 mTBI patients and the 137 control

participants who completed the study are shown in Table 2. The mean age of the mTBI group was significantly higher than the mean age of the control group. The proportions reporting alcohol use, headache, and depression were significantly different between the mTBI and control groups. The percentages of mTBI patients who reported headache or depression were higher than those of the control group. Transportation accidents and falls caused 39% and 34% of the mTBI cases, respectively. Considering the clinical cut-off for each questionnaire, most control patients did not have depression, anxiety, daytime sleepiness, or diminished sleep quality, whereas most of mTBI patients had high PSQI scores.

The mean scores of the 4 outcome measures are shown in Figure 1. The average scores for the mTBI patients at baseline were the highest. After 6 weeks, the average scores for the mTBI patients decreased. The differences between the outcomes of the mTBI and control groups are shown in Table 3. The average baseline and 6-week BAI scores for mTBI group were 10.74 and 7.23, respectively. The BAI scores of the patients in the mTBI group significantly improved at 6 weeks post-injury. However, the mean BAI scores for the mTBI group for both the baseline and 6 week assessments were significantly different from those of the control groupat the baseline assessment. The mean BDI scores of the mTBI group were 9.8 and 7.99 at the baseline and 6-week assessments, respectively. The mean BDI score for mTBI group significantly decreased to the value of 1.81 at 6 weeks post-injury. The mean BDI score of the control group was 5.72. The mean BDI scores of the mTBI group were significantly different from those of the control group.

No significant difference was observed between the baseline and 6-week ESS scores for the mTBI group. The mean daytime sleepiness score for the control group was 6.62, which was not significantly different from that of the mTBI group. The mean baseline PSQI score for the mTBI group was greater than 9, which was higher than the clinical cut-off point of 5. In addition, the mean PSQI score of mTBI at baseline assessment was higher than the mean score of 5.7 for the control group. The mean 6-week PSQI score for the mTBI group improved significantly to 6.4. The sleep quality of the mTBI group at 6 weeks post-injury was not significantly different from that of the control group. Because of the significant difference in mean age between the mTBI and control groups and the predominance of women in both groups, we performed generalized linear regression analysis of the outcome measures with adjusting for age and sex (Table 4). The differences in depression, anxiety, and sleep quality between the mTBI and control patients kept significance after adjusting for age or sex. However, sex was found to be a significant predictor of sleep quality, anxiety, and depression in the baseline and 6-week assessments. After adjusting for age and sex, the ESS score was significantly different between the control and mTBI groups at the baseline and 6-week assessments, and age was determined to be a significant predictor of daytime sleepiness. In addition, the scores for all 4 outcome measures were higher among women than among men.

DISCUSSION

Previous studies have shown that 85% of mTBI patients demonstrate improvement in psychiatric-related symptoms, whereas the remainder develop chronic psychosocial problems [14-16]. Often presenting with anxiety, depression, or sleep disturbances, TBI patients are at an increased risk of developing a psychiatric disorder within 3 months to 1 year post-injury [4]. It is unclear whether post-mTBI sleep disturbances are related to depression or anxiety. Thus, sleep disturbance may be a risk factor of subsequent depression. A meta-analysis of 21 studies demonstrated that insomnia patients have a 2-fold risk of developing depression [17]. The detailed course of post-mTBI depression, anxiety, and diminished sleep quality, especially during the early stages of recovery, have not been well characterized.

We examined the early stages of recovery from mTBI by using self-reported measures of depression, anxiety, sleep quality, and daytime sleepiness. Most of them injured by transportation accident and falls. Other mechanism of injury included hit by something, and sport injury. There was no participant who injured by an industrial accident. We determined that daytime sleepiness is not significantly affected by mTBI. Both the anxiety and depression symptoms in the mTBI group improved by the sixth week of recovery, but remained more severe than those of the control participants. However, sleep quality significantly improved within 6 weeks of experiencing mTBI, returning to a level that did not differ significantly from that of the control group. These results indicate that recovery from diminished sleep quality occurred more rapidly than did recovery from depression and anxiety.

Our prospective cohorts contained more women than men, and the mean ages of the mTBI and control groups differed significantly. Thus, we adjusted our analysis for effects of age and sex. The BAI, BDI, PSQI, and ESS scores were influenced by sex. However, our results demonstrated that the BAI, BDI, and PSQI scores were significantly affected by mTBI, whereas the ESS scores were not. We found the women in the mTBI group reported more severe symptoms for depression, anxiety, and diminished sleep quality at baseline. After 6 weeks of recovery, although the depression- and anxiety-related symptoms of both male and female mTBI patients improved, those of the female mTBI patients remained more severe than those of the male mTBI patients. Female mTBI patients also reported more severe symptoms related to diminished sleep quality and daytime sleepiness than did male mTBI patients.

Previous reports of the incidence of insomnia among post-acute TBI patients have ranged from 2% to 56% [18, 19]. Bryan found that sleep disturbance increases in patients who suffer repetitive TBI [20]. In our study, 90% of the mTBI patients and 44% of the control participants reported sleep disturbances. The average score of PSQI in the control group (5.7) is higher than previously published values (2.7) [10], but it is close to the result of

another study in Taiwan also by use of the Chinese PSQI study in healthy group (5.7) [13]. It may result from the different versions of questionnaire (English and Chinese) or other uncertain reasons. Our data showed that recovery from sleep disturbance occurred more rapidly among the mTBI patients than did recovery from post-injury depression and anxiety. There are 2 possible reasons for this finding. Sleep disturbance may be an independent symptom of mTBI that alters the circadian rhythm through injury-related changes in gene expression [21]. Alternatively, sleep disturbance may simply be a symptom of depression or anxiety that improves early during recovery [22].

Previous studies have demonstrated significant changes in anxiety- and depression-related symptoms between 1 week and 3 months following mTBI [23]. We observed improvement in the depression and anxiety assessment scores in our mTBI cohort at 6 weeks post-injury. Nonetheless, the BDI and the BAI scores differed significantly between the mTBI and control groups at the 6-week post-injury assessment.

Depression and PTSD have been shown to be critical mediators of the recovery of physical health following mTBI [24]. Multiple studies have investigated the incidence of PTSD following TBI [25]. Psychiatric comorbidities have been associated with PTSD following TBI, and depression was shown to be a predictor of the post-TBI chronicity of PTSD [26, 27]. We did not explore the role of PTSD in recovery from depression, anxiety, and diminished sleep quality, but we speculate that PTSD is associated with all of these mental disorders in mTBI patients.

Certain limitations to our findings should be considered. First, some of our mTBI patients may have used medications before or after suffering mTBI that may have influenced their assessment scores. Second, it is possible that some of our mTBI patients may have had unrelated diseases or pre-injury conditions that were not identified before or during their participation in our study. Third, we investigated only the subacute stages of depression, anxiety, and diminished sleep quality, rather than the chronic stages of these diseases. In addition, REM sleep plays an important role in mood disorders. The changes of REM sleep after mTBI are still controversial[28, 29]. This is certainly a major issue for study. However, sleep architecture was not measured in our study. Although long-term observational studies are required to confirm our findings, our results provide valuable information for understanding the development and recovery of mental disorders following mTBI.

Table 1. The demographic and clinical data of all mTBI patients initially enrolled in our study

	Lost to follow up	Completed 6-wk follow up	*P* value
Age (y)	38.88	39.53	NS
Male / Female (n)	56/94	35/65	NS
Education (y)	15.04	15.46	NS
Smoker (N/Y)	113 / 37	82 / 18	NS
Drink alcohol (N/Y)	94/56	58/ 42	NS
Headache (N/Y)	50/100	25/75	.02
Depression (N/Y)	91 / 59	51 / 49	NS
GCS	14.80	14.98	NS
Mechanism of Injury			
Transportation accident	77	39	NS
Falls	40	34	
Other	33	27	
BAI	7.85	10.74	.03
BDI	8.19	9.80	NS
ESS	6.89	7.95	NS
PSQI	6.27	9.51	<.01

mTBI: mild traumatic brain injury; NS: $P > .05$; GCS: Glasgow Coma Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

Table 2. The demographic and clinical data of the mTBI patients and the control participants who completed the 6-week follow up

	mTBI	Control	*P* value
Sample size (n)	100	137	
Age (y)	39.53	29.86	<.001
Male / Female (n)	35/65	47/90	NS
Education (y)	15.46	14.91	.045
Smoker (N/Y)	82/18	115/22	NS
Drink (N/Y)	58/42	51/82	<.01
Headache (N/Y)	25/75	98/39	<.01
Depression (N/Y)	51 / 49	103/ 34	<.01
GCS	14.98	-	-
Questionnaires			
BAI >7 (N/Y)	57 / 43	125 / 12	<.01
BDI >9 (N/Y)	53 / 47	111 / 26	<.01
ESS >9 (N/Y)	66 / 34	108 / 29	<.01
PSQI >5 (N/Y)	10 / 90	77 / 60	<.01
Mechanisms of Injury			
Transportation accident	39	-	-
Falls	34	-	-
Other	27	-	-

mTBI: mild traumatic brain injury; NS: *P* >.05; GCS: Glasgow Coma Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

Table 3. Differences between control participants and mTBI patients at baseline and 6 weeks post-injury

	BAI	BDI	ESS	PSQI
mTBI Baseline vs Control	8.02*	4.08*	1.33	3.81*
mTBI 6 wk vs Control	4.51*	2.27*	0.87	0.7
mTBI Baseline vs mTBI 6 wk[+]	3.51*	1.81*	0.46	3.11*

mTBI: mild traumatic brain injury; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

*$P < .05$

[+]paired *t* test

Table 4. Coefficients of generalized linear model between control participants and mTBI patients at baseline and 6 weeks post-injury

	Control vs mTBI (baseline)				Control vs mTBI (6-week)			
	BAI	BDI	ESS	PSQI	BAI	BDI	ESS	PSQI
mTBI	1.4*	0.567*	0.245*	0.487*	1.026*	2.632*	1.309*	0.557
Age	0.0007	-0.003	-0.007*	0.003	-0.001	-0.035	-0.045*	0.016
Women	0.437*	0.056*	0.137*	0.137*	0.562*	2.945*	1.263*	1.170*

mTBI: mild traumatic brain injury; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

*$P < .05$

Conflict of interest

None declared.

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Data sharing

There is no additional data available.

Contributorship statement

The six authors are justifiably credited with authorship, according to the authorship criteria. In detail: Hon-Ping Ma – conception, design and interpretation of data, drafting of the manuscript, final approval given; Ju-Chi Ou–analysis and interpretation of data, drafting of the manuscript, final approval given; Chun-Ting Yeh – acquisition of data, final approval given; Dean Wu – final approval given; Shin-Han Tsai – final approval given; Wen-Ta Chiu – Conception, design, final approval given; Chaur-Jong Hu – Conception, design, analysis and interpretation of data, drafting of the manuscript, final approval given.

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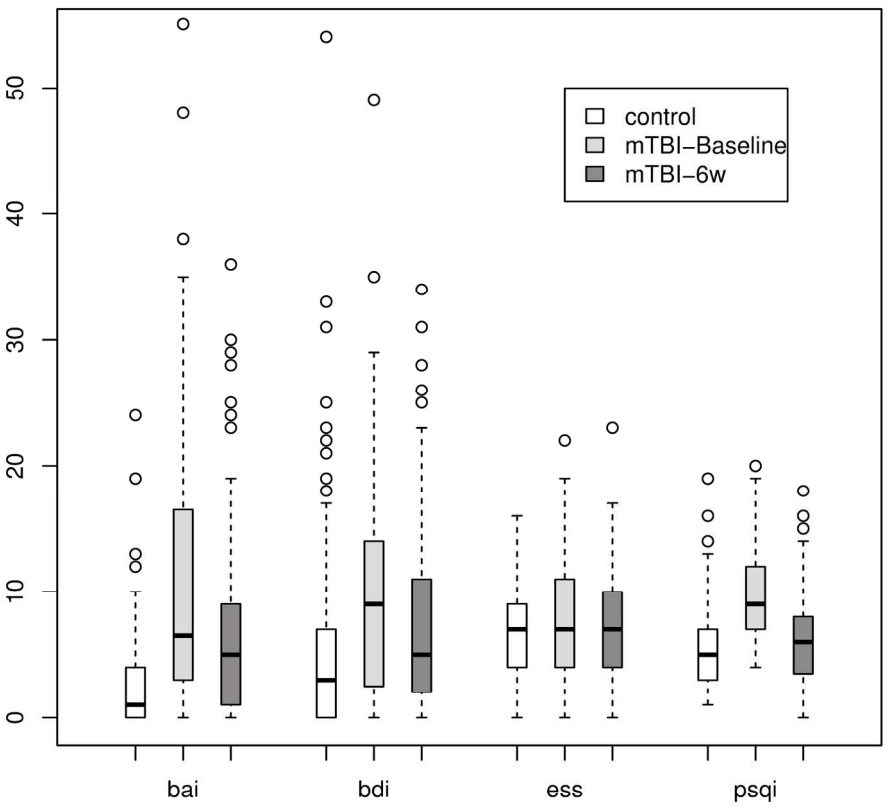

Figure 1. Box plot of the baseline and 6-wk post-injury assessments of the clinical outcomes. White bars represent the data for the control group. Light gray and dark gray bars represent the mild traumatic brain injury (mTBI) patients at baseline and 6 weeks post-injury, respectively. From left to right, the data for the Beck Anxiety Inventory (BAI), the Beck Depression Inventory-II (BDI), the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI) scores are represented.
177x177mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		Page 2 – observational study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
		Page 2 – results and conclusions
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
		Page 3
Objectives	3	State specific objectives, including any prespecified hypotheses
		Page 3
Methods		
Study design	4	Present key elements of study design early in the paper
		Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
		Page 3
Participants	6	(*a*) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		Page 3
		(*b*) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
		Not matched study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
		Page 3 & 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
		Page 4
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
		Page 4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		Page 4
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		Not applicable
		(*e*) Describe any sensitivity analyses
		Not applicable
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		Page 4
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		Page 4 & 5, table2
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
		Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Page 4 & 5
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		Page 5
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
		Not applicable
Discussion		
Key results	18	Summarise key results with reference to study objectives
		Page 6

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
		Page 6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
		Page 6 & 7
Generalisability	21	Discuss the generalisability (external validity) of the study results
		Page 6 & 7
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
		Page 11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Recovery from Sleep Disturbance Precedes that of Depression and Anxiety Following Mild Traumatic Brain Injury: A Six-Week Follow-up Study

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Recovery from Sleep Disturbance Precedes that of Depression and Anxiety Following Mild Traumatic Brain Injury: A Six-Week Follow-up Study

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Number of reference: 29

ABSTRACT

Introduction: Previous studies of recovery after mild traumatic brain injury (mTBI) have focused on chronic mental disorders. The detailed course of these disorders at the acute and subacute stages, especially with regard to recovery from sleep disturbances, has not been well characterized. The aim of our study was to determine the course of mental disorders, including depression, anxiety, and sleep disturbance, following mTBI.

Methods: We recruited 250 mTBI patients and 100 healthy participants (control group) for our observational study between January 2011 to July 2012. The mTBI and control participants were assessed at baseline and 6 weeks after mTBI using the Beck Anxiety Inventory (BAI), the Beck Depression Inventory II (BDI), the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI).

Results: The ESS scores were not significantly different between the 2 groups at baseline or at 6 weeks after mTBI. Although the BAI, BDI, and PSQI scores of the mTBI group were significantly different than those of the control group at baseline, all had improved significantly 6 weeks later. However, only the PSQI score improved to a level that was not significantly different from that of the control group.

Conclusions: Daytime sleepiness is not affected by mTBI. However, mTBI causes depression and anxiety and diminished sleep quality. Although all these conditions improve significantly within 6 weeks post-mTBI, only sleep quality improves to a pre-mTBI level. Thus, recovery from mTBI-induced sleep disturbance occurs more rapidly than that of mTBI-induced depression and anxiety.

Article summary

- 100 mTBI patients and the 137 control participants who completed the questionnaires.
- The number of women is more than the number of men that jointed our study
- Sleep disturbance, depression, anxiety improved after 6 weeks post-injury.
- Recovery from sleep disturbance occurred more rapidly

Strengths and limitations of this study

Previous reports of the incidence of insomnia among post-acute TBI patients have ranged from 2% to 56%. In our study, 90% of the mTBI patients and 44% of the control participants reported sleep disturbances. Our data showed that recovery from sleep disturbance occurred more rapidly among the mTBI patients than did recovery from post-injury depression and anxiety. Previous studies have demonstrated significant changes in anxiety- and depression-related symptoms between 1 week and 3 months following mTBI. We observed improvement in the depression and anxiety assessment scores in our mTBI cohort at 6 weeks post-injury. Nonetheless, the BDI and the BAI scores differed significantly between the mTBI and control groups at the 6-week post-injury assessment.

Some of our mTBI patients may have used medications before or after suffering mTBI that may have influenced their assessment scores. It is also possible that some of our mTBI patients may have had unrelated diseases or pre-injury conditions that were not identified before or during their participation in our study. In addition, we investigated only the subacute stages of depression, anxiety, and diminished sleep quality, rather than the chronic stages of these diseases.

INTRODUCTION

Traumatic brain injury (TMI) and mild traumatic brain injury (mTBI) are major public health problems. Studies in Australia have estimated lifetime costs of over $2.5 million per TMI survivor [1]. Headache, blurred vision, fatigue, and sleep disturbance are the most common physical symptoms following brain injury [2]. Previous studies have reported that the symptom scores following mTBI were equal to that of control patients within 7 days post-injury [3].

However, increasing evidence suggests that the risk of developing a psychiatric disorder increases following mTBI [4]. Although multiple studies have investigated post-traumatic stress disorder (PTSD), the risk of other disorders, such as depression, have also been found to increase following mTBI [5]. The most common psychiatric disorders during the first 12 months following injury are depression, anxiety disorder, and agoraphobia [4].

Diminished sleep quality is one of the most commonly reported symptoms following mTBI [6], and depression and anxiety are also prevalent. However, these conditions are often under-reported, and may become chronic in the absence of treatment. The objectives of our study were to characterize the course of post-mTBI depression, anxiety, and diminished sleep quality during a 6-week follow up, and to compare the baseline and 6-week clinical assessments of mTBI patients with those of healthy participants.

METHODS

Participants and Study Design

Our prospective study was approved by the Joint Institutional Review Board of Taipei Medical University. Eligible patients aged ≥20 years who were treated in an emergency room within 24 hours after closed head trauma were recruited from 3 hospitals in Taiwan between January 2011 and July 2012. The definition of mTBI was based on the diagnostic criteria established by the American Congress of Rehabilitation Medicine, which consist of a Glasgow Coma Scale (GCS) score of 13 to 15 at presentation and loss of consciousness for < 30 min. Patients with a history of cerebrovascular disease, mental retardation, previous TBI, epilepsy, or severe systemic medical illness were excluded from our study. The inclusion of the healthy control participants were no brain injury history and older than 20 years old.

Patients were initially contacted by phone. A total of 607 mTBI patients were recruited for our study, among whom 250 (41.19%) provided informed consent, and completed a baseline assessment during an initial evaluation within 1 month after experiencing an mTBI. Six weeks after completing the baseline assessment, 100 (40%) of the mTBI patients completed the final assessment. The baseline and 6-week assessments consisted of 4 investigator-administered questionnaires, namely, the Beck Anxiety Inventory (BAI) [7], the Beck Depression Inventory-II (BDI) [8], the Epworth Sleepiness Scale (ESS) [9], and the Pittsburgh Sleep Quality Index (PSQI) [10].

Outcome Measures

The patients' demographic information, injury-related data, and smoking and drinking history were recorded at the baseline evaluation. Chinese versions of the BDI, the BAI, the ESS, and the PSQI were used in our study [11-13]. Depression was assessed using the BDI, which scored the patient's selection of 1 of 4 possible responses to 21 multiple-choice items on a scale of 0 to 3 based on their response. The severity of anxiety symptoms was assessed using the BAI, which also scored the patient's selection of 1 of 4 possible responses to 21 multiple-choice items on a scale of 0 to 3 based on their response. A high score on the BAI indicates a high level of anxiety. Daytime sleepiness was subjectively assessed using the ESS, which asked the patient to rate their risk of falling asleep on a 4-point Likert scale (0-3) in 8 different situations. Overall sleep quality was assessed using the PSQI, which evaluated 7 aspects of sleep quality. A high overall score on the PSQI indicates poor sleep quality.

Statistical methods

Associations between the categorical variables were evaluated using a chi-squared analysis, and the Fisher exact test was used when at least one of the values was <5. Associations between the normally distributed continuous variables were evaluated using *t* tests, and the Mann-Whitney U test was used to evaluate the continuous variables with an asymmetrical distribution. Paired *t* tests and a paired Mann-Whitney U test were used to evaluate the intragroup differences between the baseline and 6-week assessments for normally and asymmetrically distributed data, respectively. In this study, all outcome were abnormally distributed thus the non-parametric method was used. In addition, Generalized linear regression analyses were conducted for outcomes with or without adjustment for age and sex. All the statistical analyses were performed using the R statistical software, version 3.0.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria). The level of statistical significance was set at $P < .05$.

RESULTS

The demographic information and clinical data of all the mTBI and control participates who were initially enrolled in the study are shown in Table 1. Six weeks following their baseline assessment, 150 patients could not be contacted, or declined to participant further in our study. The age; sex; education level; smoking status; alcohol use; proportion reporting depression; mechanism of injury; and GCS, BDI, ESS scores of patients who completed the study did not differ significantly from those of patients who did not complete the study. The patients who did not complete the study had lower mean scores for the BAI and the PSQI than the patients who completed the study.

The demographic information and clinical data of the 100 mTBI patients and the 137 control

participants who completed the study are shown in Table 2. The mean age of the mTBI group was significantly higher than the mean age of the control group. The proportions reporting alcohol use, headache, and depression were significantly different between the mTBI and control groups. The percentages of mTBI patients who reported headache or depression were higher than those of the control group. Transportation accidents and falls caused 39% and 34% of the mTBI cases, respectively. Considering the clinical cut-off for each questionnaire, most control patients did not have depression, anxiety, daytime sleepiness, or diminished sleep quality, whereas most of mTBI patients had high PSQI scores.

The mean scores of the 4 outcome measures are shown in Figure 1. The average scores for the mTBI patients at baseline were the highest. After 6 weeks, the average scores for the mTBI patients decreased. The differences between the outcomes of the mTBI and control groups are shown in Table 3. The average baseline and 6-week BAI scores for mTBI group were 10.74 and 7.23, respectively. The BAI scores of the patients in the mTBI group significantly improved at 6 weeks post-injury. However, the mean BAI scores for the mTBI group for both the baseline and 6 week assessments were significantly different from those of the control groupat the baseline assessment. The mean BDI scores of the mTBI group were 9.8 and 7.99 at the baseline and 6-week assessments, respectively. The mean BDI score for mTBI group significantly decreased to the value of 1.81 at 6 weeks post-injury. The mean BDI score of the control group was 5.72. The mean BDI scores of the mTBI group were significantly different from those of the control group.

No significant difference was observed between the baseline and 6-week ESS scores for the mTBI group. The mean daytime sleepiness score for the control group was 6.62, which was not significantly different from that of the mTBI group. The mean baseline PSQI score for the mTBI group was greater than 9, which was higher than the clinical cut-off point of 5. In addition, the mean PSQI score of mTBI at baseline assessment was higher than the mean score of 5.7 for the control group. The mean 6-week PSQI score for the mTBI group improved significantly to 6.4. The sleep quality of the mTBI group at 6 weeks post-injury was not significantly different from that of the control group. Because of the significant difference in mean age between the mTBI and control groups and the predominance of women in both groups, we performed generalized linear regression analysis of the outcome measures with adjusting for age and sex (Table 4). The differences in depression, anxiety, and sleep quality between the mTBI and control patients kept significance after adjusting for age or sex. However, sex was found to be a significant predictor of sleep quality, anxiety, and depression in the baseline and 6-week assessments. After adjusting for age and sex, the ESS score was significantly different between the control and mTBI groups at the baseline and 6-week assessments, and age was determined to be a significant predictor of daytime sleepiness. In addition, the scores for all 4 outcome measures were higher among women than among men.

DISCUSSION

Previous studies have shown that 85% of mTBI patients demonstrate improvement in psychiatric-related symptoms, whereas the remainder develop chronic psychosocial problems [14-16]. Often presenting with anxiety, depression, or sleep disturbances, TBI patients are at an increased risk of developing a psychiatric disorder within 3 months to 1 year post-injury [4]. It is unclear whether post-mTBI sleep disturbances are related to depression or anxiety. Thus, sleep disturbance may be a risk factor of subsequent depression. A meta-analysis of 21 studies demonstrated that insomnia patients have a 2-fold risk of developing depression [17]. The detailed course of post-mTBI depression, anxiety, and diminished sleep quality, especially during the early stages of recovery, have not been well characterized.

We examined the early stages of recovery from mTBI by using self-reported measures of depression, anxiety, sleep quality, and daytime sleepiness. Most of them injured by transportation accident and falls. Other mechanism of injury included hit by something, and sport injury. There was no participant who injured by an industrial accident. We determined that daytime sleepiness is not significantly affected by mTBI. Both the anxiety and depression symptoms in the mTBI group improved by the sixth week of recovery, but remained more severe than those of the control participants. However, sleep quality significantly improved within 6 weeks of experiencing mTBI, returning to a level that did not differ significantly from that of the control group. These results indicate that recovery from diminished sleep quality occurred more rapidly than did recovery from depression and anxiety.

Our prospective cohorts contained more women than men, and the mean ages of the mTBI and control groups differed significantly. Thus, we adjusted our analysis for effects of age and sex. The BAI, BDI, PSQI, and ESS scores were influenced by sex. However, our results demonstrated that the BAI, BDI, and PSQI scores were significantly affected by mTBI, whereas the ESS scores were not. We found the women in the mTBI group reported more severe symptoms for depression, anxiety, and diminished sleep quality at baseline. After 6 weeks of recovery, although the depression- and anxiety-related symptoms of both male and female mTBI patients improved, those of the female mTBI patients remained more severe than those of the male mTBI patients. Female mTBI patients also reported more severe symptoms related to diminished sleep quality and daytime sleepiness than did male mTBI patients.

Previous reports of the incidence of insomnia among post-acute TBI patients have ranged from 2% to 56% [18, 19]. Bryan found that sleep disturbance increases in patients who suffer repetitive TBI [20]. In our study, 90% of the mTBI patients and 44% of the control participants reported sleep disturbances. The average score of PSQI in the control group (5.7) is higher than previously published values (2.7) [10], but it is close to the result of

another study in Taiwan also by use of the Chinese PSQI study in healthy group (5.7) [13]. It may result from the different versions of questionnaire (English and Chinese) or other uncertain reasons. Our data showed that recovery from sleep disturbance occurred more rapidly among the mTBI patients than did recovery from post-injury depression and anxiety. There are 2 possible reasons for this finding. Sleep disturbance may be an independent symptom of mTBI that alters the circadian rhythm through injury-related changes in gene expression [21]. Alternatively, sleep disturbance may simply be a symptom of depression or anxiety that improves early during recovery [22].

Previous studies have demonstrated significant changes in anxiety- and depression-related symptoms between 1 week and 3 months following mTBI [23]. We observed improvement in the depression and anxiety assessment scores in our mTBI cohort at 6 weeks post-injury. Nonetheless, the BDI and the BAI scores differed significantly between the mTBI and control groups at the 6-week post-injury assessment.

Depression and PTSD have been shown to be critical mediators of the recovery of physical health following mTBI [24]. Multiple studies have investigated the incidence of PTSD following TBI [25]. Psychiatric comorbidities have been associated with PTSD following TBI, and depression was shown to be a predictor of the post-TBI chronicity of PTSD [26, 27]. We did not explore the role of PTSD in recovery from depression, anxiety, and diminished sleep quality, but we speculate that PTSD is associated with all of these mental disorders in mTBI patients.

Certain limitations to our findings should be considered. First, some of our mTBI patients may have used medications before or after suffering mTBI that may have influenced their assessment scores. Second, it is possible that some of our mTBI patients may have had unrelated diseases or pre-injury conditions that were not identified before or during their participation in our study. Third, we investigated only the subacute stages of depression, anxiety, and diminished sleep quality, rather than the chronic stages of these diseases. In addition, REM sleep plays an important role in mood disorders. The changes of REM sleep after mTBI are still controversial[28, 29]. This is certainly a major issue for study. However, sleep architecture was not measured in our study. Although long-term observational studies are required to confirm our findings, our results provide valuable information for understanding the development and recovery of mental disorders following mTBI.

Table 1. The demographic and clinical data of all mTBI patients initially enrolled in our study

	Lost to follow up	Completed 6-wk follow up	*P* value
Age (y)	38.88	39.53	NS
Male / Female (n)	56/94	35/65	NS
Education (y)	15.04	15.46	NS
Smoker (N/Y)	113 / 37	82 / 18	NS
Drink alcohol (N/Y)	94/56	58/ 42	NS
Headache (N/Y)	50/100	25/75	.02
Depression (N/Y)	91 / 59	51 / 49	NS
GCS	14.80	14.98	NS
Mechanism of Injury			
Transportation accident	77	39	NS
Falls	40	34	
Other	33	27	
BAI	7.85	10.74	.03
BDI	8.19	9.80	NS
ESS	6.89	7.95	NS
PSQI	6.27	9.51	<.01

mTBI: mild traumatic brain injury; NS: $P > .05$; GCS: Glasgow Coma Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

Table 2. The demographic and clinical data of the mTBI patients and the control participants who completed the 6-week follow up

	mTBI	Control	*P* value
Sample size (n)	100	137	
Age (y)	39.53	29.86	<.001
Male / Female (n)	35/65	47/90	NS
Education (y)	15.46	14.91	.045
Smoker (N/Y)	82/18	115/22	NS
Drink (N/Y)	58/42	51/82	<.01
Headache (N/Y)	25/75	98/39	<.01
Depression (N/Y)	51 / 49	103/ 34	<.01
GCS	14.98	-	-
Questionnaires			
BAI >7 (N/Y)	57 / 43	125 / 12	<.01
BDI >9 (N/Y)	53 / 47	111 / 26	<.01
ESS >9 (N/Y)	66 / 34	108 / 29	<.01
PSQI >5 (N/Y)	10 / 90	77 / 60	<.01
Mechanisms of Injury			
Transportation accident	39	-	-
Falls	34	-	-
Other	27	-	-

mTBI: mild traumatic brain injury; NS: *P* >.05; GCS: Glasgow Coma Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

Table 3. Differences between control participants and mTBI patients at baseline and 6 weeks post-injury

	BAI	BDI	ESS	PSQI
mTBI Baseline vs Control	8.02*	4.08*	1.33	3.81*
mTBI 6 wk vs Control	4.51*	2.27*	0.87	0.7
mTBI Baseline vs mTBI 6 wk[+]	3.51*	1.81*	0.46	3.11*

mTBI: mild traumatic brain injury; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

*$P < .05$

[+]paired *t* test

Table 4. Generalized linear regression coefficient estimates of four measurements in controls and mTBI patients at baseline and 6 weeks post-injury

	Control vs mTBI (baseline)				Control vs mTBI (6-week)			
	BAI	BDI	ESS	PSQI	BAI	BDI	ESS	PSQI
mTBI	1.4*	0.567*	0.245*	0.487*	1.026*	2.632*	1.309*	0.557
Age	0.0007	-0.003	-0.007*	0.003	-0.001	-0.035	-0.045*	0.016
Women	0.437*	0.056*	0.137*	0.137*	0.562*	2.945*	1.263*	1.170*

mTBI: mild traumatic brain injury; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

*$P < .05$

Figure legend

Figure 1. Box plot of the baseline and 6-wk post-injury assessments of the clinical outcomes. White bars represent the data for the control group. Light gray and dark gray bars represent the mild traumatic brain injury (mTBI) patients at baseline and 6 weeks post-injury, respectively. From left to right, the data for the Beck Anxiety Inventory (BAI), the Beck Depression Inventory-II (BDI), the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI) scores are represented.

Contributorship statement

The six authors are justifiably credited with authorship, according to the authorship criteria. In detail: Hon-Ping Ma – conception, design and interpretation of data, drafting of the manuscript, final approval given; Ju-Chi Ou–analysis and interpretation of data, drafting of the manuscript, final approval given; Chun-Ting Yeh– acquisition of data, final approval given; Dean Wu – final approval given; Shin-Han Tsai – final approval given; Wen-Ta Chiu – Conception, design, final approval given; Chaur-Jong Hu – Conception, design, analysis and interpretation of data, drafting of the manuscript, final approval given.

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Data sharing

No additional data available.

Conflict of interest

None declared.

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Recovery from Sleep Disturbance Precedes that of Depression and Anxiety Following Mild Traumatic Brain Injury: A Six-Week Follow-up Study

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ABSTRACT

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Methods: We recruited 250 mTBI patients and 100 healthy participants (control group) for our observational study between January 2011 to July 2012. The mTBI and control participants were assessed at baseline and 6 weeks after mTBI using the Beck Anxiety Inventory (BAI), the Beck Depression Inventory II (BDI), the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI).

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Article summary

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- Recovery from sleep disturbance occurred more rapidly

Strengths and limitations of this study

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Some of our mTBI patients may have used medications before or after suffering mTBI that may have influenced their assessment scores. It is also possible that some of our mTBI patients may have had unrelated diseases or pre-injury conditions that were not identified before or during their participation in our study. In addition, we investigated only the subacute stages of depression, anxiety, and diminished sleep quality, rather than the chronic stages of these diseases.

INTRODUCTION

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However, increasing evidence suggests that the risk of developing a psychiatric disorder increases following mTBI [4]. Although multiple studies have investigated post-traumatic stress disorder (PTSD), the risk of other disorders, such as depression, have also been found to increase following mTBI [5]. The most common psychiatric disorders during the first 12 months following injury are depression, anxiety disorder, and agoraphobia [4].

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METHODS

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Patients were initially contacted by phone. A total of 607 mTBI patients were recruited for our study, among whom 250 (41.19%) provided informed consent, and completed a baseline assessment during an initial evaluation within 1 month after experiencing an mTBI. Six weeks after completing the baseline assessment, 100 (40%) of the mTBI patients completed the final assessment. The baseline and 6-week assessments consisted of 4 investigator-administered questionnaires, namely, the Beck Anxiety Inventory (BAI) [7], the Beck Depression Inventory-II (BDI) [8], the Epworth Sleepiness Scale (ESS) [9], and the Pittsburgh Sleep Quality Index (PSQI) [10].

Outcome Measures

The patients' demographic information, injury-related data, and smoking and drinking history were recorded at the baseline evaluation. Chinese versions of the BDI, the BAI, the ESS, and the PSQI were used in our study [11-13]. Depression was assessed using the BDI, which scored the patient's selection of 1 of 4 possible responses to 21 multiple-choice items on a scale of 0 to 3 based on their response. The severity of anxiety symptoms was assessed using the BAI, which also scored the patient's selection of 1 of 4 possible responses to 21 multiple-choice items on a scale of 0 to 3 based on their response. A high score on the BAI indicates a high level of anxiety. Daytime sleepiness was subjectively assessed using the ESS, which asked the patient to rate their risk of falling asleep on a 4-point Likert scale (0-3) in 8 different situations. Overall sleep quality was assessed using the PSQI, which evaluated 7 aspects of sleep quality. A high overall score on the PSQI indicates poor sleep quality.

Statistical methods

Associations between the categorical variables were evaluated using a chi-squared analysis, and the Fisher exact test was used when at least one of the values was <5. Associations between the normally distributed continuous variables were evaluated using *t* tests, and the Mann-Whitney U test was used to evaluate the continuous variables with an asymmetrical distribution. Paired *t* tests and a paired Mann-Whitney U test were used to evaluate the intragroup differences between the baseline and 6-week assessments for normally and asymmetrically distributed data, respectively. In this study, all outcome were abnormally distributed thus the non-parametric method was used. In addition, Generalized linear regression analyses were conducted for outcomes with or without adjustment for age and sex. All the statistical analyses were performed using the R statistical software, version 3.0.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria). The level of statistical significance was set at $P < .05$.

RESULTS

The demographic information and clinical data of all the mTBI and control participates who were initially enrolled in the study are shown in Table 1. Six weeks following their baseline assessment, 150 patients could not be contacted, or declined to participant further in our study. The age; sex; education level; smoking status; alcohol use; proportion reporting depression; mechanism of injury; and GCS, BDI, ESS scores of patients who completed the study did not differ significantly from those of patients who did not complete the study. The patients who did not complete the study had lower mean scores for the BAI and the PSQI than the patients who completed the study.

The demographic information and clinical data of the 100 mTBI patients and the 137 control

participants who completed the study are shown in Table 2. The mean age of the mTBI group was significantly higher than the mean age of the control group. The proportions reporting alcohol use, headache, and depression were significantly different between the mTBI and control groups. The percentages of mTBI patients who reported headache or depression were higher than those of the control group. Transportation accidents and falls caused 39% and 34% of the mTBI cases, respectively. Considering the clinical cut-off for each questionnaire, most control patients did not have depression, anxiety, daytime sleepiness, or diminished sleep quality, whereas most of mTBI patients had high PSQI scores.

The mean scores of the 4 outcome measures are shown in Figure 1. The average scores for the mTBI patients at baseline were the highest. After 6 weeks, the average scores for the mTBI patients decreased. The differences between the outcomes of the mTBI and control groups are shown in Table 3. The average baseline and 6-week BAI scores for mTBI group were 10.74 and 7.23, respectively. The BAI scores of the patients in the mTBI group significantly improved at 6 weeks post-injury. However, the mean BAI scores for the mTBI group for both the baseline and 6 week assessments were significantly different from those of the control groupat the baseline assessment. The mean BDI scores of the mTBI group were 9.8 and 7.99 at the baseline and 6-week assessments, respectively. The mean BDI score for mTBI group significantly decreased to the value of 1.81 at 6 weeks post-injury. The mean BDI score of the control group was 5.72. The mean BDI scores of the mTBI group were significantly different from those of the control group.

No significant difference was observed between the baseline and 6-week ESS scores for the mTBI group. The mean daytime sleepiness score for the control group was 6.62, which was not significantly different from that of the mTBI group. The mean baseline PSQI score for the mTBI group was greater than 9, which was higher than the clinical cut-off point of 5. In addition, the mean PSQI score of mTBI at baseline assessment was higher than the mean score of 5.7 for the control group. The mean 6-week PSQI score for the mTBI group improved significantly to 6.4. The sleep quality of the mTBI group at 6 weeks post-injury was not significantly different from that of the control group. Because of the significant difference in mean age between the mTBI and control groups and the predominance of women in both groups, we performed generalized linear regression analysis of the outcome measures with adjusting for age and sex (Table 4). The differences in depression, anxiety, and sleep quality between the mTBI and control patients kept significance after adjusting for age or sex. However, sex was found to be a significant predictor of sleep quality, anxiety, and depression in the baseline and 6-week assessments. After adjusting for age and sex, the ESS score was significantly different between the control and mTBI groups at the baseline and 6-week assessments, and age was determined to be a significant predictor of daytime sleepiness. In addition, the scores for all 4 outcome measures were higher among women than among men.

DISCUSSION

Previous studies have shown that 85% of mTBI patients demonstrate improvement in psychiatric-related symptoms, whereas the remainder develop chronic psychosocial problems [14-16]. Often presenting with anxiety, depression, or sleep disturbances, TBI patients are at an increased risk of developing a psychiatric disorder within 3 months to 1 year post-injury [4]. It is unclear whether post-mTBI sleep disturbances are related to depression or anxiety. Thus, sleep disturbance may be a risk factor of subsequent depression. A meta-analysis of 21 studies demonstrated that insomnia patients have a 2-fold risk of developing depression [17]. The detailed course of post-mTBI depression, anxiety, and diminished sleep quality, especially during the early stages of recovery, have not been well characterized.

We examined the early stages of recovery from mTBI by using self-reported measures of depression, anxiety, sleep quality, and daytime sleepiness. Most of them injured by transportation accident and falls. Other mechanism of injury included hit by something, and sport injury. There was no participant who injured by an industrial accident. We determined that daytime sleepiness is not significantly affected by mTBI. Both the anxiety and depression symptoms in the mTBI group improved by the sixth week of recovery, but remained more severe than those of the control participants. However, sleep quality significantly improved within 6 weeks of experiencing mTBI, returning to a level that did not differ significantly from that of the control group. These results indicate that recovery from diminished sleep quality occurred more rapidly than did recovery from depression and anxiety.

Our prospective cohorts contained more women than men, and the mean ages of the mTBI and control groups differed significantly. Thus, we adjusted our analysis for effects of age and sex. The BAI, BDI, PSQI, and ESS scores were influenced by sex. However, our results demonstrated that the BAI, BDI, and PSQI scores were significantly affected by mTBI, whereas the ESS scores were not. We found the women in the mTBI group reported more severe symptoms for depression, anxiety, and diminished sleep quality at baseline. After 6 weeks of recovery, although the depression- and anxiety-related symptoms of both male and female mTBI patients improved, those of the female mTBI patients remained more severe than those of the male mTBI patients. Female mTBI patients also reported more severe symptoms related to diminished sleep quality and daytime sleepiness than did male mTBI patients.

Previous reports of the incidence of insomnia among post-acute TBI patients have ranged from 2% to 56% [18, 19]. Bryan found that sleep disturbance increases in patients who suffer repetitive TBI [20]. In our study, 90% of the mTBI patients and 44% of the control participants reported sleep disturbances. The average score of PSQI in the control group (5.7) is higher than previously published values (2.7) [10], but it is close to the result of

another study in Taiwan also by use of the Chinese PSQI study in healthy group (5.7) [13]. It may result from the different versions of questionnaire (English and Chinese) or other uncertain reasons. Our data showed that recovery from sleep disturbance occurred more rapidly among the mTBI patients than did recovery from post-injury depression and anxiety. There are 2 possible reasons for this finding. Sleep disturbance may be an independent symptom of mTBI that alters the circadian rhythm through injury-related changes in gene expression [21]. Alternatively, sleep disturbance may simply be a symptom of depression or anxiety that improves early during recovery [22].

Previous studies have demonstrated significant changes in anxiety- and depression-related symptoms between 1 week and 3 months following mTBI [23]. We observed improvement in the depression and anxiety assessment scores in our mTBI cohort at 6 weeks post-injury. Nonetheless, the BDI and the BAI scores differed significantly between the mTBI and control groups at the 6-week post-injury assessment.

Depression and PTSD have been shown to be critical mediators of the recovery of physical health following mTBI [24]. Multiple studies have investigated the incidence of PTSD following TBI [25]. Psychiatric comorbidities have been associated with PTSD following TBI, and depression was shown to be a predictor of the post-TBI chronicity of PTSD [26, 27]. We did not explore the role of PTSD in recovery from depression, anxiety, and diminished sleep quality, but we speculate that PTSD is associated with all of these mental disorders in mTBI patients.

Certain limitations to our findings should be considered. First, some of our mTBI patients may have used medications before or after suffering mTBI that may have influenced their assessment scores. Second, it is possible that some of our mTBI patients may have had unrelated diseases or pre-injury conditions that were not identified before or during their participation in our study. Third, we investigated only the subacute stages of depression, anxiety, and diminished sleep quality, rather than the chronic stages of these diseases. In addition, REM sleep plays an important role in mood disorders. The changes of REM sleep after mTBI are still controversial[28, 29]. This is certainly a major issue for study. However, sleep architecture was not measured in our study. Although long-term observational studies are required to confirm our findings, our results provide valuable information for understanding the development and recovery of mental disorders following mTBI.

Table 1. The demographic and clinical data of all mTBI patients initially enrolled in our study

	Lost to follow up	Completed 6-wk follow up	*P* value
Age (y)	38.88	39.53	NS
Male / Female (n)	56/94	35/65	NS
Education (y)	15.04	15.46	NS
Smoker (N/Y)	113 / 37	82 / 18	NS
Drink alcohol (N/Y)	94/56	58/ 42	NS
Headache (N/Y)	50/100	25/75	.02
Depression (N/Y)	91 / 59	51 / 49	NS
GCS	14.80	14.98	NS
Mechanism of Injury			
Transportation accident	77	39	NS
Falls	40	34	
Other	33	27	
BAI	7.85	10.74	.03
BDI	8.19	9.80	NS
ESS	6.89	7.95	NS
PSQI	6.27	9.51	<.01

mTBI: mild traumatic brain injury; NS: $P > .05$; GCS: Glasgow Coma Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

Table 2. The demographic and clinical data of the mTBI patients and the control participants who completed the 6-week follow up

	mTBI	Control	*P* value
Sample size (n)	100	137	
Age (y)	39.53	29.86	<.001
Male / Female (n)	35/65	47/90	NS
Education (y)	15.46	14.91	.045
Smoker (N/Y)	82/18	115/22	NS
Drink (N/Y)	58/42	51/82	<.01
Headache (N/Y)	25/75	98/39	<.01
Depression (N/Y)	51 / 49	103/ 34	<.01
GCS	14.98	-	-
Questionnaires			
BAI >7 (N/Y)	57 / 43	125 / 12	<.01
BDI >9 (N/Y)	53 / 47	111 / 26	<.01
ESS >9 (N/Y)	66 / 34	108 / 29	<.01
PSQI >5 (N/Y)	10 / 90	77 / 60	<.01
Mechanisms of Injury			
Transportation accident	39	-	-
Falls	34	-	-
Other	27	-	-

mTBI: mild traumatic brain injury; NS: *P* >.05; GCS: Glasgow Coma Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

Table 3. Differences between control participants and mTBI patients at baseline and 6 weeks post-injury

	BAI	BDI	ESS	PSQI
mTBI Baseline vs Control	8.02*	4.08*	1.33	3.81*
mTBI 6 wk vs Control	4.51*	2.27*	0.87	0.7
mTBI Baseline vs mTBI 6 wk[+]	3.51*	1.81*	0.46	3.11*

mTBI: mild traumatic brain injury; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

*$P < .05$

[+]paired *t* test

Table 4. Generalized linear regression coefficient estimates of four measurements in controls and mTBI patients at baseline and 6 weeks post-injury

	Control vs mTBI (baseline)				Control vs mTBI (6-week)			
	BAI	BDI	ESS	PSQI	BAI	BDI	ESS	PSQI
mTBI	1.4*	0.567*	0.245*	0.487*	1.026*	2.632*	1.309*	0.557
Age	0.0007	-0.003	-0.007*	0.003	-0.001	-0.035	-0.045*	0.016
Women	0.437*	0.056*	0.137*	0.137*	0.562*	2.945*	1.263*	1.170*

mTBI: mild traumatic brain injury; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory-II; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index

*$P < .05$

Conflict of interest

None declared.

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Data sharing

There is no additional data available.

Contributorship statement

The six authors are justifiably credited with authorship, according to the authorship criteria. In detail: Hon-Ping Ma – conception, design and interpretation of data, drafting of the manuscript, final approval given; Ju-Chi Ou–analysis and interpretation of data, drafting of the manuscript, final approval given; Chun-Ting Yeh– acquisition of data, final approval given; Dean Wu – final approval given; Shin-Han Tsai – final approval given; Wen-Ta Chiu – Conception, design, final approval given; Chaur-Jong Hu – Conception, design, analysis and interpretation of data, drafting of the manuscript, final approval given.

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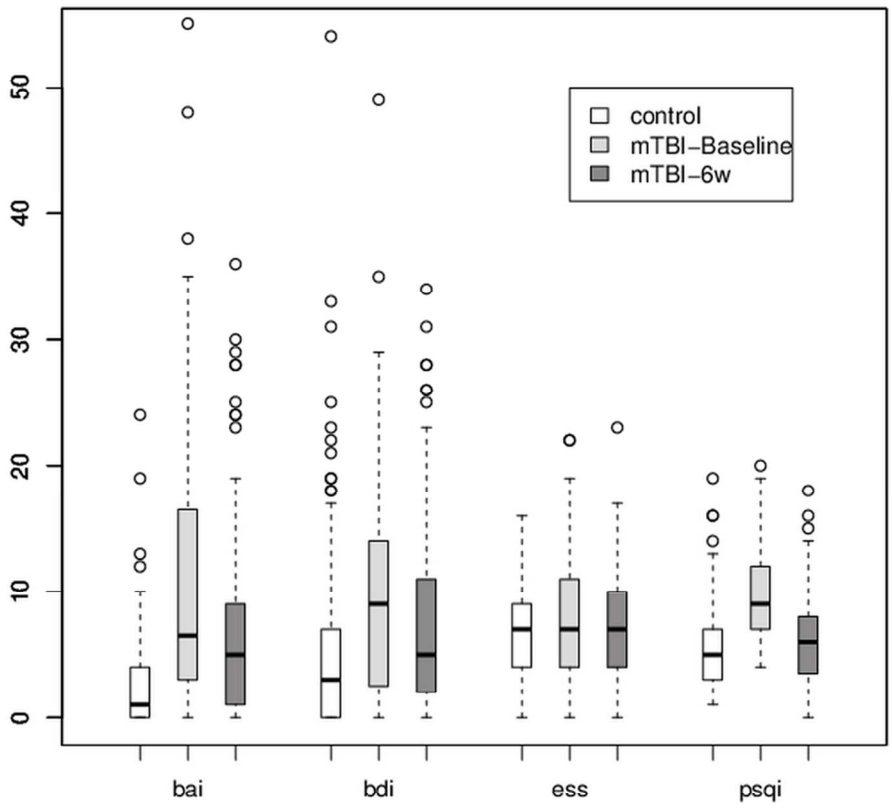

Figure 1. Box plot of the baseline and 6-wk post-injury assessments of the clinical outcomes. White bars represent the data for the control group. Light gray and dark gray bars represent the mild traumatic brain injury (mTBI) patients at baseline and 6 weeks post-injury, respectively. From left to right, the data for the Beck Anxiety Inventory (BAI), the Beck Depression Inventory-II (BDI), the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI) scores are represented.
90x90mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		Page 2 – observational study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
		Page 2 – results and conclusions
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
		Page 3
Objectives	3	State specific objectives, including any prespecified hypotheses
		Page 3
Methods		
Study design	4	Present key elements of study design early in the paper
		Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
		Page 3
Participants	6	(*a*) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		Page 3
		(*b*) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
		Not matched study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
		Page 3 & 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
		Page 4
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
		Page 4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		Page 4
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		Not applicable
		(*e*) Describe any sensitivity analyses
		Not applicable
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		Page 4
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		Page 4 & 5, table2
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
		Not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Page 4 & 5
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		Page 5
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
		Not applicable
Discussion		
Key results	18	Summarise key results with reference to study objectives
		Page 6

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
		Page 6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
		Page 6 & 7
Generalisability	21	Discuss the generalisability (external validity) of the study results
		Page 6 & 7
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
		Page 11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.