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REVIEW ARTICLES

# Sleep Disturbances in Traumatic Brain Injury: A Meta-Analysis

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**Study Objectives:** Sleep disturbances are frequently reported following traumatic brain injury (TBI); however, the exact disturbances remain unclear. This meta-analysis aimed to characterize sleep disturbance in community dwelling patients with TBI as compared to controls.

**Methods:** Two investigators independently conducted a systematic search of multiple electronic databases from inception to May 27, 2015. Studies were selected if they compared sleep in community dwelling individuals with TBI relative to a control population without head injury. Data were pooled in meta-analysis with outcomes expressed as the standard mean difference (SMD) and 95% confidence interval (CI). The primary outcomes were derived from polysomnography and secondary outcomes were derived from subjective sleep measures.

**Results:** Sixteen studies were included, combining 637 TBI patients and 567 controls, all of whom were community dwelling. Pooled polysomnography data revealed that TBI patients had poorer sleep efficiency (SMD = −0.47, CI: −0.89, −0.06), shorter total sleep duration (SMD = −0.37, CI: −0.59, −0.16), and greater wake after sleep onset time (SMD = 0.60, CI: 0.33, 0.87). Although sleep architecture was similar between the groups, a trend suggested that TBI patients may spend less time in REM sleep (SMD = −0.22, CI: −0.45, 0.01). Consistent with polysomnographic derangement, TBI patients reported greater subjective sleepiness and poorer perceived sleep quality.

**Conclusions:** The evidence suggests that TBI is associated with widespread objective and subjective sleep deficits. The present results highlight the need for physicians to monitor and address sleep deficits following TBI.

**Keywords:** traumatic brain injury, TBI, sleep, brain injury, polysomnography

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## INTRODUCTION

Sleep disturbances are frequently reported following traumatic brain injury (TBI), with over 50% of people experiencing some form of sleep disturbance post TBI.[1] Although a large majority of people with TBI generally make a good physical recovery, disrupted sleep can often go untreated, impacting quality of life, impeding rehabilitation and return to pre-injury activities.[2–5] Our recent work showed significant interrelationships between daytime sleepiness, daytime fatigue, cognitive impairment, and mood disturbances in TBI.[6]

While individuals with TBI are known to report sleep problems,[1] the specific changes to sleep remain poorly characterized.[7] Studies have been limited by small sample sizes, with variable and inconsistent findings.[8–12] This makes for a difficult characterization of sleep post TBI. Thus, there is a need to establish the specific aspects of sleep that are most affected post TBI as these have important implications for treatment and rehabilitation. The aim of the current meta-analysis was to characterize both objective sleep disturbances and subjective sleep complaints in individuals with TBI relative to healthy controls. Study outcomes included the comparison of TBI patients to controls across both polysomnography and subjective measures of sleep. It was hypothesized that those with TBI would display widespread objective and subjective sleep deficits as compared to controls without head injury. The present study aimed to summarize current literature, which would identify important avenues for future research.

## METHODS

### Study Design

The search strategy was conducted in accordance with the meta-analysis of observational studies in epidemiology guidelines.[13]

### Article Searching

Ovid Medline, Embase, PsychInfo, Scopus, and the Cochrane Library were systematically searched until May, 27 2015. The search was initially developed by all authors and refined by a librarian at Monash University. The references of recent publications were also hand searched for additional eligible studies. Databases were searched using combinations of the following terms: *TBI* and *sleep*. The complete documentation of the search procedure is outlined in **Table S1** in the supplemental material.

## Inclusion Criteria for Study Selection

Studies were screened on the basis of their title and abstract. If relevance was unclear, two authors (NG and MP) read the article in its entirety and discussed with all authors. Studies were limited to those written in English. To be considered appropriate for inclusion, a study must have compared objective or subjective sleep function in adults with TBI with that of a comparison group. Studies of any design were considered for inclusion provided patients with TBI were compared to a control sample. Conference abstracts, book reviews and letters to the editor were not included in review.

To be eligible for inclusion, studies had to use a sample described as having sustained a TBI or a head injury resulting in a period of loss of consciousness or posttraumatic amnesia. Only studies conducted in men or women aged 16 years or over were included. Those in the TBI sample had to be community dwelling (indicating that they are not in the acute phase of head injury) and not be assessed during posttraumatic amnesia. This was imposed to remove the effect of the hospital environment on sleep. To reduce heterogeneity, studies combining TBI patients with other acquired brain injuries (e.g., stroke) were excluded. Consistent with similar reviews, closed head injuries of all severity were considered appropriate, including concussion, coupe and contrecoup injury, contusions and diffuse axonal injury.[14]

The comparison group was restricted to controls described as being healthy or described as being without a history of TBI, neurological illness or sleep disturbance. Control samples described as being 'healthy' were assumed to have no formally diagnosed sleeping condition or significant neurological illness.

## Primary Outcomes

The primary outcomes were the comparison between TBI individuals and controls on recommended polysomnography measures as outlined by the American Academy of Sleep Medicine (AASM).[15] These included (1) total sleep time (min), (2) sleep latency (lights out to first epoch of any sleep in min), (3) REM sleep latency (sleep onset to first epoch of REM sleep in min), (4) wake after sleep onset (total recording time – sleep latency – total sleep time, in min), (5) sleep efficiency (total sleep time / total recording time × 100) as well the percentage of total sleep time in (6) REM sleep, (7) stage 1 sleep, (8) stage 2 sleep, and (9) slow wave sleep (stage 3 and 4 combined). All included studies used either The AASM Manual for the Scoring of Sleep and Associated Events (2007 or 2012) or Rechtschaffen and Kales as criteria for scoring,[15–17] and scoring was performed or verified by a qualified sleep technologist. Actigraphy and multiple sleep latency data were not included as an outcome in this study given that these measures have been infrequently reported in the TBI literature. Primary outcomes were decided a priori. Based on our previous work[8,11,18] and that of others,[9,19–21] we hypothesized that patients with TBI would show increased wake after sleep onset and longer sleep onset latency, relative to controls.

## Secondary Outcomes

To reduce the risk of type I error, the authors adopted a parsimonious approach, analyzing only secondary outcomes that were reported across the greatest number of studies. Based on their frequency of use, secondary outcomes were limited to the Epworth Sleepiness Scale,[22] as well as domains of the Pittsburgh sleep quality index (PSQI),[23] including the global score, daytime dysfunction, sleep duration, sleep efficiency, sleep latency, sleep medication, sleep disturbance, and sleep quality. The secondary outcomes thus compared TBI patients with controls across subjective measures of sleep. In light of previous findings,[9,11,18,21,24,25] it was hypothesized that when compared to controls, patients with TBI would display increased daytime sleepiness, and score higher across all domains of the PSQI, indicating poorer sleep quality.

## Data Extraction

Article searching, assessment of inclusion criteria, and data extraction were completed independently by two investigators (NG and MP), with results later compared and combined according to consensus. To limit bias, data were only extracted after confirmation that the study satisfied inclusion criteria. Study characteristics, means, standard deviations, and sample sizes were extracted for each study, for the TBI and control samples. Corresponding authors were contacted in cases where data were missing or inappropriately reported. In such cases, the corresponding authors were emailed and asked to provide group means, standard deviations or sample sizes. Of the 15 authors contacted,[9–12,18–21,24–30] 7 replied with the requested objective data,[11,12,19,21,25–27] with 4 supplying subjective data.[9,18,24,29] Two authors were unable to provide data for all measures of interest,[10,20] but these studies were able to be included in some analyses. Two authors were unable to provide objective data and these studies were excluded,[28,30] as the data were inadequately reported. The later study[30] was also excluded as part of a control sample featured in a previous publication already included in the current meta-analysis.[27] The study author did not respond to our email request for data, excluding the overlapping sample. For the one study that reported means and ranges,[27] we calculated the standard deviation (SD) as one-quarter of the range.[31] A further study reported duration of each sleep stage in minutes. In this case we converted the mean and SD to a percentage of total sleep time. One study did not explicitly state that controls were screened to exclude those with a history of TBI, although this was assumed to be the case.[32] As suggested by Cochrane guidelines, the quality of the studies included in review was not quantified.[33]

## Statistical Analysis

### *Effect Size Calculation*

Meta-analysis was conducted using comprehensive meta-analysis (version 2; Biostat Englewood). For each sleep measure, the mean, standard deviation and sample size was entered for both the TBI and control group. This was repeated for each study. Data were then pooled in meta-analysis comparing TBI patients with controls across each primary and secondary outcome. Results were expressed as the standard mean difference (SMD [Cohen's d]) and 95% confidence interval (CI).

### *Heterogeneity Analysis*

For each analysis, heterogeneity between studies was examined using the Cochrane Q statistic and Higgins $I^2$ statistic.[33]

A fixed-effects model is reported in the absence of statistical heterogeneity, and a random-effects model is reported in the presence of statistical heterogeneity (when the Cochrane q statistic $p < 0.10$).[34]

### *Publication Bias*

The presence of bias was investigated using Begg adjusted rank correlations[35] and Egger regression tests.[36] In the absence of publication bias, effect sizes are symmetrically distributed around the pooled mean effect, and the sampling error is considered random. Begg adjusted rank correlation is a technique used for identifying publication bias in meta-analysis. The Egger test evaluated whether the amount of asymmetry was significant.

### *Meta-Regression and Sensitivity Analysis*

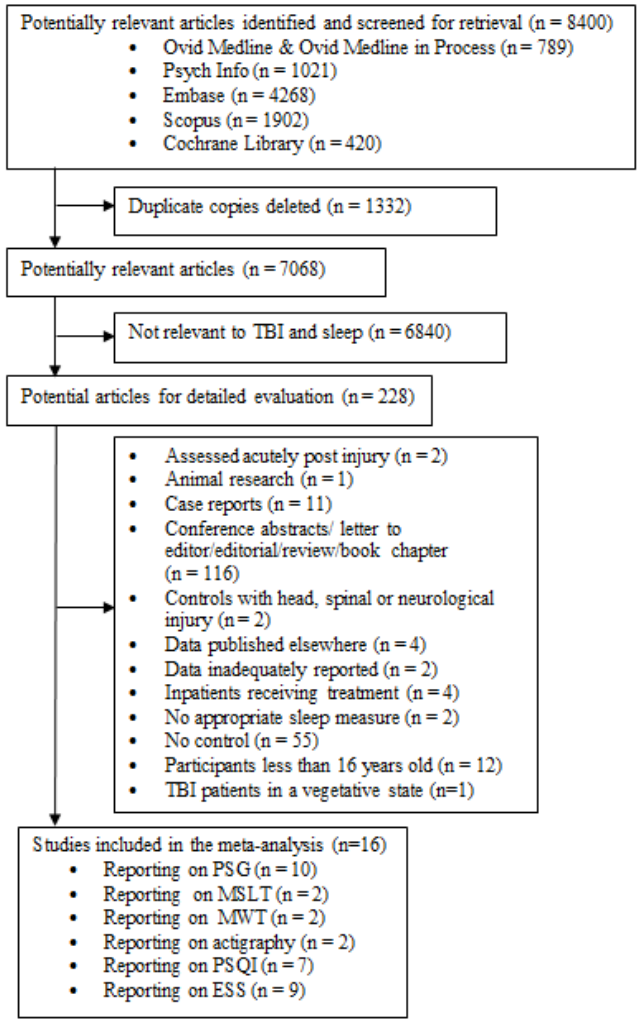
Fixed effects meta-regression was used to investigate whether polysomnography SMD's were associated with predefined covariates, including time since TBI injury, and mean age of the TBI sample. To investigate the role of injury severity and psychoactive drugs on sleep deficits post TBI, we performed a set of sensitivity analyses including only those studies focusing on mild TBI, moderate-to-severe TBI, and TBI patients not receiving psychoactive medications, respectively. Sensitivity analysis was also conducted to compare polysomnography sleep parameters between TBI and controls, excluding those studies that used an epoch duration inconsistent with standard scoring criteria.[15–17] In light of the heterogeneity in the definition of sleep onset between studies, a further analysis was conducted, excluding those studies that calculated sleep onset relative to stage 2 sleep. This later sensitivity analysis was performed for both sleep onset latency and latency to REM sleep, given that latency to REM sleep is calculated relative to sleep onset. Publication bias and meta-regression statistics were only computed for analyses comprising 10 or more studies given that these tests are not recommended when fewer studies are available.[33]

## RESULTS

Of the 7,068 articles that were screened, 228 were identified as potentially relevant (**Figure 1**). Sixteen studies satisfied the inclusion criteria and were included in the review. Of the studies reporting objective sleep measures, 10 reported on polysomnography and 2 reported on the multiple sleep latency test, 2 on the maintenance of wakefulness test, and 2 on actigraphy, respectively. Of those reporting subjective measures, the most widely utilized measures were the Epworth Sleepiness Scale and the PSQI (**Table 1**).

Across the 16 included studies, the total pooled sample included 637 TBI patients and 567 controls. The characteristics of included studies are shown in **Table 1**. A large majority of studies were cross-sectional in nature, with the mean age of the pooled TBI sample 32 years (SD = 7). The majority of the TBI sample was male (71%), reflecting TBI prevalence in the general community.[37] On average, time since injury ranged from 1–59 months, with severity ranging from mild to severe head injuries. Only a handful of studies limited their sample to

**Figure 1**—Systematic review flowchart.




ESS, Epworth Sleepiness Scale; MSLT, multiple sleep latency test; MWT, maintenance wakefulness test; PSG; polysomnography; PSQI, Pittsburgh Sleep Quality Index; TBI, traumatic brain injury.

mild[12,21,25,29,38] and severe TBI,[10,11,32] with the remainder of studies collapsing TBIs across the spectrum of severity.[18–20,24,26,27,39] Of the control samples, 10 were matched for age and gender,[11,12,18,19,24–27,32,38] 2 were matched for age,[10,20] with 4 studies not specifying.[9,21,29,39] The mean age of the control sample was 32 years (SD = 10), with a majority of the sample male (66%). Four studies objectively assessed TBI patients with sleep complaints.[12,19,21,27] More specific details about analytical methods for polysomnography in each study are summarized in **Table S2** (supplemental material).

### Primary Analysis: Objective Sleep Complications Post TBI

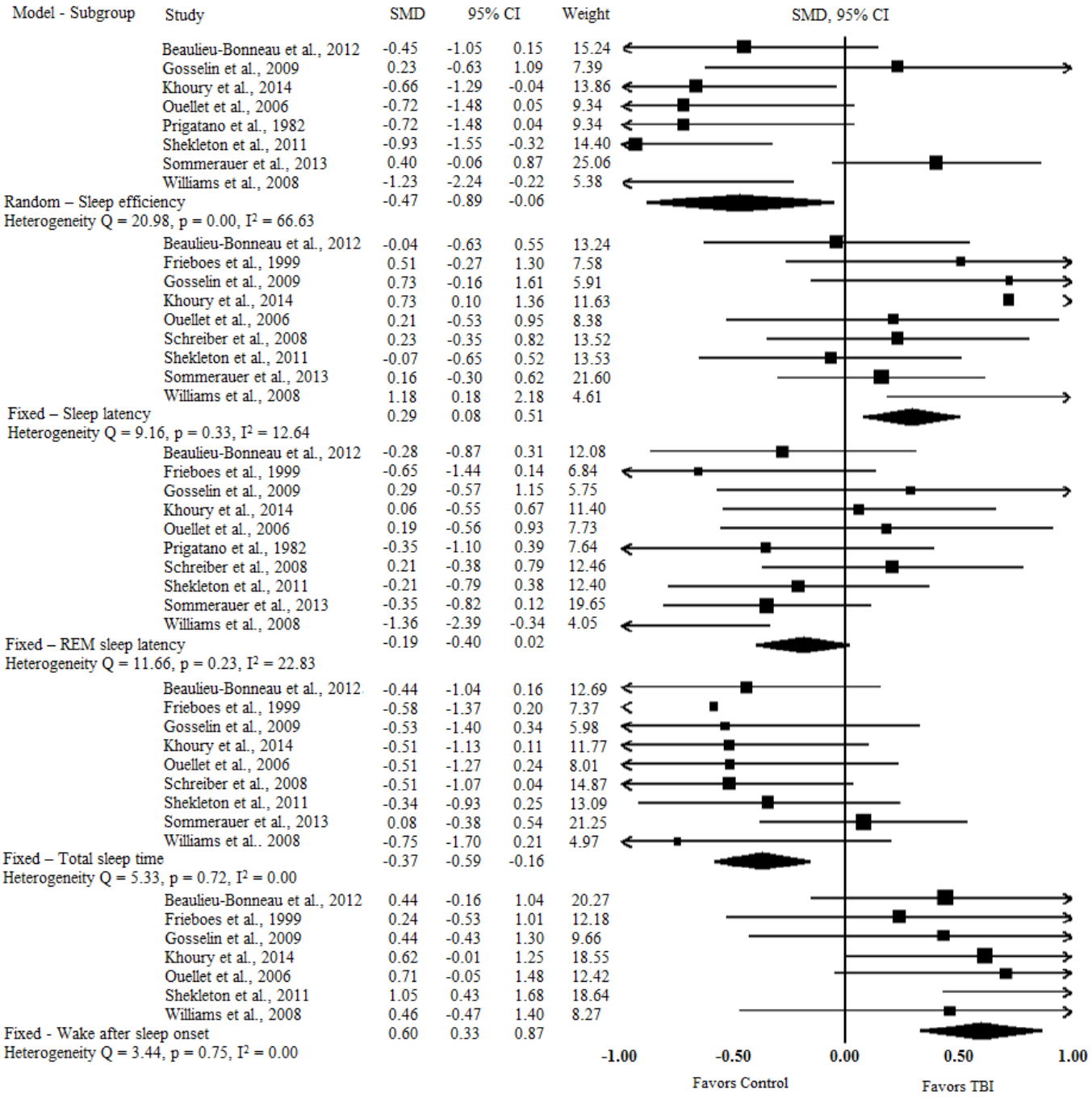
Meta-analysis of the polysomnography outcomes, including forest plots, are shown in **Figures 2** and **3**. As compared to controls, individuals with TBI had poorer sleep efficiency (SMD = −0.47, CI: −0.89, −0.06, n = 298), longer sleep onset latencies (SMD = 0.29; CI: 0.08, 0.51, n = 342), shorter total sleep duration (SMD = −0.37, CI: −0.59, −0.16, n = 348),

**Table 1**—Characteristics of the studies included in meta-analysis.

| | | | TBI Sample | | | | | | | | Control Sample | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | Objective Measures | Subjective Measures | Characteristics | n | Age, y* | Months Since Injury* | Severity | % Male | Medications | Comorbidities | Characteristics | n | Matched |
| Beaulieu-Bonneau et al.[26] | PSG; MWT | ESS; ISI; Sleep diary | Outpatients | 22 | 37 | 53 | PTA 25 d* (moderate-severe) | 77 | SNRI; SSRI; non-benzo; TCA; antiepileptics [a] | No Hx of medical conditions causing sleepiness, fatigue or cognitive issues. No bipolar, psychotic disorder or depression. | Healthy. | 22 | Yes‡ |
| Chaumet et al.[32] | MWT | ESS | Outpatients | 36 | 33 | > 6 | ≥ 24 h of coma (severe) | 78 | Mainly antiepileptics, Muscle relaxants | No hypersomnia prior to injury, no sensory motor handicap | Without chronic fatigue. Assumed to be healthy | 22 | Yes‡ |
| Fogelberg et al.[39] | – | PSQI | Community dwelling | 129 | 38 | 12 | GCS 9.3* (mild-severe) | 78 | NS | Anxiety (n = 1), depression (n = 6), pain (n = 13) | Healthy. Without sleep disorders. | 52 | NS |
| Frieboes et al.[10] | PSG | – | Community dwelling | 13 | 27 | 15.5 | GCS (severe) | 100 | None in preceding three months | No psychiatric disorders, drug or alcohol abuse or endocrine disorders | Healthy males. | 13 | Yes† |
| Gosselin et al.[25] | PSG | ESS; PSQI | Self-reported sport concussion | 10 | 24 | 12 | PTA ≤ 24 h (mild) | 70 | No drugs affecting sleep [b] | No neurological or psychiatric illnesses | Non-athletes. Regular bedtimes/ awakenings. | 11 | Yes‡ |
| Khoury et al.[21] | PSG | PSQI | Outpatients with sleep complaints | 24 | 38 | 45 d | PTA < 30 min (mild) | 63 | No psychotropic or other drugs affecting sleep | No major neurological or psychiatric disorders. No Hx of chronic pain (prior to TBI) | Healthy. No sleep or pain symptom. | 18 | NS |
| Ma et al.[29] | – | ESS; PSQI | Community dwelling | 100 | 39 | 1.5 | GCS 13–15 (mild) | 35 | NS | No Hx cerebrovascular disease, mental retardation, epilepsy or severe medical illness | Healthy. No brain injury. | 137 | NS |
| Ouellet et al.[19] | PSG | DBAS; ISI | Community dwelling with insomnia | 14 | 30 | 21 | PTA 0 min–35 d** (mild-severe) | 64 | Six TBI on medications -hypnotics; anticonvulsant; & antidepressant [c] | Some experienced symptoms of anxiety (n = 4), depression (n = 4) or PTSD (n = 1) | Healthy sleepers. | 14 | Yes‡ |
| Ponsford et al.[18] | – | ESS; GSQ; PSQI | Community dwelling | 153 | 34 | 9.9 | PTA 22.3 d* 4% mild, 22% mod, 49% severe, 25% very severe (mild-severe) | 69 | Antidepressant; antiepileptics; analgesics & other [d] | No Hx of neurological or major psychiatric disorders | Healthy, non-injured. | 120 | Yes‡ |
| Prigatano et al.[20] | PSG | – | Community dwelling | 10 | 26 | 6–59** | GOR 3 mild, 4 moderate, 3 severe (mild-severe) | 100 | No drugs affecting sleep [e] | NS | Healthy. No medication. No sleep disorders. | 10 | Yes† |
| Schreiber et al.[12] | PSG; MSLT | – | Sleep symptoms | 26 | 32 | ≥ 12 | PTA & GCS NS (mild) | NS | NS | No Hx or neurological pathology, no past or present axis I major psychiatric diagnosis | Healthy. | 26 | Yes‡ |
| Shekleton et al.[11] | PSG | ESS; MEQ | Community dwelling | 23 | 33 | 14 | PTA 29.7 d* (severe) | 74 | No benzodiazepine or sleeping medications [f] | No self-reported Hx of psychiatric and substance abuse. | Healthy. | 23 | Yes‡ |
| Sinclair et al.[24] | Actigraphy | ESS; PSQI; Sleep diary | Community dwelling | 21 | 45 | 37 | PTA 19.65 d* 33% mild, 19% moderate, 48% severe. (mild-severe) | 81 | Antidepressants, antispasmodics, analgesics, cardiovascular medications [g] | No Hx of obesity, chronic fatigue or neurological illness (pre-TBI). No current untreated or unstable psychiatric condition | Healthy. No Hx. of sleep disturbance. | 21 | Yes‡ |
| Sommerauer et al.[27] | PSG; MSLT; Actigraphy | ESS | Sleep symptoms | 36 | 36 | 32 | GCS 3–15** 36% mild, 19 % moderate, 45% severe (mild-severe) | 72 | Sleep-wake drugs not permitted [h] | No neurological, psychiatric or systemic disorders | Without sleep disorders, neurological or psychiatric Hx. | 36 | Yes‡ |
| Sullivan et al.[38] | – | ESS; ISI; PROMIS-SD-SF8; PROMIS-SRI-SF8; STQ | Community dwelling | 33 | 22 | 1–6** | Self-reported (mild) | 42 | Three on sleep medications; two on stimulants | No Hx in last 12 months of mental impairment, neurological/ psychiatric disorders or self reported sleep disorders | Healthy. No Hx of mild TBI. | 33 | Yes‡ |
| Williams et al.[9] | PSG | PSQI; SDQ; BSIQ | Community dwelling university students | 9 | 21 | 28 | PTA 5–60 min** (mild) | 67 | NS | NS although the TBI group displayed more symptoms of anxiety and depression on questionnaires | University students. | 9 | Yes† |

*Mean value reported. **Range reported. †Matched for age only. ‡Control sample matched for age and gender.
[a] Beaulieu-Bonneau et al 2012.[26] Less than half of the TBI participants (n = 10) consumed medication, with the remainder 11 participants medication free. Medications included amitriptyline (Tryptizol; Endep) citalopram (Cipramil; Lexapro), clonazepam (Clonazepam; Klonopin), duloxetine (Cymbalta), lorazepam (Ativan), Quetiapine (Seroquel), venlafaxine (Effexor; Effexor), zopiclone (Zimovane).
[b] Gosselin et al., 2009.[25] Included medications not specified.
[c] Ouellet et al., 2006.[19] Eight participants did not receive medication. One participant received one medication with five participants taking two medications. Medications included amitriptyline, citalopram, diphenhydramine, gabapentin (Neurontin), paroxetine (Seroxat; Paxil), venlafaxine, zopiclone.
[d] Ponsford et al., 2013.[18] Specific medications not specified, with 38.6% of TBI individuals consuming medication. Medications included antidepressants (11%), Anticonvulsants (9%), antiepileptics (3%), regular pain medication (16%), and other (14%).
[e] Prigatano et al., 1982.[20] Specific medications not specified; however, no participant consumed medication known to alter sleep patterns.
[f] Shekelton et al 2011.[11] Participants were excluded if they consumed benzodiazepines and sleeping medications.
[g] Sinclair et al., 2014.[24] Sleeping medications were not permitted; however other medications were permitted, with specific medications not stated. Six TBI patients received antidepressants, 2 received antispasmodics, 7 consumed analgesics, 6 had cardiovascular medication, and 2 received anticonvulsant medication.
[h] Sommerauer et al., 2013.[27] All participants were assessed without sleep-wake modulating drugs.
BSIQ, brock sleep and insomnia questionnaire; d, days; DBAS, dysfunctional beliefs and attitudes about sleep scale; GCS, Glasgow coma scale; GOR, Glasgow outcome ratings; GSQ, general sleep questionnaire; Hx, history; ISI, insomnia severity index; MEQ, morning-eveningness questionnaire; mins, minutes; MSLT, multiple sleep latency test; MWT, maintenance wakefulness test; n, study sample size; non-benzo, non-benzodiazepines; NS, not specified; PSG, polysomnography; PSQI, Pittsburgh sleep quality index; PTA, posttraumatic amnesia; PTSD, posttraumatic stress disorder; PROMIS-SD-SF8, patient-reported outcomes information system – sleep disturbance – short form 8 items; PROMIS-SRI-SF8, patient-reported outcomes information system – sleep related impairment – short form 8 items; SDQ, sleep disorders questionnaire; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; STQ, sleep quantity and timing; TBI, traumatic brain injury; TCA, tricyclic antidepressant.

**Figure 2**—Forest plot for primary outcomes.

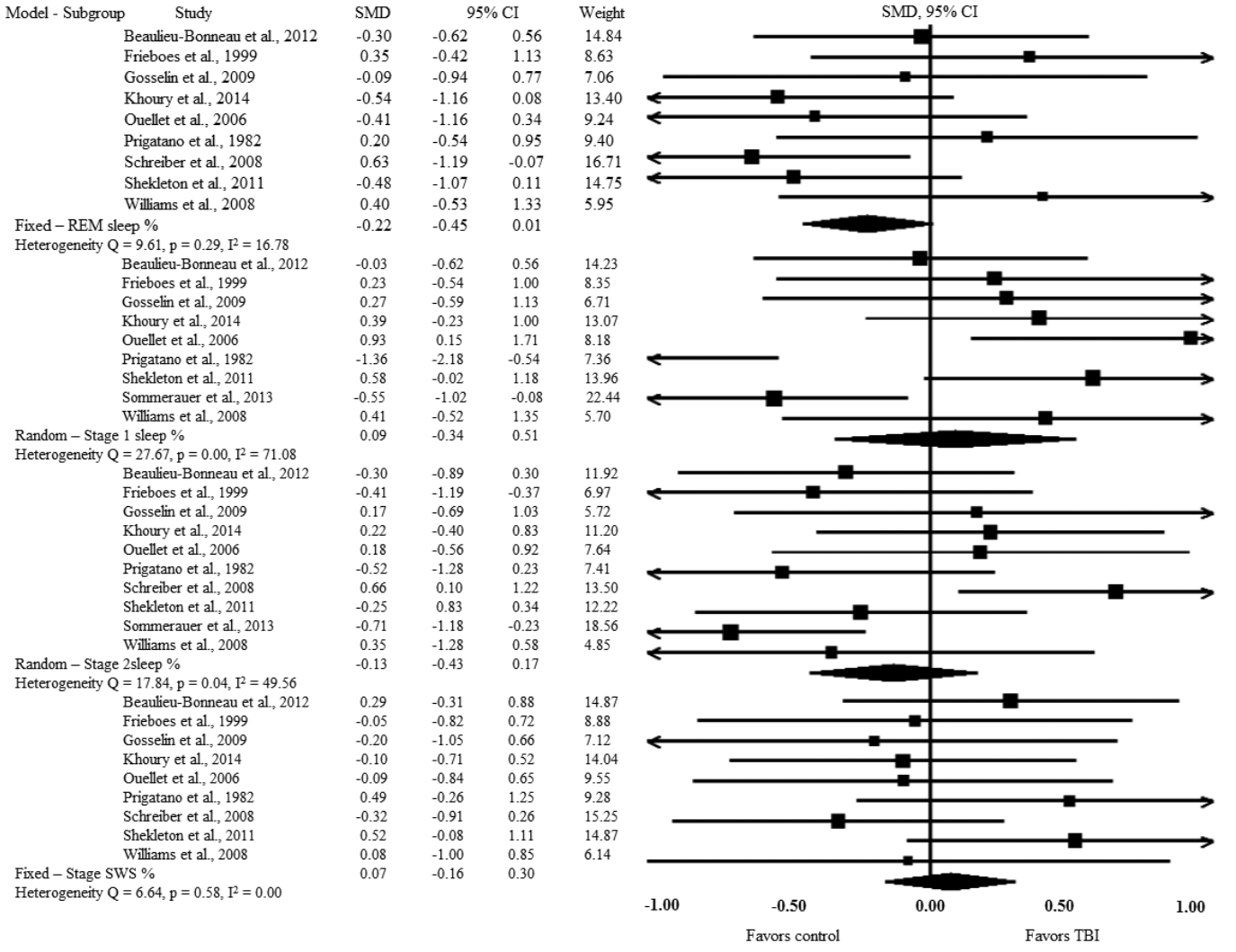



Sleep quality as measured by polysomnography in patients with traumatic brain injury relative to control. Favors TBI indicates that TBI patients score higher values while favors control indicates that controls score higher values. $I^2$, heterogeneity index; SMD, standard mean difference; TBI, traumatic brain injury.

and more wake after sleep onset time (SMD = 0.60, CI: 0.33, 0.87, n = 224). There was no difference in REM sleep latencies between TBI and control (SMD = −0.19, CI: −0.40, 0.02, n = 370).

With respect to the percentage of time spent in each sleep stage (**Figure 3**), there was a trend for those with TBI to spend a lower percentage of time in REM sleep (SMD = −0.22, CI: −0.45, 0.01, n = 304). There was no difference between TBI and control in percentage of time in stage 1 (SMD = 0.09, CI: −0.34, 0.51, n = 324), stage 2 (SMD = −0.13, CI: −0.43, 0.17, n = 376), or slow wave sleep (SMD = 0.07, CI: −0.16, 0.30, n = 298). Across each pooled estimate involving polysomnography, there was little evidence of statistical heterogeneity between studies, with the exception of sleep efficiency (**Figure 2**) and the percentage of time in stage 1 and 2 sleep (**Figure 3**).

**Figure 3**—Forest plot for sleep architecture.




Sleep architecture as measured by polysomnography in patients with traumatic brain injury relative to control. Favors TBI indicates that TBI patients score higher values, while favors control indicates that controls score higher values. $I^2$, heterogeneity index; REM, rapid eye movement sleep; SMD, standard mean difference; SWS, slow wave sleep TBI, traumatic brain injury.

## Secondary Analysis: Subjective Sleep Complaints Post TBI

Meta-analysis of secondary outcomes can be seen in **Table 2**. Those with TBI scored significantly higher on the Epworth Sleepiness Scale as compared with controls, indicating higher subjective sleepiness. With respect to the PSQI, individuals with TBI reported higher global scores, poorer sleep quality, longer sleep onset latency, shorter sleep duration, poorer sleep efficiency, more daytime dysfunction, more sleep disturbance, and more sleep medication. There was no evidence of heterogeneity except for the Epworth Sleepiness Scale and PSQI global scores (**Table 2**).

## Assessment of Publication Bias

Only latency to REM sleep and percentage of stage 2 sleep were available from ≥ 10 studies, and therefore these outcomes were assessed for publication bias. There was no evidence of publication bias for either of these outcomes (latency to REM sleep, Begg P = 0.47; Egger P = 0.47; percentage of stage 2 sleep, Begg: P = 0.86 Egger P = 0.76).

## Meta-Regression and Sensitivity Analysis

Meta-regression was conducted to examine whether the difference in means between the TBI and control samples was associated with time since injury or age of the TBI sample (**Table S3**, supplemental material). This was only performed for sleep latency and percentage of stage 2 sleep, as these were the only 2 outcomes with ≥ 10 studies. The longer the time since injury the smaller the difference in means for the percentage of stage 2 sleep ($Q = 5.89$, $p < 0.05$). There were no other significant associations observed in meta-regression.

Separate polysomnographic analysis was conducted on studies focusing on patients with mild TBI [9,12,21,25] and moderate to severe TBI[10,11,26] (**Tables S4** and **S5**, supplemental material). For both mild TBI and moderate to severe TBI, total sleep time (SMD = −0.43 to −0.55) and sleep efficiency (SMD = −0.53 to −0.69) were

**Table 2**—Pooled estimates for secondary analyses.

| Measure | # of Studies/Reference #s | n | SMD (95% CI) | $I^2$ | Model |
|---|---|---|---|---|---|
| ESS | 9[11,18,24–27,29,32,38] | 858 | 0.40 (0.17, 0.62) | 53.49 | Random |
| PSQI global score | 8[9,11,18,21,24,25,29,39] | 703 | 1.02 (0.65, 1.39) | 79.60 | Random |
| PSQI daytime dysfunction | 6[9,18,21,24,25,39] | 435 | 0.84 (0.63, 1.05) | 14.68 | Fixed |
| PSQI sleep disturbance | 6[9,18,21,24,25,39] | 431 | 0.39 (0.19, 0.60) | 24.39 | Fixed |
| PSQI sleep duration | 6[9,18,21,24,25,39] | 435 | 0.41 (0.21, 0.61) | 33.89 | Fixed |
| PSQI sleep efficiency | 6[9,18,21,24,25,39] | 432 | 0.51 (0.31, 0.71) | 0.00 | Fixed |
| PSQI sleep latency | 6[9,18,21,24,25,39] | 430 | 0.60 (0.40, 0.81) | 25.67 | Fixed |
| PSQI sleep medication | 4*[18,21,24,39] | 397 | 0.31 (0.10, 0.52) | 30.37 | Fixed |
| PSQI sleep quality | 5**[9,18,21,25,39] | 394 | 0.79 (0.58, 1.01) | 64.77 | Fixed |

*Two studies[9,25] were excluded as the control sample had a mean and SD of 0. **One study[24] excluded as the control sample had a mean and SD of 0. CI, confidence interval; ESS, Epworth sleepiness scale; $I^2$, heterogeneity index; n, pooled sample size; PSQI, Pittsburgh Sleep Quality Index; SMD, standard mean difference.

reduced while wake after sleep onset was increased (SMD = 0.54 to 0.62), relative to controls. Sleep onset latency was also longer (SMD = 0.60, CI: 0.24, 0.96) and REM sleep percentage was shorter (SMD = −0.37, CI: −0.72, −0.02) in those with mild TBI. When limiting analysis to studies that excluded patients taking psychoactive medications[11,20,21,25,27] (**Table S6**, supplemental material), wake after sleep onset (SMD = 0.76, CI: 0.36, 1.15) was increased and the percentage of stage 2 sleep (SMD = −0.30, CI: −0.58, −0.02) was reduced, relative to controls.

The primary analysis of polysomnography was repeated, excluding two studies[21,25] that did not use 30-sec epochs (**Table S7**, supplemental material). Results remained generally consistent after the exclusion of these two studies, with the exception that there was no group difference in sleep onset latency (SMD = 0.20, CI: −0.04, 0.44, n = 286), and latency to REM sleep was significantly shorter in those with TBI (SMD = −0.26, CI: −0.49, −0.03, n = 306). Analyses of sleep onset latency and latency to REM sleep were repeated excluding studies that did not use a definition of sleep onset latency in accordance with standard criteria[10,12,19] or epoch length that was consistent with recommended guidelines.[21,25] This analysis showed no difference in sleep onset latency between TBI and controls (SMD = 0.14, CI: −0.15, 0.44, n = 180); however, those with TBI displayed a shorter latency to REM sleep (SMD = −0.38, CI: −0.65, −0.10, n = 200).

## DISCUSSION

Sleep complaints are commonly reported after TBI, but remain poorly characterized. This meta-analysis found that individuals with TBI experienced widespread objective sleep deficits, when compared with controls. As anticipated, patients with TBI displayed increased wake after sleep onset, reduced total sleep time and poorer sleep efficiency. There were no differences in sleep architecture between the groups; however, there was a trend for decreased percentage of REM sleep in those with TBI. Objective sleep deficits were largely corroborated by subjective measures, although differences between TBI and control were generally larger for subjective outcomes.

Analysis of all eligible studies revealed that sleep latency was longer in the TBI group when compared to controls. Although our hypothesis regarding sleep onset latency was initially supported, the increase in sleep onset latency appeared to be driven by studies defining sleep onset relative to the commencement of stage 2 sleep, rather than using recommended scoring criteria: lights out to first epoch of any sleep.[15–17] This highlights the need for greater consistency in the way studies define sleep outcomes, such as sleep onset latency.

Although all studies utilized standard scoring criteria, studies differed in epoch durations, with two studies using 20-second epochs, with the remainder using the recommended 30-second epochs. Such differences in epoch length make it difficult to compare findings across studies and limit the transferability of this information to the clinical setting. To overcome this limitation, we performed a sensitivity analysis on those studies that used 30-second epochs. In this analysis, patients with TBI continued to display reduced total sleep time, increased wake after sleep onset, and reduced sleep efficiency. Interestingly, this sensitivity analysis also revealed that latency to REM sleep was shorter in the TBI group. Reduced latency to REM sleep has been identified in patients suffering from depression.[40,41] As depressive symptoms are commonly reported in those with TBI, depressive symptomatology could be contributing to this finding.

Although not examined in the current meta-analysis, anxiety and depression are strongly associated with sleep disturbance[40] and both are common symptoms following TBI.[19,42] While anxiety and depression have been associated with disrupted objective and subjective sleep in TBI,[11,18] the profile of sleep deficits observed in TBI patients is not entirely consistent with the effects likely to be caused by anxiety and depression. Anxiety and depression are both associated with reduced sleep quality, yet they are also associated with prolonged sleep onset latency.[43,44] Depression has also been associated with decreased slow wave sleep and increased percentage of REM sleep.[40,41] In contrast, our analysis of patients with mild TBI revealed less REM sleep percentage relative to controls. The reasons for this finding are unclear. Anxiety disorders have been associated with reductions in REM sleep percentage,[45] although results

are not consistent.[46] Medications used to treat depression, such as selective serotonin reuptake inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors[41,45] are also known to suppress REM sleep, yet no patients in our mild TBI analysis were medicated.

Various mechanisms may underpin sleep disturbances post TBI. Damage to key brain regions implicated in the sleep-wake cycle may account for the sleep disturbances. Insult to the retino-hypothalamic tract, which synchronizes the hypothalamic circadian pacemaker with the light-dark cycle, can result in abnormally timed circadian rhythms. Damage to the hypothalamus, brain stem and reticular activating system may also be responsible for changes to the sleep-wake cycle. Diffuse axonal injury can alter the biochemical substrates of wake and sleep, namely hypocretin and melatonin. Lower levels of cerebrospinal fluid Hypocretin-1 have been associated with excessive daytime sleepiness in TBI.[3] Reduced endogenous melatonin in the evening is associated with reductions in REM sleep in TBI.[11] Reduced sleep efficiency has also been observed in tetraplegic patients, who have no detectable melatonin in plasma.[47] Individuals with TBI tend to use more medications than the general population, including medications that cross the blood-brain barrier, such as antidepressants.[48] The use of medications may thus contribute to sleep deficits observed in those with TBI. Other secondary complications following TBI, such as medical comorbidities, may also contribute to sleeping difficulties. Taken together, multiple mechanisms likely underlie sleep deficits following TBI.

At present, the role of TBI severity in causing sleep deficits is unclear. The present study implemented a sensitivity analysis to explore this issue. Patients with mild TBI and moderate to severe TBI were both found to display reductions in total sleep time and sleep efficiency as well as increases in wake after sleep onset. Interestingly, sleep latency was prolonged and percentage REM sleep was reduced only in patients with mild TBI, however, these findings should be interpreted with caution given that patients with self-reported mild TBI were collapsed with patients diagnosed by a physician. Some previous studies have shown that mild TBI is associated with more sleep complaints as compared to moderate to severe TBI.[49,50] This may be because those with mild TBI retain more self-awareness.[7] Insult to the brain is considered a determinant of sleep disturbances, however, no convincing neuroimaging evidence has linked location of cerebral injury with sleep disturbance.[51,52] Although some studies have failed to show that injury severity is a predictor of sleep deficits following TBI,[3,11,24] recent research suggests that intracranial hemorrhage and lower Glasgow Coma Scores are strongly associated with increased sleep need, suggesting that widespread cerebral trauma contributes to sleep disturbances post TBI.[30] Furthermore, Glasgow Coma Scores are independently associated with the presence of excessive sleepiness.[52] It has been postulated that lesion location may be more important than TBI severity in predicting sleep outcomes, with damage to the sleep wake centers causing the most sleep disturbance.[7] Neurological impairment is often difficult to identify in mild TBI, particularly with the use of gross imagining techniques, such as computerized topography, making it hard to disentangle the roles of injury severity and lesion location in the etiology of sleep disturbance. Postmortem investigations in TBI patients have identified significant reductions in wake-promoting hypocretin[53] and histaminergic neuronal populations,[54] which may underpin increased sleep drive. Pinpointing the aspects of TBI that best predict sleep disturbance is an important area for future research. Relatively recent advances in sensitive neuroimaging methods, such as susceptibility-weighted imaging, may help relate subtle differences in neurological damage to functional outcomes in TBI,[55] such as sleep.

Despite many available treatments for sleep disturbance, relatively few have proven efficacious in TBI.[7,56] Common pharmacological interventions for sleep disturbance include antidepressants and sedatives. While benzodiazepines provide short-term benefit, long-term use is not recommended, given the deleterious effects on cognitive functioning, daytime alertness, and sleep architecture.[57] Moreover, benzodiazepines, selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors have been shown to reduce REM sleep percentage,[58–61] and therefore their use may have deleterious effects on sleep architecture in people with TBI, given that we observed a trend for those with TBI to spend a lower percentage of total sleep time in REM as compared to controls. Consequently, other interventions are needed to treat sleep disturbance post TBI.

A strength of the current study was the use of polysomnographic data, providing objective quantification of sleep deficits associated with TBI. A further strength was the comparison of TBI patients with controls, providing a point of reference for examining sleep in those with TBI. This study cannot, however, imply causality between the TBI event and the sleep disturbances, given that sleep was not measured before and after the event. A further limitation was that studies scheduled sleep in various ways and this is something we were unable to control for in our analysis. Furthermore, we were unable to comprehensively investigate the association between time post injury and sleep given that studies collapsed patients at various time points post injury. Thus, we are unable to separate the changes in sleep that occur in the months and years following TBI. Psychiatric comorbidities[62] and medication use are also prevalent in TBI,[48] potentially exacerbating sleeping difficulties. Future studies are required to investigate how such factors relate to the risk of sleep disturbance. Lastly, sufficient information was not available to examine the potential contributions of sleep disorders. Sleep disorders are common in TBI, including insomnia,[49,63,64] hypersomnia,[30,52] circadian rhythm sleep disorders,[65–67] and obstructive sleep apnea.[68–70] While our study provides an overall picture of the polysomnographic and subjective sleep deficits experienced in TBI, it does not elucidate the specific sleep disorders contributing to these findings.

This meta-analysis found that TBI was associated with widespread objective and subjective sleep deficits. These findings should be viewed in light of the fact that the existent literature has generally neglected to elucidate the contribution of TBI severity, location of TBI lesions, medical comorbidities, and medication use in the development of sleep deficits post TBI. This remains an important area for future research in order to fully understand the etiology of sleep deficits post TBI.

Nevertheless, the present results suggest the need for physicians to monitor and address sleep deficits following TBI in treatment and rehabilitation programs.

## ABBREVIATIONS

CI, confidence interval
PSQI, Pittsburgh Sleep Quality Index
REM, rapid eye movement
SD, standard deviation
SMD, standard mean difference
TBI, traumatic brain injury

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