Sleep quality in the chronic stage of concussion is associated with poorer recovery: A systematic review

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Abstract

Objective: To examine the association between sleep quality during the chronic stage of concussion and post-concussion outcomes.

Literature Survey: Literature searches were performed during July 1st to August 1st, 2019 in selected databases along with searching grey literature. Out of the 733 results, 702 references were reviewed after duplicate removal.

Methodology: Three reviewers independently reviewed and consented on abstracts meeting eligibility criteria (n=35). The full-text articles were assessed independently by two reviewers. Consensus was achieved, leaving four articles. Relevant data from each study was extracted using a standard data-extraction table. Quality appraisal was conducted to assess potential bias and the quality of articles.

Synthesis: One study included children (18-60 months) and three studies included adolescents and/or adults (ranging 12 years to 35). The association between sleep and cognition (two studies), physical activity (one study), and emotion symptoms (one study) was examined. Sleep quality was associated with decreased cognition and emotional symptoms, but not with meeting physical activity guidelines 6 months post-concussion injury.

Conclusions: The heterogeneity in age of participants and outcomes across studies and limited number of included studies made interpretations difficult. Future studies may consider if addressing sleep quality following concussion will improve outcomes.
Introduction

The prevalence of a concussion is 1.7-3.8 million people each year in the United States.\textsuperscript{1} Concussion injuries occur in a variety of settings including motor vehicle accidents, sports, recreation, falls, work environments, and war blast zones\textsuperscript{4,5} and are commonly a result of a high magnitude of force placed to the head, neck, or face.\textsuperscript{2,6} Symptoms caused by a concussion are often categorized into four domains: somatic, cognitive, mood disruption, and sleep dysregulation.\textsuperscript{3,7} Somatic symptoms include vertigo, sensitivity to light and sound, nausea, vomiting, headaches, and migraines.\textsuperscript{7} Slower processing speed, decreased focus, disrupted short term memory, and difficulty concentrating are commonly reported impairments in cognition following a concussion.\textsuperscript{7} Mood disruptions after a concussion consist of an increase or onset of anxiety, depression, or irritability.\textsuperscript{7} Sleep dysregulation often manifests in the form of hypersomnia, insomnia, or circadian rhythm disruption.\textsuperscript{7} Acutely following the injury, headache, fatigue, dizziness, and difficulty with information processing are the most endorsed symptoms.\textsuperscript{8,9} Symptoms that are commonly reported at follow-up visits are sleep disturbances, frustration, forgetfulness, and fatigue.\textsuperscript{8}

Recovery time frames after the concussion injury are different for each individual and commonly are grouped in the following stages: acute stage (the first seven days), sub-acute stage (8-89 days), and chronic stage (≥ 90 days) following the concussion injury.\textsuperscript{10} Symptoms resolve for 80-90% of individuals 1-3 weeks post-injury.\textsuperscript{1,4,6,7} However, for the remaining 10-20% of individuals, symptoms persist for months to years post injury.\textsuperscript{11-14}

While symptom severity and duration are difficult to predict,\textsuperscript{15} there are certain factors from prior to the injury, the injury itself, and after the injury that increase the risk of prolonged symptoms. Pre-injury risk factors include age (0-4 years old and 65+ years old), history of
learning disabilities, migraines, previous concussions, psychiatric conditions, female gender, lower cognitive reserve, lower socioeconomic status, substance abuse, and premorbid sleep disturbance.\textsuperscript{16-20} Concussion-specific risk factors for prolonged symptoms consist of loss of consciousness, injuries to other areas of the body, lower (<15) Glasgow Coma score, and a higher velocity mechanism of injury.\textsuperscript{16,17} Post-injury anxiety, depression, post-traumatic stress disorder, migraine, sleep disturbances, fogginess, difficulty concentrating, vestibular dysfunction, and ocular motor dysfunction post-injury have also been associated with prolonged symptom recovery.\textsuperscript{13,14,21} Variability in length of recovery following a concussion is likely due to multiple reasons, including fluctuation of cellular effects, extent of axonal injury, location of impact, and the number and severity of symptoms following a concussion.\textsuperscript{22-25} Research is still investigating why various risk factors and combinations of risk factors contribute to delayed concussion recovery.

Sleep disturbance prior to concussion as well as the development of sleep disturbances following a concussion have also been associated with prolonged concussion symptoms. Poor sleep quality is related to increased pain,\textsuperscript{26} more frequent headaches,\textsuperscript{27} and vestibular issues.\textsuperscript{28} Our recently published systematic review found that sleep disturbances in the acute phase have been shown to be predictive of prolonged symptom recovery following a concussion.\textsuperscript{17} Short sleep duration and poor quality during the acute and subacute stage of concussion are associated with a range of prolonged post-concussion symptoms including poorer cognitive function, reduced productivity at work or school, decreased social engagement, increased pain, daytime sleepiness, depression, and anxiety.\textsuperscript{17,29,30}

The association between sleep and post-concussion symptoms in the acute and sub-acute stages has been well documented.\textsuperscript{19,31-36} There remains a gap in the literature assessing the
association between sleep and post-concussion symptoms in the chronic phase of concussion recovery. Therefore, the purpose of this systematic review is to examine the association between sleep disturbance and post-concussive symptoms at >6 months post-injury.

Methods

To conduct this systematic review, literature searches were performed between July 1st to August 1st, 2019 in the following databases: Ovid MEDLINE(R), Cumulative Index of Nursing & Allied Health Literature (CINAHL), and Web of Science - Science Citation Index Expanded. Relevant cited references and grey literature including clinical trials and conference papers were searched. The review was limited to studies published in the English language using the databases’ language limit feature. Publication date limits to the search were not applied.

A combination of keywords and controlled vocabulary terms were used in Medline and CINAHL to execute the searches in the databases. Medical subject headings including “brain concussion”, “brain injuries”, “traumatic brain injuries”, “sleep”, “pain”, “pain management”, and keywords (text-words) such as “mild traumatic injuries”, “concussion”, “post-concussion” were used in various combinations to increase recall.

PRISMA guidelines were followed for the article selection. Studies included in the systematic review, had to meet the following inclusion criteria: (1) included people with concussive or mild traumatic brain injury; (2) assessed sleep using subjective or objective measures > 6 months post-concussion; (3) used a prospective or cross-sectional study design; (4) reported other non-sleep outcomes > 6 months post-concussion; and (5) included statistical analyses to relate sleep outcomes to other reported outcome(s). Studies were excluded if they: (1) included animals; (2) included participants with moderate and/or severe traumatic brain injury;
(3) included participants with other neurologic conditions; (4) used a study design other than prospective or cross-sectional; (5) were irrelevant to the objective of the systematic review; (6) were published in a language other than English; or (7) included a duplicate data set.

Three reviewers (R.L., K.S., A.P.) assessed titles and abstracts of all potentially eligible articles for inclusion/exclusion criteria to identify which titles/abstracts met those criteria and would be considered for the systematic review. The full-text article of all considered studies was then retrieved and reviewed independently by two reviewers (R.L., E.N.) to establish article relevance. The reviewers came to a consensus on which abstracts met the inclusion/exclusion criteria and which full-text articles were included in the systematic review.

Data Extraction

Relevant data were extracted from each included study by two reviewers (R.L., E.N.) using a data-extraction table. Extracted information included the author(s), year published, study location, study design, sample size, participant demographic characteristics, time since injury, measures used to assess sleep, measures used to assess other outcomes, and results.

Quality Assessment

The risk of potential bias as well as the overall quality of the included studies was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross Sectional Studies. The checklist is comprised of eight questions regarding defined study inclusion criteria, description of study participants, exposure validity and reliability, standard criteria for measurement conditions, identification of confounding factors, strategies for dealing with confounding factors, valid and reliable outcomes measured, and appropriate statistical analysis. All articles were scored independently by two reviewers (R.L., E.N.) as “yes”, “no”,...
“unclear”, or “not applicable” for each item on the checklist. The reviewers met to reach consensus.

Results

The search strategy generated a total of 733 articles. There were 31 duplicates removed, leaving 702 titles/abstracts to review. After the review of title/abstracts for inclusion/exclusion criteria, 662 articles were removed. A total of 40 full-text articles were reviewed. Thirty-six articles were removed due to: reasons related to unclear assessment time since injury (n=22), no statistical analyses conducted to determine the association between sleep and other post-concussion outcomes (n=11), and inability to locate the full-text article (n=3). A total of four articles met the criteria to be included in this review (Figure 1).

The studies in this review are summarized in the data extraction table (Table 1) and the risk of bias is reported in the quality appraisal table (Table 2). The number of participants in each study ranged from 49-232 individuals. One article included pediatric patients (18-60 months), and three articles included adolescents and adults (>12 years old).

Landry-Roy et al. (2018) evaluated the relationship between sleep and executive function in preschool children. Children aged 18-60 months (n=167) who either had a concussion (n=84) or were typically developing children (TDC) (n=83) participated. The results indicated there was a significant interaction of children’s group (concussion or TDC) and the Children Behavior Checklist (CBCL) sleep scores on the Delay of Gratification assessment (p=.05) at 6-months. Suggesting that children with a concussion and sleep disturbance have disrupted executive function. There was a significant group difference for the Delay of Gratification assessment performance for children with higher levels of sleep problems on the CBCL (p=.03). Children with a concussion had decreased performance compared to TDC on the
delay of gratification if they had higher levels of sleep problems on the CBCL. Similarly, in a post hoc analysis there was a significant group difference on Conflict Scale performance for children with shorter sleep duration (p=.004). Thus, children with a concussion exhibited poorer conflict scale performance than TDC only if they had shorter nighttime sleep duration. There was a small subgroup of children (n=68; 33 concussion 35 TDC) who wore actigraphy but no association between actigraphy and sleep diary and executive function was found. The results of this study indicate that the combination of a concussion and poor sleep result in poorer executive functions in pre-school aged children.

The study by Dean and Sterr (2013) evaluated working memory and information processing speed in adults (n=36; 20-30 years of age) at least one-year post concussion injury compared to a non-head injury control group (n=36; 20-30 years of age). Participants were divided into one of four groups: 1. Concussion + Post-Concussion Syndrome (PCS); 2. Concussion – PCS; 3. Control (non-head injury) + PCS; 4. Control (non-head injury) - PCS. Nighttime sleep quality was lower in the Concussion + PCS participants compared to the Concussion - PCS and Control - PCS (p=.018). Mean Pittsburg Sleep Quality Index (PSQI) scores for the Concussion + PCS (8.6 +/- .8) and the Control + PCS (6.6 +/- .7) were indicative of poor nighttime sleep. There was a significant correlation for all individuals with a concussion between lower PSQI scores and poorer performance on the N Back (working memory) and Paced Visual Serial Addition Task (information processing speed) (Rho=.62, p<.001).

Theadom et al. (2018) evaluated how sleep predicts post-concussion symptoms and community and social engagements in adolescents and adults (n =232; age ≥ 16) from the population based BIONIC study four years after the initial concussion injury. The study used the Rivermead Post Concussion Symptoms Questionnaire to assess post-concussion symptoms
and the PSQI for sleep quality. The concussion group reported significantly more cognitive symptoms four years post-injury compared to controls. There was no difference between the concussion and control groups on somatic and emotional scores. Regression modeling revealed that sleep quality was a significant predictor for emotional symptoms on the Rivermead Post Concussion symptom questionnaire (p=.02) but not for cognitive (p=.99) or somatic symptoms (p=.06). In particular, poorer sleep quality was a predictor of higher anxiety, depression, and irritable mood symptoms 4 years following concussion.

Van Markus-Doornbosch et al. (2019) evaluated the relationship between sleep quality and physical activity level in adolescents and adults who had a concussion. A total of 49 participants (12-25 years old) who had a concussion 6-18 months prior were enrolled in the study. If the participant was < 18 years old, a parent completed the questionnaires. Physical activity was assessed by the Activity Questionnaire for Adults and Adolescents, and sleep quality was assessed using the PSQI. Twenty-five out of 49 (51%) participants did not meet the Dutch Health Enhancing Physical Activity (D-HEPA) recommendations. The median PSQI total score was 4.5 for the entire study group with no significant association with meeting or not meeting the D-HEPA recommendations (OR .99, 95% CI .82,1.19).

The two contributing factors for bias were not adequately controlling for confounding factors and not using an appropriate assessment tool for measuring sleep outcomes (Table 2). In two out of the four studies, the confounding factors were not adequately described or controlled for in the statistical analysis. One out of the four studies did not use an assessment that was specific to assess sleep outcomes. The sleep portion of the CBCL used in Landry-Roy et al. has good convergent validity, but there is debate on if this assessment is specific to sleep when compared to other pediatric sleep assessments.
Discussion

This systematic review found that poor sleep quality is associated with concussion symptoms 6 months to 4 years following the injury. Poor sleep quality was associated with impaired executive function in preschoolers at 6 months following concussion, and working memory and information processing speed in adults. Poor sleep quality was also found to be a predictor of emotional symptoms in adults 4 years post-concussive injury. However, one study did not find a significant association between sleep quality and meeting physical activity guidelines in adolescents. Only four articles met the criteria for inclusion in this systematic review, thus limiting the scope of interpretation, while simultaneously highlighting the lack of research on how poor sleep quality and sleep disturbances are associated with prolonged symptoms in individuals with chronic concussion.

Two articles in this systematic review examined the association between sleep and executive function, working memory, and information processing speed. Cognitive function has been shown to be impaired in the acute and subacute stages of concussion. Symptoms such as taking longer to think, decreased focus, and decreased processing speed are commonly reported in the acute and subacute stages. What was observed from this systematic review was that executive function, working memory, and processing speed was still impaired. Sleep disturbance and cognitive disturbance are ranked as the most common complaints of patients at follow-up visits. The association between sleep disturbance and cognitive disturbance is not a surprise as sleep disturbance can influence cognition. Individuals recovering from a TBI have shown sleep fragmentation and altered sleep architecture on polysomnography. More specifically, individuals recovering from a TBI spend more time in slow wave sleep (SWS) and less time in rapid eye movement (REM) sleep. While SWS is
necessary for cellular and structural recovery, REM is needed for information processing and memory consolidation. Therefore, a reduction in REM could contribute to impairments of executive functioning, working memory, and information processing that are often experienced by individuals following concussion. 47-51 Psychological factors such as depression, anxiety, and mood influence cognition as well. 52-54 Sleep disturbances and psychological factors are interrelated, so it is likely a combination of sleep disturbance and psychological factors impact cognitive function following a concussion. 55

Sleep quality was also found to be predictive of emotional symptoms including anxiety, depression, and irritability 4 years following a concussion. 40 This finding supports evidence that chronic poor sleep and insomnia can contribute to the development of depression, anxiety, irritability. 56-60 Furthermore, screening and treating insomnia reduces concomitant symptoms of depression, anxiety, and stress. 61-63 While sleep quality and insomnia contributes to emotional symptoms, research also shows that emotional symptoms can contribute to the development of sleep issues. 64 A negative mood (anxious, stressed, tense, sad, or irritable) is more common in individuals with poor sleep. 65,66 There is a strong relationship between the development of anxiety and the development of poor sleep and insomnia as many core features (intense worry or fear, and avoidance behavior) are the same. 67 Health care providers should screen for both sleep and emotional issues in people following concussion, and more studies are needed to determine optimal prioritization of treatment for sleep and emotional issues.

One study found that meeting physical activity guidelines was not associated with sleep quality six months post-injury. 41 This is surprising as physical activity and sleep have been shown to have a reciprocal relationship. 68 If an individual does not have a quality night of sleep, there is decreased motivation to be physically active the following day. 68 Also, physical activity
improves sleep duration and quality by increasing sleep drive. The lack of association in Van Markus-Doornbosch might be due to the mean PSQI score was 4.5, indicating the participations on average had good quality sleep. Also, the authors assessed the relationship between sleep quality and adherence to physical activity guidelines, not physical activity specifically. Van Markus-Doornbosch reported that within their sample 51% of individuals following concussion met physical activity guidelines which is comparable to the national average in the United States. For adults in the United States, 44.8% of individuals meet physical activity guidelines. Therefore, it is questionable on if guidelines for physical activity matter when assessing sleep in individuals with a concussion.

The limitations within the articles for this systematic review is due to not controlling for confounding factors and the specific sleep assessments used. Within the studies reviewed two out of the four articles did not describe confounding factors or address them within their statistical analysis. This made interpretation of the results challenging as it is unclear what effect the confounding factors had on the results described. Additionally, the sleep portion of the CBCL used in Landry-Roy et al., 2018 had good convergent validity, but it is of question on if this assessment is specific enough to assess sleep in comparison to other pediatric sleep questionnaires.

This systematic review does not come without limitations. One limitation is there are only four articles included within this review, limiting the breadth and depth for interpretation. Additionally, the studies included in this systematic review includes a variety of outcomes. The heterogeneity limits interpretation as each study addresses different outcomes (cognition, physical activity, and emotional symptoms). There needs to be more studies evaluating these
outcomes to strengthen the knowledge base on how sleep affects cognition, physical activity, and emotional symptoms.

This systematic review indicates that poor sleep quality is associated with impairment in executive function, working memory, information processing, and emotional symptoms, but not physical activity in individuals >6 months post-concussion. Additional studies are needed to more thoroughly understand how sleep is associated with various post-concussion symptoms in the chronic stage. Also, investigating how addressing sleep issues may impact symptom resolution and recovery in people with a concussion is warranted.
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References

1. Mahooti N. Sports-Related Concussion: Acute Management and Chronic Postconcussive Issues. Child and adolescent psychiatric clinics of North America. 2018;27(1):93-108.

2. Duclos C, Dumont M, Wiseman-Hakes C, et al. Sleep and wake disturbances following traumatic brain injury. Pathologie-biologie. 2014;62(5):252-261.

3. Bramley H, Hong J, Zacko C, Royer C, Silvis M. Mild Traumatic Brain Injury and Post-concussion Syndrome: Treatment and Related Sequela for Persistent Symptomatic Disease. Sports Med Arthrosc Rev. 2016;24(3):123-129.

4. Tator CH. Concussions and their consequences: current diagnosis, management and prevention. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013;185(11):975-979.

5. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. The Journal of head trauma rehabilitation. 2006;21(5):375-378.

6. Chancellor SE, Franz ES, Minaeva OV, Goldstein LE. Pathophysiology of Concussion. Semin Pediatr Neurol. 2019;30:14-25.

7. McCrea MA, Nelson LD, Guskiewicz K. Diagnosis and Management of Acute Concussion. Physical medicine and rehabilitation clinics of North America. 2017;28(2):271-286.

8. Eisenberg MA, Meehan WP, 3rd, Mannix R. Duration and course of post-concussive symptoms. Pediatrics. 2014;133(6):999-1006.

9. Howell DR, O'Brien MJ, Beasley MA, Mannix RC, Meehan WP, 3rd. Initial somatic symptoms are associated with prolonged symptom duration following concussion in adolescents. Acta paediatrica (Oslo, Norway : 1992). 2016;105(9):e426-432.

10. Krainin BM, Forsten RD, Kotwal RS, Lutz RH, Guskiewicz KM. Mild traumatic brain injury literature review and proposed changes to classification. J Spec Oper Med. 2011;11(3):38-47.

11. Daneshvar DH, Riley DO, Nowinski CJ, McKee AC, Stern RA, Cantu RC. Long-term consequences: effects on normal development profile after concussion. Physical medicine and rehabilitation clinics of North America. 2011;22(4):683-700, ix.

12. Iverson GL. Network Analysis and Precision Rehabilitation for the Post-concussion Syndrome. Frontiers in neurology. 2019;10:489.
13. McMahon P, Hricik A, Yue JK, et al. Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study. *Journal of neurotrauma.* 2014;31(1):26-33.

14. Hiploylee C, Dufort PA, Davis HS, et al. Longitudinal Study of Postconcussion Syndrome: Not Everyone Recovers. *Journal of neurotrauma.* 2017;34(8):1511-1523.

15. Kenzie ES, Parks EL, Bigler ED, Lim MM, Chesnutt JC, Wakeland W. Concussion As a Multi-Scale Complex System: An Interdisciplinary Synthesis of Current Knowledge. *Frontiers in neurology.* 2017;8:513.

16. Tator CH, Davis HS, Dufort PA, et al. Postconcussion syndrome: demographics and predictors in 221 patients. *Journal of neurosurgery.* 2016;125(5):1206-1216.

17. Ludwig R, D'Silva L, Vaduvathiriyan P, Rippee MA, Siengsukon C. Sleep Disturbances in the Acute Stage of Concussion are Associated With Poorer Long-Term Recovery: A Systematic Review. *Pm r.* 2019.

18. Meehan WP, 3rd, Mannix R. Pediatric concussions in United States emergency departments in the years 2002 to 2006. *The Journal of pediatrics.* 2010;157(6):889-893.

19. Schmidt AT, Li X, Hanten GR, McCauley SR, Faber J, Levin HS. A Longitudinal Investigation of Sleep Quality in Adolescents and Young Adults After Mild Traumatic Brain Injury. *Cognitive and behavioral neurology : official journal of the Society for Behavioral and Cognitive Neurology.* 2015;28(2):53-62.

20. Papa L, Mendes ME, Braga CF. Mild Traumatic Brain Injury among the Geriatric Population. *Curr Transl Geriatr Exp Gerontol Rep.* 2012;1(3):135-142.

21. Collins MW, Kontos AP, Reynolds E, Murawski CD, Fu FH. A comprehensive, targeted approach to the clinical care of athletes following sport-related concussion. *Knee Surg Sports Traumatol Arthrosc.* 2014;22(2):235-246.

22. Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery.* 2014;75 Suppl 4:S24-33.

23. Barkhoudarian G, Hovda DA, Giza CC. The molecular pathophysiology of concusive brain injury. *Clin Sports Med.* 2011;30(1):33-48, vii-iii.

24. Frati A, Cerretani D, Fiaschi AI, et al. Diffuse Axonal Injury and Oxidative Stress: A Comprehensive Review. *Int J Mol Sci.* 2017;18(12).

25. Wiseman-Hakes C, Duclos C, Blais H, et al. Sleep in the Acute Phase of Severe Traumatic Brain Injury: A Snapshot of Polysomnography. *Neurorehabilitation & Neural Repair.* 2016;30(8):713-721.
26. Suzuki Y, Khoury S, El-Khatib H, et al. Individuals with pain need more sleep in the early stage of mild traumatic brain injury. *Sleep medicine*. 2017;33:36-42.

27. Chaput G, Giguere JF, Chauny JM, Denis R, Lavigne G. Relationship among subjective sleep complaints, headaches, and mood alterations following a mild traumatic brain injury. *Sleep medicine*. 2009;10(7):713-716.

28. Sufrinko AM, Howie EK, Elbin RJ, Collins MW, Kontos AP. A Preliminary Investigation of Accelerometer-Derived Sleep and Physical Activity Following Sport-Related Concussion. *The Journal of head trauma rehabilitation*. 2018;33(5):E64-e74.

29. Wickwire EM, Williams SG, Roth T, et al. Sleep, Sleep Disorders, and Mild Traumatic Brain Injury. What We Know and What We Need to Know: Findings from a National Working Group. *Neurotherapeutics*. 2016;13(2):403-417.

30. Raikes AC, Schaefer SY. Sleep Quantity and Quality during Acute Concussion: A Pilot Study. *Sleep*. 2016;39(12):2141-2147.

31. Theadom A, Cropley M, Parmar P, et al. Sleep difficulties one year following mild traumatic brain injury in a population-based study. *Sleep Medicine*. 2015;16(8):926-932.

32. Theadom A, Starkey N, Jones K, et al. Sleep difficulties and their impact on recovery following mild traumatic brain injury in children. *Brain Injury*. 2016;30(10):1243-1248.

33. Mollayeva T, Mollayeva S, Colantonio A. The Risk of Sleep Disorder Among Persons with Mild Traumatic Brain Injury. *Current neurology and neuroscience reports*. 2016;16(6):55.

34. Farrell-Carnahan L, Franke L, Graham C, McNamee S. Subjective sleep disturbance in veterans receiving care in the Veterans Affairs Polytrauma System following blast-related mild traumatic brain injury. *Military medicine*. 2013;178(9):951-956.

35. Gosselin N, Lassonde M, Petit D, et al. Sleep following sport-related concussions. *Sleep medicine*. 2009;10(1):35-46.

36. Kalmbach DA, Conroy DA, Falk H, et al. Poor sleep is linked to impeded recovery from traumatic brain injury: Characterizing sleep onset insomnia symptoms and short sleep in functional impairment. *Sleep*. 2018;24:24.

37. Moola S MZ, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E MZ, ed. *Joanna Briggs Institute Reviewer's Manual*. 2017.

38. Landry-Roy C, Bernier A, Gravel J, Beauchamp MH. Executive Functions and Their Relation to Sleep Following Mild Traumatic Brain Injury in Preschoolers. *Journal of the International Neuropsychological Society*. 2018;24(8):769-780.
39. Dean PJ, Sterr A. Long-term effects of mild traumatic brain injury on cognitive performance. *Frontiers in Human Neuroscience*. 2013;7:30.

40. Theadom A, Starkey N, Barker-Collo S, et al. Population-based cohort study of the impacts of mild traumatic brain injury in adults four years post-injury. *PLoS ONE [Electronic Resource]*. 2018;13(1):e0191655.

41. van Markus-Doornbosch F, Peeters E, van der Pas S, Vlieland TV, Meesters J. Physical activity after mild traumatic brain injury: What are the relationships with fatigue and sleep quality? *European Journal of Paediatric Neurology*. 2019;23(1):53-60.

42. Meares S, Shores EA, Taylor AJ, et al. The prospective course of postconcussion syndrome: the role of mild traumatic brain injury. *Neuropsychology*. 2011;25(4):454-465.

43. Martindale SL, Morissette SB, Rowland JA, Dolan SL. Sleep quality affects cognitive functioning in returning combat veterans beyond combat exposure, PTSD, and mild TBI history. *Neuropsychology*. 2017;31(1):93-104.

44. Parcell DL, Ponsford JL, Redman JR, Rajaratnam SM. Poor sleep quality and changes in objectively recorded sleep after traumatic brain injury: a preliminary study. *Archives of physical medicine and rehabilitation*. 2008;89(5):843-850.

45. Schreiber S, Barkai G, Gur-Hartman T, et al. Long-lasting sleep patterns of adult patients with minor traumatic brain injury (mTBI) and non-mTBI subjects. *Sleep medicine*. 2008;9(5):481-487.

46. Verma A, Anand V, Verma NP. Sleep disorders in chronic traumatic brain injury. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*. 2007;3(4):357-362.

47. Vyazovskiy VV, Delogu A. NREM and REM Sleep: Complementary Roles in Recovery after Wakefulness. *Neuroscientist*. 2014;20(3):203-219.

48. Perogamvros L, Dang-Vu TT, Desseilles M, Schwartz S. Sleep and dreaming are for important matters. *Front Psychol*. 2013;4:474.

49. Karni A, Tanne D, Rubenstein BS, Askenasy JJ, Sagi D. Dependence on REM sleep of overnight improvement of a perceptual skill. *Science*. 1994;265(5172):679-682.

50. Baran B, Pace-Schott EF, Ericson C, Spencer RM. Processing of emotional reactivity and emotional memory over sleep. *J Neurosci*. 2012;32(3):1035-1042.

51. Rasch B, Born J. About sleep’s role in memory. *Physiol Rev*. 2013;93(2):681-766.

52. Sleep and sadness: exploring the relation among sleep, cognitive control, and depressive symptoms in young adults. *Sleep Medicine*. 2014;15(1):144 - 149.
53. Vytal KE, Cornwell BR, Letkiewicz AM, Arkin NE, Grillon C. The complex interaction between anxiety and cognition: insight from spatial and verbal working memory. *Front Hum Neurosci.* 2013;7:93.

54. Storbeck J, Clore GL. On the interdependence of cognition and emotion. *Cogn Emot.* 2007;21(6):1212-1237.

55. van der Naalt J, Timmerman ME, de Koning ME, et al. Early predictors of outcome after mild traumatic brain injury (UPFRONT): an observational cohort study. *The Lancet Neurology.* 2017;16(7):532-540.

56. Zhai L, Zhang H, Zhang D. Sleep duration and depression among adults: a meta-analysis of prospective studies. *Depress Anxiety.* 2015;32(9):664-670.

57. Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia as a risk factor for developing anxiety and depression. *Sleep.* 2007;30(7):873-880.

58. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord.* 2011;135(1-3):10-19.

59. Li L, Wu C, Gan Y, Qu X, Lu Z. Insomnia and the risk of depression: a meta-analysis of prospective cohort studies. *BMC Psychiatry.* 2016;16(1):375.

60. Ramsawh HJ, Stein MB, Belik SL, Jacobi F, Sareen J. Relationship of anxiety disorders, sleep quality, and functional impairment in a community sample. *J Psychiatr Res.* 2009;43(10):926-933.

61. Siengsukon CF, Alshehri M, Aldughmi M. Self-report sleep quality combined with sleep time variability distinguishes differences in fatigue, anxiety, and depression in individuals with multiple sclerosis: A secondary analysis. *Mult Scler J Exp Transl Clin.* 2018;4(4):2055217318815924.

62. Siengsukon CF, Alshehri M, Williams C, Drerup M, Lynch S. Feasibility and treatment effect of cognitive behavioral therapy for insomnia in individuals with multiple sclerosis: A pilot randomized controlled trial. *Mult Scler Relat Disord.* 2020;40:101958.

63. Garland SN, Carlson LE, Stephens AJ, Antle MC, Samuels C, Campbell TS. Mindfulness-based stress reduction compared with cognitive behavioral therapy for the treatment of insomnia comorbid with cancer: a randomized, partially blinded, noninferiority trial. *J Clin Oncol.* 2014;32(5):449-457.

64. Alvaro PK, Roberts RM, Harris JK. A Systematic Review Assessing Bidirectionality between Sleep Disturbances, Anxiety, and Depression. *Sleep.* 2013;36(7):1059-1068.
65. Buysse DJ, Thompson W, Scott J, et al. Daytime symptoms in primary insomnia: a prospective analysis using ecological momentary assessment. *Sleep medicine.* 2007;8(3):198-208.

66. McCrae CS, McNamara JP, Rowe MA, et al. Sleep and affect in older adults: using multilevel modeling to examine daily associations. *Journal of sleep research.* 2008;17(1):42-53.

67. Jansson-Frojmark M, Lindblom K. A bidirectional relationship between anxiety and depression, and insomnia? A prospective study in the general population. *J Psychosom Res.* 2008;64(4):443-449.

68. Chennaoui M, Arnal PJ, Sauvet F, Léger D. Sleep and exercise: a reciprocal issue? *Sleep medicine reviews.* 2015;20:59-72.

69. Dolezal BA, Neufeld EV, Boland DM, Martin JL, Cooper CB. Interrelationship between Sleep and Exercise: A Systematic Review. *Adv Prev Med.* 2017;2017:1364387.

70. Zenko Z, Willis EA, White DA. Proportion of Adults Meeting the 2018 Physical Activity Guidelines for Americans According to Accelerometers. *Front Public Health.* 2019;7:135.
| Authors, year, country | Study Design | Number of Participants | Participant demographic characteristics | Time since injury | Measures used to assess sleep | Measures used to assess other outcomes | Results | Outcomes in favor of concussion |
|------------------------|-------------|------------------------|------------------------------------------|------------------|-----------------------------|----------------------------------------|---------|-----------------------------|
| Landry-Roy et al., 2018, Canada | Prospective Cross-sectional | 167 participants aged 18-60 months. 84 individuals in the mTBI group 83 in the control typically developing children | Age at injury 36.80 months (11.54) Accidental cause of trauma: car accident, accidental fall, collision related (struck by or against something) | 6 months | Child Behavior Checklist: Parent report questionnaire pertaining to children’s behavioral difficulties | Executive functions Delay of gratification Conflict Scale Shape Stroop | Demographics between groups The two groups did not differ significantly on age, sex, socioeconomic status, ethnicity, or post-concussive symptoms. There was no significant difference between the two groups on executive function measures and sleep measures 6 months post injury |  |
| Dean et al., 2013, United Kingdom | Cross-sectional | 72 participants, 18 per group: mTBI with PCS mTBI with no PCS Controls with PCS Controls with no PCS | Individuals with an mTBI at least one year post injury and controls participants with no history of head injury. (n=72) | one year | Epworth sleepiness scale -daytime sleepiness Pittsburgh Sleep Quality Index - sleep quality Karolinska Sleepiness Scale – Sleepiness in different contexts before and after cognitive testing | N-Back for working memory PVSAT for information processing | Bivariate correlations CBCL sleep scale scores were not correlated with actigraphy-derived variables Significant interaction effect of children’s group and CBCL sleep scale scores on delay of gratification (p=.05) There was no significant interaction between children’s group and nighttime sleep duration in the prediction of conflict scale (p=.38) Significant group difference for Delay gratification performance for children with higher levels of sleep problems (p=.03) Group differences for children with lower levels of sleep problems was not significant (p=.66) |  | Pre-injury and 6 month post injury CBCL sleep scale for mTBI children Pre-injury and 6-months post injury CBCL sleep scale were intercorrelated (p=.001) There was no significant difference between pre and post injury CBCL sleep scale scores (p=.66) Both pre-injury and 6-month post injury CBCL sleep scale scores significantly predicted Delay of Gratification performance (p=.03) |  |
| Study | Design | Participants | Age and TBI Details | Measures | Findings |
|-------|--------|--------------|---------------------|----------|----------|
| Theadom et al., 2018, New Zealand | Prospective Cross-sectional | 232 mTBI 232 controls | Mean Age for MTBI: 40.39 (18.5) Male:130 (56%) Female:102 (44%) Prior TBI’s in lifetime: None (104:44.8%) 1 to 2 (76 32.8%) 3 or more(43 18.5%) Unknown (9 3.9%) | Mean 4 years post injury Pittsburg sleep quality index –sleep quality Rivermead Post concussion Symptoms Questionnaire-Post-concussion symptoms Hospital Anxiety and Depression Scale- Anxiety and depression Participation in everyday life-participation/ community integration measure. | There was no statistical difference in total score on the RPQ between mild TBI and controls (p=.009) The concussion group experienced significantly more self-report cognitive symptoms four-years post injury than controls (p=.000) There was no significant difference for somatic and emotional scores between the concussion group and the control group (p=.89; P=.58 respectively) Concussion group reported significantly poorer participation across all domains of the Community Participation Questionnaire domains: Productivity (P=.000), Social Relations (p=.000), Out and About P=.000) Regression prediction models Sleep quality was not a significant predictor of cognitive symptoms (p=.99) Sleep quality was a significant predictor of emotional symptoms (p=.02) Sleep quality was not a significant predictor of somatic symptoms (p=.06) |
| Van Auver-Doornbosch et al., 2019, Netherlands | Prospective Cross-sectional | 49 Participants with mTBI | Participants were aged 12-25 years Mean Age at injury (16.8 years (3.7) Time since injury mean 1.6 years (.5) | 6-18 months post injury Checklist individual strength- Fatigue Pittsburgh sleep quality index –sleep quality Activity Questionnaire for Adults and Adolescents- Physical Activity and individual strength | Physical activity minutes Participants performed general physical activity on average 1350 min/week Moderate to vigorous activities were performed on average 793 min/week Sedentary activities were 2670 min/week Meeting guidelines The median PSQI total score was 4.5 for the total group with no significant association with meeting our not meeting the D-HEPA recommendations |
| Authors (year) | Criteria for inclusion clearly defined | Participants described in detail | Exposure measured in valid and reliable way | Objective standard criteria used for measurement | Confounding factors identified | Strategies to deal with confounding factors | Outcomes measured in a valid and reliable way | Appropriate statistical analysis used |
|---------------|----------------------------------------|---------------------------------|---------------------------------------------|-----------------------------------------------|-------------------------------|--------------------------------|---------------------------------------------|--------------------------------|
| Landry-Roy et al., 2018 | Yes-defined inclusion/exclusion criteria | Yes-gave specific ages, and criteria for meeting concussion standards | Yes-concussion was evaluated and defined in a valid reliable way | Yes-used standard, valid, and reliable assessment tools | No-did not identify confounding factors | No-did not control for confounding factors in their statistical analysis | Unsure-Use of the CBCL sleep portion may not be specific enough | Unsure-did not describe in detail how the statistical analysis answered their research question |
| Dean and Sterr, 2013 | Yes-defined inclusion/exclusion criteria | Yes-Gave criteria for meeting concussion standards | Yes-concussion was evaluated and defined in a valid reliable way | Yes-used standard, valid, and reliable assessment tools | No-did not identify confounding factors | Unsure-Did not identify confounding factors and unclear if they statistically controlled for factors. | No-the researchers allowed for rest breaks and potential days between assessment times | Yes-used appropriate statistical analysis |
| Thea.dorn et al., 2018 | Yes-defined inclusion/exclusion criteria | Yes-gave criteria for meeting concussion standard | Yes-concussion was evaluated and defined in a valid reliable way | Yes-used standard, valid, and reliable assessment tools | Yes-identified confounding factors | Yes-controlled for confounding factors in statistical analysis | Yes-met in homes or over phone, done by trained research personnel | Yes-used appropriate statistical analysis |
| Markus-Doonbosch et al., 2018 | Yes-defined inclusion/exclusion criteria | Yes – gave criteria for meeting concussion standard | Yes-concussion was evaluated and defined in a valid reliable way | Yes-used standard, valid, and reliable assessment tools | Yes-identified confounding factors | Not Applicable | Unsure | Yes-used appropriate statistical analysis |
Records identified through database searching (n = 733)
- CINHAL (n = 4)
- Medline (n = 560)
- Sports Discuss (n = 78)
- Web of Science (n = 116)

Duplicates removed (n = 31)

Titles/abstracts screened (n = 702)

Articles excluded after screening titles/abstracts (n = 662)

Full-text articles assessed for eligibility (n = 40)

Studies included in systematic review (n = 4)
- Unclear time since injury (n = 22)
- No statistical analysis ran on association of sleep and PCS (n = 11)
- Could not find (n = 3)