Circadian Rhythm – A Neglected Aspect of the Post-Concussion Insomnia Assessment

A Cross-sectional, Observational Study

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Abstract

Background: Insomnia is a major predictor of adverse outcomes in mild traumatic brain injury (mTBI), including concussion. Insomnia symptoms may be maintained by circadian rhythm sleep-wake disorders (CRSWD). While previous studies have focused on insomnia symptom assessment, we provide a diagnostic circadian workup in a homogeneous sample of patients with chronic insomnia symptoms following a mTBI. Detection and treatment CRSWD may open a new avenue to facilitate recovery from mTBI. Objective: To determine the prevalence of CRSWD in individuals with chronic insomnia following a mTBI.

Methods: Individuals with mTBI (Glasgow Coma Scale 13-15) and chronic insomnia (Insomnia Severity Index > 11 and assessed in a clinical interview) were recruited from diverse community clinics 3 - 24 months post-injury to participate in this cross-sectional observational study. Potential participants (n = 81) were screened by phone and participated in an intake clinical interview (n = 62) before enrollment (n = 50). Exclusion criteria: (a) alcohol/ substance use problems; (b) pre-existing brain disorders/previous neurosurgery; (c) travelled across more than two time zones less than three weeks prior to the screening; (d) shift work schedule. Assessments (clinical interview, standard questionnaire; 2 weeks of actigraphy and sleep diary and dim light melatonin onset test) were conducted in a sleep and circadian clinic. Outcome measure: Percentage of patients with CRSWD.

Results: Among the 50 participants, (median age: 39.5 – IQR 23.8; 64% females) 26% had a CRSWD. The most common (77%) circadian diagnosis was delayed sleep-wake phase disorder.

Interpretation: The prevalence of CRSWD is exceptionally high among individuals with chronic insomnia symptoms following a mTBI. Accurate diagnosis and treatment of these

disorders may improve the post-concussion recovery of approximately a quarter of all patients and half of adolescents and young adults who suffer from chronic insomnia following a mTBI.

Traumatic brain injury (TBI) – a brain trauma caused by an external mechanical force - is the leading cause of disability among young adults and has rising incidence rate in Canada, especially in the 18-34 age group (1, 2). Mild TBI (mTBI) - including concussion - constitute the majority (70-90%) of all treated TBI cases and has the largest contribution to the burden of injury-related disability (3). Early detection and effective management of medical conditions that hinder recovery could prevent disability and substantially reduce societal costs.

Difficulties with falling asleep, staying asleep or early morning final awakening (insomnia) are the most common persistent sleep symptoms after mTBI, including concussion (4, 5). Insomnia after concussion worsens fatigue, pain, cognition and mood and predicts poor overall prognosis for recovery (6-8). Since the disorders of sleep and wakefulness that cause chronic insomnia symptoms can be effectively treated, it becomes important to characterize and diagnose the sleep disorders that maintain insomnia symptoms after mTBI. Effective treatment of these disorders holds the promise of improving the management of persistent post-concussive symptoms and hastening recovery from mTBI.

Chronic insomnia is a shared symptom of circadian rhythm sleep-wake disorders; see Table 1. These disorders arise if there is a disruption of the endogenous circadian system or a misalignment between the internal circadian rhythm and the external environment. The best biological marker of circadian rhythm sleep-wake disorders is abnormal dim light melatonin onset (DLMO), while the behavioural diagnostic feature is that sleep phase is significantly delayed, advanced or irregular relative to environmental time and social norms.

A neuroimaging study suggests that mTBI may cause pineal gland injury and disrupt circadian regulation via its effect on melatonin secretion (9). Only one clinical study has performed diagnostic circadian assessment in a group of patients with mTBI hitherto (10). This

study selected 15 individuals from 42 sleep clinic patients with mTBI and insomnia; however, selection criteria were not provided; DLMOs were not reported; time since injury was not specified, and the age range was restricted to young and early-middle age adults. Each of the 15 patients was diagnosed with a circadian rhythm sleep-wake disorder - 7 with delayed sleep-wake phase disorder and 6 with irregular sleep-wake rhythm disorder. These results suggest that the prevalence of circadian rhythm sleep-wake disorders may be higher among mTBI patients with chronic insomnia symptoms than the known prevalence in relevant comparisons groups (i.e. sleep clinic insomnia samples) but the above shortcomings limit the interpretability of the above results.

Given that circadian rhythm sleep-wake disorders require specific circadian assessment and treatment, it is pertinent to establish if patients with mTBI and insomnia symptoms comprise one of the few clinical groups where circadian rhythm sleep-wake disorders are prevalent. If this is the case, circadian assessment and treatment becomes an important part of chronic insomnia work-up and management following mTBI.

Objective and Hypothesis

The objective was to determine the rate of circadian rhythm sleep-wake disorders according to standard diagnostic criteria using evidence-based comprehensive assessment – including actigraphy and DLMO - in a large consecutive and representative sample of individuals with chronic insomnia following mTBI. The hypothesis was that circadian rhythm sleep-wake disorders would be more common in this clinical group than it is in individuals who seek treatment for chronic insomnia in sleep clinics (5-10%) (11).

Method

Participants. Participant characteristics are summarized in Table 2. Inclusion criteria: (a) mTBI (Glasgow Coma Score ≥ 13 at the time of injury) three to 24 months prior to the screening assessment; (b) chronic insomnia symptoms that started or significantly amplified following the injury; (c) age between 17 and 65 years. When participants had multiple concussions, the mTBI after which the sleep problem started was in the time frame of three to 24 months. Exclusion criteria: (a) had alcohol or other substance use problems within three months prior to enrollment based on DSM 5 criteria; (b) needed immediate psychiatric help based on in-person assessment; (c) had pre-existing brain disorders or neurosurgery; (d) had travelled across more than two time zones less than three weeks prior to the phone screening; or (e) had a shift work schedule.

Procedures. Information of the study was distributed widely to hospitals and community clinics in South Ontario, in the Georgian Bay and Sudbury areas and it was published on brain injury organization and sleep clinic websites (Referral sources are summarized in Table 2). We received 81 referrals within the 12-month recruitment phase. Following phone screens, a semi-structured interview and completion of the Insomnia Severity Index, however, 22 were ineligible. Another 5 had scheduling or assessment conflicts, and four failed to show in person. Nobody needed to be excluded for reasons of shift work, travel across time zones or psychiatric conditions (Figure 1). Thus, final enrollment comprised 50 patients with mTBI and chronic insomnia symptoms. In the subsequent 12-14 days after their enrollment, participants kept a sleep diary and wore an actiwatch on their non-dominant wrist. Finally, they participated in a DLMO test in 12-14 days following their initial interview.

Assessment tools and methods.

Insomnia Assessment:

The *Duke Structured Interview for Sleep Disorders* (DSISD) assesses sleep disorders according to clinical and research diagnostic criteria (12). The study used an updated version of the DSISD in which the insomnia section has been modified to match the new DSM 5 criteria. The DSISD was used to select individuals with chronic insomnia.

The *Insomnia Severity Index* (ISI; Morin, 1993) measures the subjective severity of insomnia symptoms (13, 14). The degree of insomnia severity is determined by the summary scores of seven items as follows: 0 to 7 -no clinical insomnia; 8 to 14- "sub-threshold" insomnia; 15 to 21 -moderate insomnia; and 22 to 28 is severe insomnia. A summary score of 11 has been recommended as a cut-off for screening for clinical insomnia research and was used as cut-off for inclusion in this study (15).

Assessment of sleep pattern:

Wrist Actigraphy is a recommended diagnostic assessment tool for circadian rhythm sleep-wake disorders (11). Participants wore a Philips Respironics Actiwach 2 on their non-dominant wrist (16). The device detects movement using a solid piezoelectric accelerometer with 0.35-7.5Hz bandwidth and 0.5-2G peak value. The device was set to record 30-second epochs at medium sensitivity to detect wake threshold. Data were scored both automatically and manually. Manual scoring involved setting the "rest period" (the period between bedtime and rise time). Rest time was set based on event markers (participants marked their bedtime and rise time using the event marker function of the actiwatch) as well as movement, light and sleep diary data. After the rest periods were set, the Actiware 6.0.7. software calculated all the sleep parameters, including sleep onset latency, wake after sleep onset, total sleep time and sleep efficiency.

The *Consensus Sleep Diary* was developed to provide a standard sleep log based on patients' input and expert consensus (17). The sleep indices in the Consensus Sleep Diary differentiate between individuals with insomnia and good sleepers and are significantly correlated with the ISI and with actigraphy measures (18). The diary was used in the study for longitudinal subjective assessment of sleep pattern.

Assessment of circadian phase:

Dim Light Melatonin Onset Test (DLMO)Test. Eight saliva samples were collected from each participant according to standard procedures (Buhlmann EK DSM © Saliva Melatonin ELISA kit; Buhlmann Laboratories, Switzerland). Light level was maximum 10 lux in the room. The three baseline samples were taken every 30 minutes and the remaining samples were collected hourly. Data collection started six hours before habitual bedtime, which was determined based on participants' self-report and was verified from their sleep-diary data. Medications that influence melatonin levels were prohibited/discontinued before the test.

All assessors (except for the first author) were blind to the study hypothesis.

Missing data. Two participants had missing actigraphy data but both provided sleep diary data that could be used to determine if they had a normal sleep phase. Altogether, 47 of the 50 participants completed the DLMO test. DLMO could not be precisely determined from five samples (in three DLMO was outside of the measurement period and there were technical problems with two samples).

Analyses

Saliva samples were frozen and analyzed using enzyme-linked immunosorbent assay as per manufacturer's instructions (Buhlmann EK DSM © Saliva Melatonin ELISA kit; Buhlmann Laboratories, Switzerland). The intra-assay and inter-assay coefficients of variation were 7.62

and 8.88. As per consensus guidelines, DLMO was determined as the clock time, when the melatonin concentration reached and remained above the threshold (two *SD* above the baseline or, when there were fewer than 3 baseline values, an absolute value of 3 pg/ml), (19).

Descriptive statistics summarized the sample characteristics, questionnaire scores, the frequency of circadian rhythm sleep-wake disorders diagnoses and the relationship between circadian rhythm sleep-wake disorders diagnoses and demographic data. Independent samples t tests, using bootstrapping with 1000 re-samples compared the sleep diary and DLMO data of patients with delayed sleep-wake phase disorder and those without circadian rhythm sleep-wake disorders (there were not enough individuals in the other sub-groups of circadian rhythm sleep-wake disorders to allow statistical comparisons). Statistical significance was set at $p \leq .008$ to correct for multiple comparisons.

Circadian rhythm sleep-wake disorders were diagnosed according to International Classification of Sleep Disorders (ICSD 3) criteria (11). The 95% confidence intervals (CIs) for the prevalence rates are based the corresponding precision afforded by our final sample size (N=50), (20).

Results

Most ($N = 46$ or 92%) participants had moderate/severe insomnia symptoms (ISI $\geq$ 15), while the remaining patients reported mild insomnia symptoms. Three quarters of the sample denied having subjective sleep problems or sleep disorders prior to their injury and 100% reported moderate or significant worsening of their sleep since the injury.

One-quarter (13 patients) of the 50 participants received a circadian rhythm sleep-wake disorder diagnosis (Table 3), corresponding to a prevalence of 26% ± 12%. The most common diagnosis (10 patients) was delayed sleep-wake phase disorder; nine of these individuals were

younger than 32 years (Table 4). All of those with advanced sleep-wake phase disorder and irregular sleep-wake rhythm disorder were over 40.

There were large and significant differences both in the subjective behavioural (sleep diary) and objective, biological (DLMO) timing of sleep and circadian rhythm between patients with delayed sleep-wake phase disorder and those without a circadian rhythm sleep-wake disorder (Table 5), confirming that the clinical diagnoses accurately separated patients with delayed sleep-wake phase disorder from those without a circadian disorder.

Interpretation

The objective of this study was to determine what percentage of patients whose main sleep symptom is chronic insomnia following a mTBI have a circadian rhythm sleep-wake disorder. The results supported the a-priori hypothesis: 26 % of the full sample received a circadian rhythm sleep-wake disorder diagnosis.

Most (77%) of these participants had delayed sleep-wake phase disorder. This proportion is one-two orders of magnitude higher than the prevalence of delayed sleep-wake phase disorder in the general population (0.17% – 1.53%) and over three times that among patients with chronic insomnia treated at sleep clinics (6.7 %) (21-23). Notably, delayed sleep-wake phase disorder was the most common sleep disorder diagnosis in the 18-31 age group with a 10-fold prevalence compared to the prevalence of delayed sleep-wake phase disorder in the general adolescent population (11, 24-26).

This study did not explore the causes of delayed sleep-wake phase disorder but several etiological factors merit consideration. One MRI study noted that patients who had sleep problems following a mTBI had a longer tentorium and a flatter tentorial angle than patients who did not have sleep problems. The authors speculated that the pineal gland (the secretion site of

melatonin) would be impacted by injuries caused by an anterior – posterior force in individuals with this anatomical predisposition (27).

Another biological predisposing factor could be a susceptibility of the sleep and circadian system for phase delay due to a long circadian period, heightened responsiveness to the melatonin supressing effect of light in the evening; or slow accumulation and dissipation of homeostatic sleep drive – mechanisms that have been implicated in the etiology of delayed sleep-wake phase disorder (28). If the social demand to wake up early in the morning lessens during the post injury recovery period, the sleep phase follows the circadian signals and shifts to later hours in individuals with a predisposition for phase delay. This can lead to a vicious cycle, in which longer light exposure in the evening and lack of light exposure in the morning further delays the circadian cycle (29).

It is also possible that individuals with a pre-injury delayed DLMO or evening chronotype are at an increased risk for sustaining a TBI, because they are sleepy in the morning when they attend sport training, school or work. Athletic performance fluctuates across the circadian cycle and excessive sleepiness impacts cognitive performance and increases the risk for accidents and injuries (30-36). Thus, the high prevalence of delayed sleep-wake phase disorder in mTBI/concussion samples may, in part, reflect a higher prevalence of TBI among individuals with a late DLMO and evening chronotype.

Two participants in this study received a diagnosis of advanced sleep-wake phase disorder. The prevalence of advanced sleep-wake phase disorder is very low both in the general population or in clinical insomnia samples, given that only individual cases and family cohorts have been described thus far (11, 22). In the current study, none of the participants with

advanced sleep-wake phase disorder had a family history of advanced sleep-wake phase disorder.

Finally, one participant was diagnosed with irregular sleep-wake rhythm disorder. This circadian rhythm sleep-wake disorder has previously been described among individuals with brain pathology (11). The person in the present study with irregular sleep-wake rhythm disorder reportedly had an alcohol use disorder until six months before the injury. There is an interaction between the circadian system and alcohol use disorders and it is possible that pre-injury alcohol use disorder increases the risk for developing an irregular sleep-wake rhythm disorder following a brain injury (37).

Clinical implications. Awareness of circadian rhythm sleep-wake disorders is generally low among clinicians but distinguishing it from insomnia disorder is crucial since the treatment of insomnia disorder (cognitive behavioural therapy or selected hypnotic medications) and the management of circadian rhythm sleep-wake disorders (melatonin and bright light therapy) are fundamentally different.

The results of this study suggest that clinicians should be attentive to symptoms of circadian rhythm sleep-wake disorders when they see patients with persistent insomnia symptoms following a mTBI, including concussion. Referral for a circadian assessment is warranted if there is a significant shift of the sleep period or if the patient sleeps only for short (maximum 4 hour) periods around the clock. The threshold for referring to a circadian assessment should be especially low if a teenager or young adult reports significant sleep onset insomnia or a delay of sleep phase following a mTBI.

This study is the first to provide a rigorous multi-method diagnostic circadian assessment based on standard criteria in a representative sample of patients with mTBI and chronic

insomnia. Previous circadian studies have included patients with moderate and severe TBI; assessed melatonin secretion without determining DLMO; or determined average DLMO in a group of patients without providing diagnostic assessment and interpretation in samples that were substantially smaller than the current sample (4, 10, 38-42). The standard clinical intake assessment at least three months after the TBI ensured that a homogeneous sample of individuals with chronic insomnia symptoms were included.

In addition to the strengths of this study, some limitations should be considered. Firstly, the sample may over-represent patients who were distressed by their insomnia symptoms. At the same time, these are the patients who (ideally) would receive some form of post-concussion sleep assessment in the community. Secondly, individuals with substance use disorders and shift workers were not recruited. It is likely that the frequency of circadian rhythm sleep-wake disorders is higher in those groups. Also, participants may not have reported insomnia symptoms that pre-dated the injury. This does not bias the diagnoses but precludes inferences about the possible role of the injury.

The results of this study apply to treatment seeking patients with chronic insomnia symptoms who had a mTBI between three months and 24 months before the sleep assessment. The percentage of circadian rhythm sleep-wake disorders may be different among individuals who do experience insomnia symptoms following the TBI, but who do not seek help in managing post-concussion or sleep symptoms, or who had a TBI more than two years before a sleep assessment.

The current sample size was limited by logistical constraints and this hampered the precision of the estimated prevalence rates; this was particularly true for the subsample analyses regarding specific circadian rhythm sleep-wake disorders and those within young and older age

groups. Future studies should assess circadian rhythm sleep-wake disorders in larger mTBI samples with insomnia. Finally, this study did not include an age and sex-matched comparison group of patients with chronic insomnia who did not have a history of TBI. Future replication of this study will benefit from an inclusion of such groups to allow for more direct comparison of rates and on the sleep-wake measures. Given that research on circadian rhythm sleep-wake disorders among patients with insomnia alone is limited, these studies will add valuable information not only for those with TBI, but also to the general insomnia and circadian rhythm sleep-wake disorder literature.

It is important to emphasise that the current study did not aim to establish a cause and effect relationship between the clinical diagnoses and the injury or control for variables that may have influenced this relationship. We took a rigorous clinical approach because there is a need to generate reliable diagnostic information which can inform clinical guidelines for insomnia assessment in this clinical group. Without clinical guidelines that are based on research evidence, patients with insomnia will not an receive evidence-based insomnia assessment and treatment after a concussion. The results of this study have direct clinical implications in that they draw attention to the need to assess circadian rhythm sleep-wake disorders in patients who suffer from chronic insomnia following a mTBI. Circadian assessment is currently not part of a standard post-concussion insomnia workup and is not a routine component of sleep clinic assessments. Consequently approximately 25% of patients with post-concussion chronic insomnia symptoms (based on the results of the current study) would not receive an appropriate diagnosis and thereby tailored treatment for their sleep difficulty which in turn leads to lower likelihood of recovery (6-8). Future longitudinal studies should identify factors that predispose individuals for developing circadian rhythm sleep-wake disorders after a concussion and test the nature and direction of

pathways between the circadian timing of sleep and wakefulness and factors that may influence this relationship in mTBI in different age groups.

Summary and Conclusions. One quarter of treatment-seeking individuals with post-concussion chronic insomnia symptoms were diagnosed with a circadian rhythm sleep-wake disorder. This implies that clinicians may include circadian rhythm sleep-wake disorders in their diagnostic algorithm and consider the potential benefits of a circadian assessment when patients report insomnia symptoms and a significant change in their sleep phase following a mTBI. The majority of these patients were adolescents and young adults with approximately 50% prevalence of delayed phase sleep-wake disorder in this age group; this finding warrants larger-scale replication. Given that insomnia symptoms are major predictors of poor post-concussion recovery, detection and effective management of circadian rhythm sleep-wake disorders may improve the recovery particularly in adolescents and young adults who suffer from chronic insomnia following a mTBI.

Author Contributions

1. Dora M. Zalai made substantial contributions to conception and design of the work, as well as to the acquisition, analysis, and interpretation of data for the work. She made a significant contribution to drafting of the work, revising it critically for important intellectual content and final approval of the version to be published. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
2. Todd A. Girard made substantial contributions to design of the work, as well as to the analysis and interpretation of data for the work. He made a significant contribution to revising the manuscript for important intellectual content and final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
3. Michael D. Cusimano made substantial contributions to design of the work as well as to the interpretation of data for the work. He made a significant contribution to revising the manuscript for important intellectual content and final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
4. Colin M. Shapiro made substantial contributions to design of the work, as well as to the acquisition and interpretation of data for the work. He made a significant contribution to revising the manuscript for important intellectual content and final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that

questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table 1. *Key Features of the Circadian Rhythm Sleep-Wake Disorders Diagnosed in this Study*

Circadian Disorder	**Characteristic sleep pattern**	**Main clinical features**	**Epidemiology**	**Treatment**
Delayed sleep-wake phase disorder	Delayed main sleep episode (usually by at least two hours) relative to the socially desired or required sleep time.	• Sleep initiation insomnia and difficulty with waking when sleep schedule is socially imposed, but significantly improved sleep when sleep schedule is freely chosen. • Excessive sleepiness in the morning. • Risk for the development of mood disorders.	• Usually starts in adolescence. • Prevalence in general population: 0.17% - 1.53% • 5-10% of individuals with chronic insomnia in sleep clinics	• Strategically timed oral melatonin based on DLMO[c,ad,a] • Post-awakening light therapy in conjunction with behavioral treatment [c,ad]

Advanced sleep-wake phase disorder	Advanced main sleep episode (at least by two hours) relative to the socially desired or required sleep time	• Inability to stay awake until the socially desirable time in the evening and inability to remain asleep until a socially desirable wake time. • Excessive sleepiness in the evening.	• Approximately 1% of the general population has advanced sleep phase • Prevalence of advanced sleep-wake phase diosrder in the general population and in sleep clinic insomnia samples is unknown but thought to be rare.	• Evening light therapy
Irregular sleep-wake rhythm disorder	Irregular sleep episodes typically shorter than 4 hours; total 24 h sleep duration can be normal.	• Insomnia at night and excessive sleepiness during the day.	• Described in neuro-developmental and neuro-degenerative disorders and after TBI.	• Light therapy in elderly patients with dementia • Melatonin [c, ad]

Note: TBI: traumatic brain injury; DLMO: dim light melatonin onset; c: children; ad: adolescents; a: adults

Table 2. *Participant Characteristics*

	No (%)	Median (IQR)	Min-max
Age (years)		39.5 (23.8) 25th percentile: 28 75th percentile: 51	17- 62
Gender			
Male	18 (36)		
Female	32 (64)		
Education			
High school	13 (26)		
College	12 (24)		
University	25 (50)		
Employment status			
Full time	21 (42)		
Part time	5 (10)		
Student	4 (8)		
Unemployed	8 (16)		
Sick leave/disability	11(22)		
Retired	1 (2)		
Number of concussions			
Single	32 (64)		
Multiple	18 (36)		
Time since the injury* (months)		11.5 (12) 25th percentile: 8 75th percentile: 20	3 - 27

Table 2. *Participant Characteristics (continued from previous page)*

	No (%)	Median (IQR)	Min-max
Cause of injury			
Car accident	18 (36)		
Sport injury	18 (36)		
Fall	9 (18)		
Object hit the head	2 (4)		
Physical assault	2 (4)		
Workplace injury	1 (2)		
Referral source			
Head injury clinic	18 (36)		
Family medicine clinic	16 (32)		
Concussion/sport clinic	6 (12)		
Sleep clinic	4 (8)		
Speech-language pathologist, neurologist, physiotherapist, emergency specialists	2 (4)		

Note: * Time elapsed since the injury. If a participant had multiple concussions, it is time elapsed since the injury that preceded the onset of the sleep problem. IQR = interquartile range

Table 3. *Circadian Rhythm Sleep-Wake Disorder Diagnoses*

	ASWPD	**DSWPD**	**ISWRD**	**No CRSWD**
In the full sample (n = 50)	4 ± 5%	20 ± 11%	2 ± 4%	74 ± 12%
In participants ≤ 31 years (n = 16)	0%	50± 25%	0%	50 ± 25%
In participants > 31 years (n = 34)	6 ± 8%	3 ± 6%	3 ± 6%	88 ± 11%

Note: Data represent the prevalence in percentages ± 95% CI. ASWPD = advanced sleep-wake phase disorder, DSWPD = delayed sleep-wake phase disorder, ISWRD = irregular sleep-wake rhythm disorder, CRSWD = circadian rhythm sleep-wake disorder

Table 4. *Age, Gender and Employment Status of Participants without a Circadian Rhythm Sleep-Wake Disorder and Participants with Delayed Phase Sleep Wake Disorder*

	Without CRSWD (N = 37)			**DPSWD (N = 10)**		
	No (%)	Median (IQR)	Min-max	No (%)	Median (IQR)	Min-max
Age (years)		40 (23.5) 25th percentile: 31 75th percentile: 54	17 - 62		26 (11) 25th percentile: 20.5 75th percentile:30	17 - 54
Gender						
Male	18 (36)			5 (50)		
Female	32 (64)			5 (50)		
Employment status						
Full time	17 (46)			3 (30)		
Part time	2 (5)			2 (20)		
Student	3 (8)			1 (10)		
Unemployed	5 (14)			3 (30)		
Sick leave/disability	9 (24)			1 (10)		
Retired	1 (3)			0 (0)		

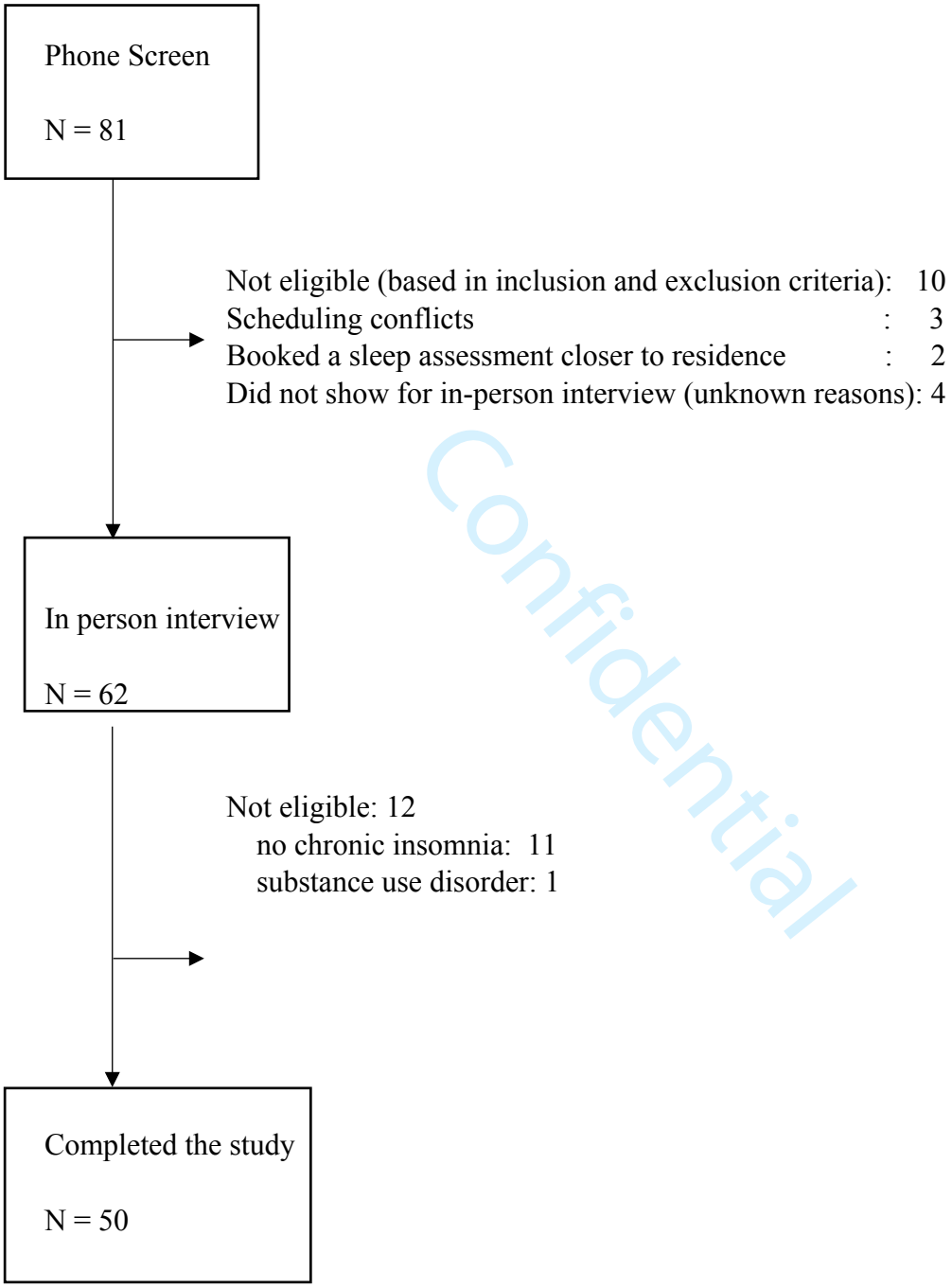
Table 5. *DLMO and Sleep Timing*

	No CRSWD (n = 37)		**DSWPD (n = 10)**		**Effect sizes (r)**
	Mean (*SD*)	95% BCa CI of the Mean	Mean (*SD*)	95% BCa CI of the Mean	
DLMO	20:24 (1.8)*	20:06 – 20:40	22:73 (0.63)*	22:18 – 23:18	.73
Bedtime	23:34 (0.8)*	23:17 - 23:50	24:55 (1.0) *	24:19 – 25:40	.58
Sleep onset time	24: 17 (0.9)*	24:01 – 24: 39	02:00 (1.0)*	01:26 – 02:36	.63
Sleep midpoint	03:50 (.53)*	03:41 - 04:03	05:20 (1.3)*	04:32 – 06:06	.81
Wake time	7:21 (0.5)*	7:14 – 7:34	8:41 (1.9)*	7:30 – 9:45	.73
Getting out of bed time	8:02 (0.6)*	7:53 – 8.18	9:41 (1.8)*	8:29 – 10:47	.80

Note: 95 BCa CI = 95% bias corrected accelerated confidence interval based on 1000 bootstrapping samples. * denotes statistically significant differences between the groups.

Time is in the International Organization for Standardization (ISO) 8601 format

Figure 1. *Participant Flow*



Circadian Rhythm – A Neglected Aspect of the Post-Concussion Insomnia Assessment

A Cross-sectional, Observational Study

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Abstract

Background: Insomnia is a major predictor of adverse outcomes in mild traumatic brain injury (mTBI), including concussion. Insomnia symptoms may be maintained by circadian rhythm sleep-wake disorders. While previous studies have focused on insomnia symptom assessment, we provide a diagnostic circadian workup in a homogeneous sample of patients with chronic insomnia symptoms following a mTBI. Detection and treatment of CRSWD may open a new avenue to facilitate recovery from mTBI. Objective: To determine the prevalence of CRSWD in individuals with chronic insomnia following a mTBI.

Methods: Individuals with mTBI (Glasgow Coma Scale 13-15) and chronic insomnia (Insomnia Severity Index > 11 and assessed in a clinical interview) were recruited from diverse community clinics 3 - 24 months post-injury to participate in this cross-sectional observational study. Potential participants (n = 81) were screened by phone and participated in an intake clinical interview (n = 62) before enrollment (n = 50). Exclusion criteria: (a) alcohol/ substance use problems; (b) pre-existing brain disorders/previous neurosurgery; (c) travelled across more than two time zones less than three weeks prior to the screening; (d) shift work schedule. Assessments (clinical interview, standard questionnaire; 2 weeks of actigraphy and sleep diary and dim light melatonin onset test) were conducted in a sleep and circadian clinic. Outcome measure: Percentage of patients with CRSWD.

Results: Among the 50 participants, (median age: 39.5 – IQR 23.8; 64% females) 26% had a CRSWD. The most common (77%) circadian diagnosis was delayed sleep-wake phase disorder. ~~with 56% prevalence in the 17-31 age group.~~

Interpretation: The prevalence of CRSWD is exceptionally high among individuals with chronic insomnia symptoms following a mTBI. Accurate diagnosis and treatment of these

disorders may improve the post-concussion recovery of approximately a quarter of all patients and half of adolescents and young adults who suffer from chronic insomnia following a mTBI.

Traumatic brain injury (TBI) – a brain trauma caused by an external mechanical force - is the leading cause of disability among young adults and has rising incidence rate in Canada, especially in the 18-34 age group (1, 2). Mild TBI (mTBI) - including concussion - constitute the majority (70-90%) of all treated TBI cases and has the largest contribution to the burden of injury-related disability (3). Early detection and effective management of medical conditions that hinder recovery could prevent disability and substantially reduce societal costs.

Difficulties with falling asleep, staying asleep or early morning final awakening (insomnia) are the most common persistent sleep symptoms after mTBI, including concussion (4, 5). Insomnia after concussion worsens fatigue, pain, cognition and mood and predicts poor overall prognosis for recovery (6-8). Since the disorders of sleep and wakefulness that cause chronic insomnia symptoms can be effectively treated, it becomes important to characterize and diagnose the sleep disorders that maintain insomnia symptoms after mTBI. Effective treatment of these disorders holds the promise of improving the management of persistent post-concussive symptoms and hastening recovery from mTBI.

Chronic insomnia is a shared symptom of circadian rhythm sleep-wake disorders ~~(CRSWD)~~; see Table 1. These disorders arise if there is a disruption of the endogenous circadian system or a misalignment between the internal circadian rhythm and the external environment. The best biological marker of ~~CRSWD~~circadian rhythm sleep-wake disorders is abnormal dim light melatonin onset (DLMO), while the behavioural diagnostic feature is that sleep phase is significantly delayed, advanced or irregular relative to environmental time and social norms.

A neuroimaging study suggests that mTBI may cause pineal gland injury and disrupt circadian regulation via its effect on melatonin secretion (9). Only one clinical study has performed diagnostic circadian assessment in a group of patients with mTBI hitherto (10). This

study selected 15 individuals from 42 sleep clinic patients with mTBI and insomnia; however, selection criteria were not provided; DLMOs were not reported; time since injury was not specified, and the age range was restricted to young and early-middle age adults. Each of the 15 patients was diagnosed with a ~~CRSWD~~circadian rhythm sleep-wake disorder -- 7 with delayed sleep-wake phase disorder ~~(DSWPD)~~ and 6 with irregular sleep-wake rhythm disorder ~~(ISWRD)~~. These results suggest that the prevalence of ~~CRSWD~~circadian rhythm sleep-wake disorders may be higher among mTBI patients with chronic insomnia symptoms than the known prevalence in relevant comparisons groups (i.e. sleep clinic insomnia samples) but the above shortcomings limit the interpretability of the above results.

Given that ~~CRSWD~~circadian rhythm sleep-wake disorders require specific circadian assessment and treatment, it is pertinent to establish if patients with mTBI and insomnia symptoms comprise one of the few clinical groups where ~~CRSWD~~circadian rhythm sleep-wake disorders are prevalent. If this is the case, circadian assessment and treatment becomes an important part of chronic insomnia work-up and management following mTBI.

Objective and Hypothesis

The objective was to determine the rate of ~~CRSWD~~circadian rhythm sleep-wake disorders according to standard diagnostic criteria using evidence-based comprehensive assessment – including actigraphy and DLMO - in a large consecutive and representative sample of individuals with chronic insomnia following mTBI. The hypothesis was that ~~CPSWD~~ circadian rhythm sleep-wake disorders would be more common in this clinical group than it is in individuals who seek treatment for chronic insomnia in sleep clinics (5-10%) (11).

Method

Participants. Participant characteristics are summarized in Table 2. Inclusion criteria: (a) mTBI (Glasgow Coma Score ≥ 13 at the time of injury) three to 24 months prior to the screening assessment; (b) chronic insomnia symptoms that started or significantly amplified following the injury; (c) age between 17 and 65 years. When participants had multiple concussions, the mTBI after which the sleep problem started was in the time frame of three to 24 months. Exclusion criteria: (a) had alcohol or other substance use problems within three months prior to enrollment based on DSM 5 criteria; (b) needed immediate psychiatric help based on in-person assessment; (c) had pre-existing brain disorders or neurosurgery; (d) had travelled across more than two time zones less than three weeks prior to the phone screening; or (e) had a shift work schedule.

Procedures. Information of the study was distributed widely to hospitals and community clinics in South Ontario, in the Georgian Bay and Sudbury areas and it was published on brain injury organization and sleep clinic websites (Referral sources are summarized in Table 2). We received 81 referrals within the 12-month recruitment phase. Following phone screens, a semi-structured interview and completion of the Insomnia Severity Index, however, 22 were ineligible. Another 5 had scheduling or assessment conflicts, and four failed to show in person. Nobody needed to be excluded for reasons of shift work, travel across time zones or psychiatric conditions (Figure 1). Thus, final enrollment comprised 50 patients with mTBI and chronic insomnia symptoms. In the subsequent 12-14 days after their enrollment, participants kept a sleep diary and wore an actiwatch on their non-dominant wrist. Finally, they participated in a DLMO test in 12-14 days following their initial interview.

Assessment tools and methods.

Insomnia Assessment:

The *Duke Structured Interview for Sleep Disorders* (DSISD) assesses sleep disorders according to clinical and research diagnostic criteria (12). The study used an updated version of the DSISD in which the insomnia section has been modified to match the new DSM 5 criteria. The DSISD was used to select individuals with chronic insomnia.

The *Insomnia Severity Index* (ISI; Morin, 1993) measures the subjective severity of insomnia symptoms (13, 14). The degree of insomnia severity is determined by the summary scores of seven items as follows: 0 to 7 -no clinical insomnia; 8 to 14- "sub-threshold" insomnia; 15 to 21 -moderate insomnia; and 22 to 28 is severe insomnia. A summary score of 11 has been recommended as a cut-off for screening for clinical insomnia research and was used as cut-off for inclusion in this study (15).

Assessment of sleep pattern:

Wrist Actigraphy is a recommended diagnostic assessment tool for ~~CRSWD~~circadian rhythm sleep-wake disorders (11). Participants wore a Philips Respironics Actiwach 2 on their non-dominant wrist (16). The device detects movement using a solid piezoelectric accelerometer with 0.35-7.5Hz bandwidth and 0.5-2G peak value. The device was set to record 30-second epochs at medium sensitivity to detect wake threshold. Data were scored both automatically and manually. Manual scoring involved setting the "rest period" (the period between bedtime and rise time). Rest time was set based on event markers (participants marked their bedtime and rise time using the event marker function of the actiwatch) as well as movement, light and sleep diary data. After the rest periods were set, the Actiware 6.0.7. software calculated all the sleep parameters, including sleep onset latency, wake after sleep onset, total sleep time and sleep efficiency.

The *Consensus Sleep Diary* was developed to provide a standard sleep log based on patients' input and expert consensus (17). The sleep indices in the Consensus Sleep Diary differentiate between individuals with insomnia and good sleepers and are significantly correlated with the ISI and with actigraphy measures (18). The diary was used in the study for longitudinal subjective assessment of sleep pattern.

Assessment of circadian phase:

Dim Light Melatonin Onset Test (DLMO)Test. Eight saliva samples were collected from each participant according to standard procedures (Buhlmann EK DSM © Saliva Melatonin ELISA kit; Buhlmann Laboratories, Switzerland). Light level was maximum 10 lux in the room. The three baseline samples were taken every 30 minutes and the remaining samples were collected hourly. Data collection started six hours before habitual bedtime, which was determined based on participants' self-report and was verified from their sleep-diary data. Medications that influence melatonin levels were prohibited/discontinued before the test.

All assessors (except for the first author) were blind to the study hypothesis.

Missing data. Two participants had missing actigraphy data but both provided sleep diary data that could be used to determine if they had a normal sleep phase. Altogether, 47 of the 50 participants completed the DLMO test. DLMO could not be precisely determined from five samples (in three DLMO was outside of the measurement period and there were technical problems with two samples).

Analyses

Saliva samples were frozen and analyzed using enzyme-linked immunosorbent assay as per manufacturer's instructions (Buhlmann EK DSM © Saliva Melatonin ELISA kit; Buhlmann Laboratories, Switzerland). The intra-assay and inter-assay coefficients of variation were 7.62

and 8.88. As per consensus guidelines, DLMO was determined as the clock time, when the melatonin concentration reached and remained above the threshold (two *SD* above the baseline or, when there were fewer than 3 baseline values, an absolute value of 3 pg/ml), (19).

Descriptive statistics summarized the sample characteristics, questionnaire scores, the frequency of ~~CRSWD~~ circadian rhythm sleep-wake disorders ~~-~~diagnoses and the relationship between ~~CRSWD~~ circadian rhythm sleep-wake ~~-diagnose~~disorders diagnoses~~s~~ and demographic data. Independent samples t tests, using bootstrapping with 1000 re-samples compared the sleep diary and DLMO data of patients with delayed sleep-wake phase disorder ~~DSWPD~~ and those without ~~CRSWD~~ circadian rhythm sleep-wake disorders ~~-~~(there were not enough individuals in the other sub-groups of ~~CRSWD~~ circadian rhythm sleep-wake ~~-t~~disorders too~~o~~ allow statistical comparisons). Statistical significance was set at $p \leq .008$ to correct for multiple comparisons.

~~CRSWD~~ Circadian rhythm sleep-wake disorders ~~-~~were diagnosed according to International Classification of Sleep Disorders (ICSD 3) criteria (11). The 95% confidence intervals (CIs) for the prevalence rates are based the corresponding precision afforded by our final sample size (N=50), (20).

Results

Most ($N = 46$ or 92%) participants had moderate/severe insomnia symptoms (ISI $\geq$ 15), while the remaining patients reported mild insomnia symptoms. Three quarters of the sample denied having subjective sleep problems or sleep disorders prior to their injury and 100% reported moderate or significant worsening of their sleep since the injury.

One-quarter (13 patients) of the 50 participants received a ~~CRSWD~~ circadian rhythm sleep-wake disorder diagnosis (Table 3), corresponding to a prevalence of 26% ± 12%. The most common diagnosis (10 patients) was ~~DSWPD~~ delayed sleep-wake phase disorder; nine of these

individuals were younger than 32 years (Table 4). All of those with advanced sleep-wake phase disorder ~~ASWPD~~ and ~~ISWRD~~ irregular sleep-wake rhythm ~~wer~~disorder were~~e~~ over 40.

There were large and significant differences both in the subjective behavioural (sleep diary) and objective, biological (DLMO) timing of sleep and circadian rhythm between patients with delayed sleep-wake phase disorder ~~DSWRD~~ and those without a ~~CRSWD~~ circadian rhythm sleep-wake disorder (Table 45), confirming that the clinical diagnoses accurately separated patients with delayed sleep-wake phase disorder ~~DSWRD~~ from those without a circadian disorder.

Interpretation

The objective of this study was to determine what percentage of patients whose main sleep symptom is chronic insomnia following a mTBI have a ~~CRSWD~~ circadian rhythm sleep-wake disorders. The results supported the a-priori hypothesis: 26 % of the full sample received a circadian rhythm sleep-wake disorder~~CPSWD~~ diagnosis.

Most (77%) of these participants had ~~DSWPD~~delayed sleep-wake phase disorder. This proportion is one-two orders of magnitude higher than the prevalence of ~~DSWPD~~ delayed sleep-wake phase ~~i~~disorder in~~n~~ the general population (0.17% – 1.53%) and over three times that among patients with chronic insomnia treated at sleep clinics (6.7 %) (21-23). Notably, delayed sleep-wake phase disorder ~~DPSWD~~ was the most common sleep disorder diagnosis in the 18-31 age group with a 10-fold prevalence compared to the prevalence of ~~DSWPD~~ delayed sleep-wake phase disorder in the general adolescent population (11, 24-26).

This study did not explore the causes of ~~DSWPD~~ delayed sleep-wake phase disorder but several etiological factors merit consideration. One MRI study noted that patients who had sleep problems following a mTBI had a longer tentorium and a flatter tentorial angle than patients who

did not have sleep problems. The authors speculated that the pineal gland (the secretion site of melatonin) would be impacted by injuries caused by an anterior – posterior force in individuals with this anatomical predisposition (27).

Another biological predisposing factor could be a susceptibility of the sleep and circadian system for phase delay due to a long circadian period, heightened responsiveness to the melatonin supressing effect of light in the evening; or slow accumulation and dissipation of homeostatic sleep drive – mechanisms that have been implicated in the etiology of ~~DSWPD~~ delayed sleep-wake phase disorder (28). If the social demand to wake up early in the morning lessens during the post injury recovery period, the sleep phase follows the circadian signals and shifts to later hours in individuals with a predisposition for phase delay. This can lead to a vicious cycle, in which longer light exposure in the evening and lack of light exposure in the morning further delays the circadian cycle (29).

It is also possible that individuals with a pre-injury delayed DLMO or evening chronotype are at an increased risk for sustaining a TBI, because they are sleepy in the morning when they attend sport training, school or work. Athletic performance fluctuates across the circadian cycle and excessive sleepiness impacts cognitive performance and increases the risk for accidents and injuries (30-36). Thus, the high prevalence of ~~DSWPD~~ delayed sleep-wake phase disorder in mTBI/concussion samples may, in part, reflect a higher prevalence of TBI among individuals with a late DLMO and evening chronotype.

Two participants in this study received a diagnosis of ~~ASWPD~~ advanced sleep-wake phase disorder. The prevalence of ~~ASWPD~~ advanced sleep-wake phase disorder is very low both in the general population or in clinical insomnia samples, given that only individual cases and family cohorts have been described thus far (11, 22). In the current study, none of the

participants with ~~ASWPD~~ advanced sleep-wake phase disorder ~~-~~had a family history of ~~ASWPD~~ advanced sleep-wake phase disorder.

Finally, one participant was diagnosed with ~~ISWRD~~ irregular sleep-wake rhythm disorder. This circadian rhythm sleep-wake disorder ~~CPSWD~~ has previously been described among individuals with brain pathology (11). The person in the present study with ~~ISWRD~~ irregular sleep-wake rhythm disorder ~~-~~reportedly had an alcohol use disorder until six months before the injury. There is an interaction between the circadian system and alcohol use disorders and it is possible that pre-injury alcohol use disorder increases the risk for developing an irregular sleep-wake rhythm disorder ~~ISWRD~~following a brain injury (37).

Clinical implications. Awareness of ~~CRSWD~~ circadian rhythm sleep-wake disorders is generally low among clinicians but distinguishing it from insomnia disorder is crucial since the treatment of insomnia disorder (cognitive behavioural therapy or selected hypnotic medications) and the management of ~~CRSWD~~ circadian rhythm sleep-wake disorders ~~-~~(melatonin and bright light therapy) are fundamentally different.

The results of this study suggest that clinicians should be attentive to symptoms of ~~CRSWD~~ circadian rhythm sleep-wake disorders ~~-~~when they see patients with persistent insomnia symptoms following a mTBI, including concussion. Referral for a circadian assessment is warranted if there is a significant shift of the sleep period or if the patient sleeps only for short (maximum 4 hour) periods around the clock. The threshold for referring to a circadian assessment should be especially low if a teenager or young adult reports significant sleep onset insomnia or a delay of sleep phase following a mTBI.

This study is the first to provide a rigorous multi-method diagnostic circadian assessment based on standard criteria in a representative sample of patients with mTBI and chronic

insomnia. Previous circadian studies have included patients with moderate and severe TBI; assessed melatonin secretion without determining DLMO; or determined average DLMO in a group of patients without providing diagnostic assessment and interpretation in samples that were substantially smaller than the current sample (4, 10, 38-42). The standard clinical intake assessment at least three months after the TBI ensured that a homogeneous sample of individuals with chronic insomnia symptoms were included.

In addition to the strengths of this study, some limitations should be considered. Firstly, the sample may over-represent patients who were distressed by their insomnia symptoms. At the same time, these are the patients who (ideally) would receive some form of post-concussion sleep assessment in the community. Secondly, individuals with substance use disorders and shift workers were not recruited. It is likely that the frequency of ~~CRSWD~~ circadian rhythm sleep-wake disorders is higher in those groups. Also, participants may not have reported insomnia symptoms that pre-dated the injury. This does not bias the diagnoses but precludes inferences about the possible role of the injury.

The results of this study apply to treatment seeking patients with chronic insomnia symptoms who had a mTBI between three months and 24 months before the sleep assessment. The percentage of circadian rhythm sleep-wake disorders may be different among individuals who do experience insomnia symptoms following the TBI, but who do not seek help in managing post-concussion or sleep symptoms, or who had a TBI more than two years before a sleep assessment.

The current sample size was limited by logistical constraints and this hampered the precision of the estimated prevalence rates; this was particularly true for the subsample analyses

regarding specific circadian rhythm sleep-wake disorders and those within young and older age groups. Future studies should assess circadian rhythm sleep-wake disorders in larger mTBI samples with insomnia. Finally, this study did not include an age and sex-matched comparison group of patients with chronic insomnia who did not have a history of TBI. Future replication of this study will benefit from an inclusion of such groups to allow for more direct comparison of rates and on the sleep-wake measures. Given that research on circadian rhythm sleep-wake disorders among patients with insomnia alone is limited, these studies will add valuable information not only for those with TBI, but also to the general insomnia and circadian rhythm sleep-wake disorder literature.

It is important to emphasise that the current study did not aim to establish a cause and effect relationship between the clinical diagnoses and the injury or control for variables that may have influenced this relationship. We took a rigorous clinical approach because there is a need to generate reliable diagnostic information which can inform clinical guidelines for insomnia assessment in this clinical group. Without clinical guidelines that are based on research evidence, patients with insomnia will not an receive evidence-based insomnia assessment and treatment after a concussion. The results of this study have direct clinical implications in that they draw attention to the need to assess ~~CRSWD~~ circadian rhythm sleep-wake disorders in patients who suffer from chronic insomnia following a mTBI. Circadian assessment is currently not part of a standard post-concussion insomnia workup and is not a routine component of sleep clinic assessments. Consequently approximately 25% of patients with post-concussion chronic insomnia symptoms (based on the results of the current study) would not receive an appropriate diagnosis and thereby tailored treatment for their sleep difficulty which in turn leads to lower likelihood of recovery (6-8). Future longitudinal studies should identify factors that predispose

individuals for developing ~~CRSWD~~ circadian rhythm sleep-wake ~~afte~~disorders after~~r~~ a concussion and test the nature and direction of pathways between the circadian timing of sleep and wakefulness and factors that may influence this relationship in mTBI in different age groups.

Summary and Conclusions. One quarter of treatment-seeking individuals with post-concussion chronic insomnia symptoms ~~had~~ were diagnosed with a ~~CRSWD~~circadian rhythm sleep-wake disorder. ~~The majority of these patients were adolescents and young adults with 56% prevalence of DPSWD in this age group.~~ This implies that clinicians may include circadian rhythm sleep-wake disorders in their diagnostic algorithm and consider the potential benefits of ~~should initiate~~ a circadian assessment when patients report insomnia symptoms and a significant change in their sleep phase following a mTBI. The majority of these patients were adolescents and young adults with approximately 50% prevalence of delayed phase sleep-wake disorder in this age group; this finding warrants larger-scale replication. Given that insomnia symptoms are major predictors of poor post-concussion recovery, detection and effective management of ~~CRSWD~~ circadian rhythm sleep-wake disorders may improve the recovery ~~of approximately a quarter of all patients and half of~~particularly in adolescents and young adults who suffer from chronic insomnia following a mTBI.

Author Contributions

1. Dora M. Zalai made substantial contributions to conception and design of the work, as well as to the acquisition, analysis, and interpretation of data for the work. She made a significant contribution to drafting of the work, revising it critically for important intellectual content and final approval of the version to be published. She agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
2. Todd A. Girard made substantial contributions to design of the work, as well as to the analysis and interpretation of data for the work. He made a significant contribution to revising the manuscript for important intellectual content and final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
3. Michael D. Cusimano made substantial contributions to design of the work as well as to the interpretation of data for the work. He made a significant contribution to revising the manuscript for important intellectual content and final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
4. Colin M. Shapiro made substantial contributions to design of the work, as well as to the acquisition and interpretation of data for the work. He made a significant contribution to revising the manuscript for important intellectual content and final approval of the version to be published. He agrees to be accountable for all aspects of the work in ensuring that

questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table 1. *Key Features of the Circadian Rhythm Sleep-Wake Disorders Diagnosed in this Study*

Circadian Disorder	Characteristic sleep pattern	Main clinical features	Epidemiology	Treatment
Delayed sleep-wake phase disorder	Delayed main sleep episode (usually by at least two hours) relative to the socially desired or required sleep time.	• Sleep initiation insomnia and difficulty with waking when sleep schedule is socially imposed, but significantly improved sleep when sleep schedule is freely chosen. • Excessive sleepiness in the morning. • Risk for the development of mood disorders.	• Usually starts in adolescence. • Prevalence in general population: 0.17% - 1.53% • 5-10% of individuals with chronic insomnia in sleep clinics	• Strategically timed oral melatonin based on DLMO[c,ad,a] • Post-awakening light therapy in conjunction with behavioral treatment [c,ad]

Advanced sleep-wake phase disorder	Advanced main sleep episode (at least by two hours) relative to the socially desired or required sleep time	• Inability to stay awake until the socially desirable time in the evening and inability to remain asleep until a socially desirable wake time. • Excessive sleepiness in the evening.	• Approximately 1% of the general population has advanced sleep phase • Prevalence of advanced sleep-wake phase diosrder in the general population and in sleep clinic insomnia samples is unknown but thought to be rare.	• Evening light therapy
Irregular sleep-wake rhythm disorder	Irregular sleep episodes typically shorter than 4 hours; total 24 h sleep duration can be normal.	• Insomnia at night and excessive sleepiness during the day.	• Described in neuro-developmental and neuro-degenerative disorders and after TBI.	• Light therapy in elderly patients with dementia • Melatonin [c, ad]

Note: TBI: traumatic brain injury; DLMO: dim light melatonin onset; c: children; ad: adolescents; a: adults

Table 2. *Participant Characteristics*

	No (%)	Median (IQR)	Min-max
Age (years)		39.5 (23.8) 25th percentile: 28 75th percentile: 51	17- 62
Gender			
Male	18 (36)		
Female	32 (64)		
Education			
High school	13 (26)		
College	12 (24)		
University	25 (50)		
Employment status			
Full time	21 (42)		
Part time	5 (10)		
Student	4 (8)		
Unemployed	8 (16)		
Sick leave/disability	11(22)		
Retired	1 (2)		
Number of concussions			
Single	32 (64)		
Multiple	18 (36)		
Time since the injury* (months)		11.5 (12) 25th percentile: 8 75th percentile: 20	3 - 27

Table 2. *Participant Characteristics (continued from previous page)*

	No (%)	Median (IQR)	Min-max
Cause of injury			
Car accident	18 (36)		
Sport injury	18 (36)		
Fall	9 (18)		
Object hit the head	2 (4)		
Physical assault	2 (4)		
Workplace injury	1 (2)		
Referral source			
Head injury clinic	18 (36)		
Family medicine clinic	16 (32)		
Concussion/sport clinic	6 (12)		
Sleep clinic	4 (8)		
Speech-language pathologist, neurologist, physiotherapist, emergency specialists	2 (4)		

Note: * Time elapsed since the injury. If a participant had multiple concussions, it is time elapsed since the injury that preceded the onset of the sleep problem. ~~Number of concussions: includes the one that preceded the sleep problem.~~ IQR = interquartile range

Table 3. *Circadian Rhythm Sleep-Wake Disorder Diagnoses*

	ASWPD	DSWPD	ISWRD	No CRSWD
In the full sample (n = 50)	4 ± 5%	20 ± 11%	2 ± 4%	74 ± 12%
In participants ≤ 31 years (n = 16)	0%	50± 25%	0%	50 ± 25%
In participants > 31 years (n = 34)	6 ± 8%	3 ± 6%	3 ± 6%	88 ± 11%

Note: Data represent the prevalence in percentages ± 95% CI. ASWPD = advanced sleep-wake phase disorder, DSWPD = delayed sleep-wake phase disorder, ISWRD = irregular sleep-wake rhythm disorder, CRSWD = circadian rhythm sleep-wake disorder

Table 4. *Age, Gender and Employment Status of Participants without a Circadian Rhythm Sleep-Wake Disorder and Participants with Delayed Phase Sleep Wake Disorder*

	Without CRSWD (N = 37)			**DPSWD (N = 10)**		
	No (%)	Median (IQR)	Min-max	No (%)	Median (IQR)	Min-max
Age (years)		40 (23.5) 25th percentile: 31 75th percentile: 54	17 - 62		26 (11) 25th percentile: 20.5 75th percentile:30	17 - 54
Gender						
Male	18 (36)			5 (50)		
Female	32 (64)			5 (50)		
Employment status						
Full time	17 (46)			3 (30)		
Part time	2 (5)			2 (20)		
Student	3 (8)			1 (10)		
Unemployed	5 (14)			3 (30)		
Sick leave/disability	9 (24)			1 (10)		
Retired	1 (3)			0 (0)		

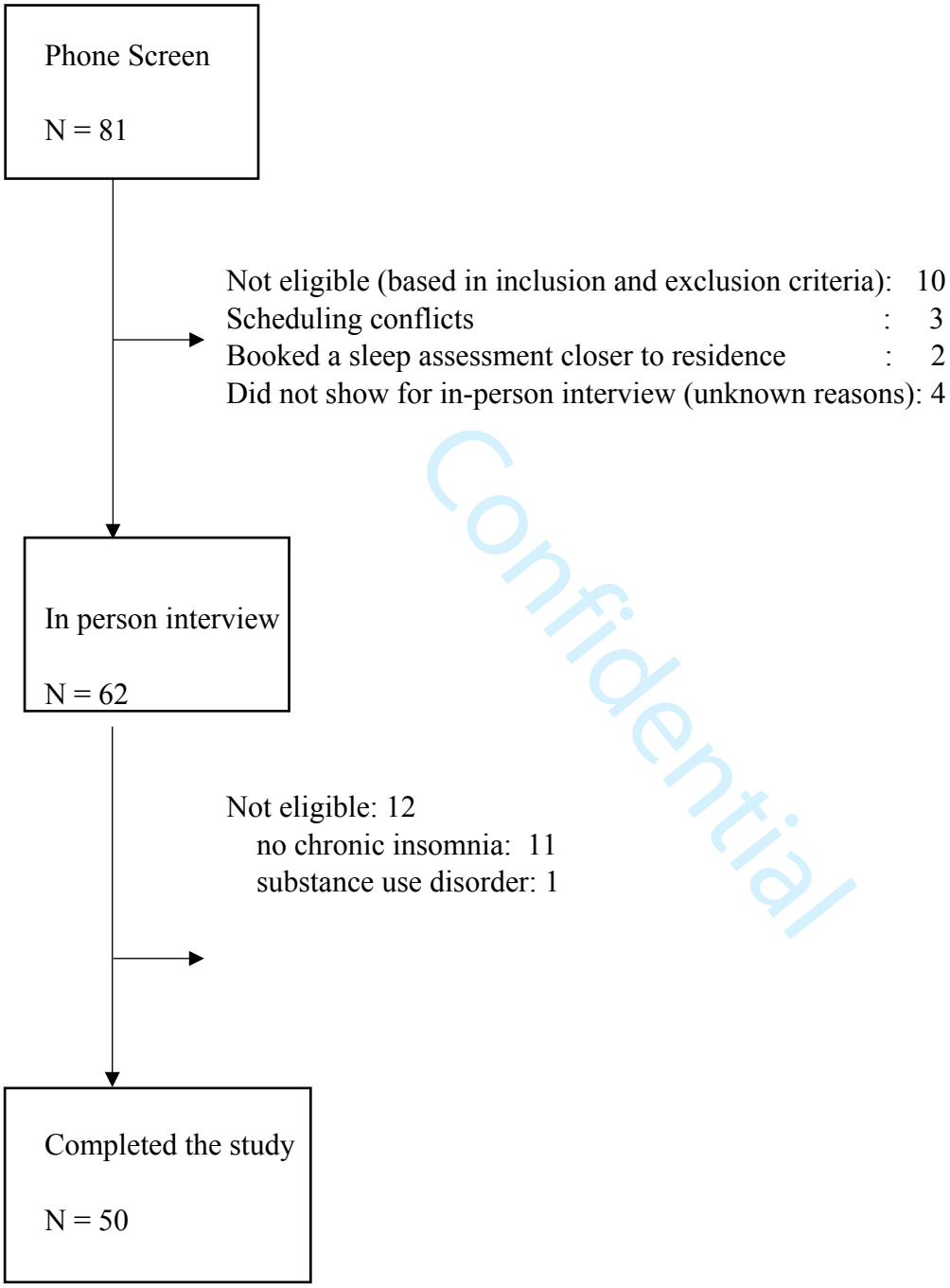
Table 45. *DLMO and Sleep Timing*

	No CRSWD (n = 37)		**DSWPD (n = 10)**		**Effect sizes (r)**
	Mean (*SD*)	95% BCa CI of the Mean	Mean (*SD*)	95% BCa CI of the Mean	
DLMO	20:24 (1.8)*	20:06 – 20:40	22:73 (0.63)*	22:18 – 23:18	.73
Bedtime	23:34 (0.8)*	23:17 - 23:50	24:55 (1.0) *	24:19 – 25:40	.58
Sleep onset time	24: 17 (0.9)*	24:01 – 24: 39	02:00 (1.0)*	01:26 – 02:36	.63
Sleep midpoint	03:50 (.53)*	03:41 - 04:03	05:20 (1.3)*	04:32 – 06:06	.81
Wake time	7:21 (0.5)*	7:14 – 7:34	8:41 (1.9)*	7:30 – 9:45	.73
Getting out of bed time	8:02 (0.6)*	7:53 – 8.18	9:41 (1.8)*	8:29 – 10:47	.80

Note: 95 BCa CI = 95% bias corrected accelerated confidence interval based on 1000 bootstrapping samples. * denotes statistically significant differences between the groups.

Time is in the International Organization for Standardization (ISO) 8601 format

Figure 1. *Participant Flow*



STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,9
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	7-8
Bias	9	Describe any efforts to address potential sources of bias	response to reviewers
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
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	6, 30
		(b) Give reasons for non-participation at each stage	30
		(c) Consider use of a flow diagram	30
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	25-26
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	9-10 27

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	9, 27
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, 28-29
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
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	13-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12 14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
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	1

*Give information separately for exposed and unexposed groups.

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.