THE RELATIONSHIP BETWEEN SLEEP AND CONCUSSION RECOVERY

by

NICOLE L. HOFFMAN

(Under the Direction of Julianne D. Schmidt)

ABSTRACT

The effects of sleep on concussion recovery are not well understood, thus are not commonly assessed or considered during concussion management. The purpose of this study was to determine the relationship between sleep and concussion recovery. Participants completed a demographic form and graded symptoms checklist at two time-points: (concussed: within 72 hours post-injury, within 48 hours of symptom recovery; non-concussed: initial visit, follow-up visit). Participants were instrumented with a validated wrist-worn ActiGraph GT9X accelerometer to wear continuously until: 1) symptom recovery (concussed), 2) follow-up (non-concussed). Two versions (original and modified questions) of each subjective sleep questionnaire, the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS), were administered to concussed individuals once they experienced symptom recovery to assess sleep since concussion and during the month prior to concussion. This study indicates that greater amounts of time spent awake each night and poorer sleep efficiency at mid-point of recovery, greater sleep duration towards the end of recovery, and poorer self-reported sleep quality post-injury may be associated with the number of days to symptom recovery. Actigraphy and subjective sleep questionnaires may separately provide unique information to guide future research in the next step of exploring benefits of sleep interventions to expedite recovery.

INDEX WORDS: Sleep, Symptom recovery, Concussion, Sleep disturbances, Actigraphy, Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale

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NICOLE L. HOFFMAN

B.S., University of Delaware, 2004

M.S., James Madison University, 2006

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NICOLE L. HOFFMAN

Major Professor:	Julianne Schmidt
Committee:	Patrick O'Connor
	Michael Schmidt
	Robert Lynall

Electronic Version Approved:

Suzanne Barbour
Dean of the Graduate School
The University of Georgia
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DEDICATION

I would like to dedicate this dissertation to my parents. Without their love and constant support throughout this journey, I would not have had the strength to make it this far. You are my rock and my foundation. I love you both.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Page

CHAPTER 1

INTRODUCTION

Background

Sport-related concussion, defined as “a traumatic brain injury induced by biomechanical forces” (McCrory et al., 2017), is a major public health concern worldwide (Kelly, 1999). Concussions are diffuse injuries that include a wide range of clinical signs and symptoms, and typically result in a rapid onset of temporary neurological function impairment as opposed to a structural injury (McCrory et al., 2017). As many as 3.8 million concussions occur each year as a result of sport and physical activity (Langlois, Rutland-Brown, & Wald, 2006), which may be a low estimate since concussions have a potential to go unrecognized, therefore are not taken into account (Llewellyn, Burdette, Joyner, & Buckley, 2014; McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). Concussions are among “the most complex injuries to diagnose, assess, and manage” (McCrory et al., 2017).

The medical community widely recognizes clinical symptoms including, but not limited to, headaches, dizziness, feeling like in a fog, and increased irritability post-injury (Harmon et al., 2013; Lovell et al., 2003; McCrory et al., 2017). Physical signs (i.e. loss of consciousness and difficulties remembering events prior to and following injury), gait unsteadiness, and poor performance on cognitive-related tasks (i.e. memory and reaction time) may also be evident following concussion (McCrory et al., 2017). However, sleep disturbances are given less attention clinically. A growing body of literature suggests that as many as 70% of concussed athletes report sleep disturbances, fatigue, daytime sleepiness, or vigilance disturbances after a concussion (Gosselin et al., 2009; Parcell, Ponsford, Rajaratnam, & Redman, 2006). Despite this evidence, sleep is not commonly assessed or considered when managing concussion recovery, which may be an important missing piece in concussion management, since abnormalities in sleep components such as duration, quality, and efficiency may negatively impact symptom severity, cognition, and balance post-injury. Sleep may be a critical variable in treatment to assist with recovery following concussion.

Traditionally, sleep disturbances have been identified as a post-concussive symptom, however, sleep may have more of an active role. Among healthy individuals, sleep has been found to be pertinent in the maintenance of cognitive functions including learning, memory formation, and neural plasticity (Carrier, 2014; Ron, Algom, Hary, & Cohen, 1980). One study showed that by addressing proper sleep hygiene, brain energy restoration significantly improved, thus enhancing memory components, such as acquisition, consolidation, and integration (Cirelli & Tononi, 2015), which may serve as a key factor in brain recovery. Makley et al. found that healthy individuals who were more efficient at sleeping (represented by the ratio of total time spent sleeping at night over the total time spent in bed) exhibited greater memory improvement (Makley et al., 2009). Studies focusing on the effects of increasing the number of hours of sleep in young adults demonstrated a significant improvement in areas such as reaction time, daytime alertness, and mood (Kamdar, Kaplan, Kezirian, & Dement, 2004; Mah, Mah, Kezirian, & Dement, 2011). Individuals that nap during daytime have also shown improvement in reaction and alertness after sleep loss (Dinges, Orne, Whitehouse, & Orne, 1987). Better sleep has provided many benefits to healthy individuals in the areas of reaction time and memory formation and has also shown to have the opposite effect in those with poor sleep quality.

The cognitive deficit and symptom recovery period typically takes 10-14 days, on average, among collegiate athletes (McCrory et al., 2017). Due to the variability of symptom presentation among individuals, clinical concussion assessments and treatment recommendations continue to be challenging (Pardini et al., 2012), especially with regards to sleep disturbances and rest. Acute rest broadly serves as a foundation to recovery during the initial days (24-48 hours) post-injury (McCrory et al., 2017). Physical and cognitive rest may ease symptom severity and promote recovery (McCrory et al., 2017). However, the amount and type of rest remains unclear due to limited literature on the effects of sleep following concussion. It is unclear if clinicians should prescribe sleep throughout recovery when managing concussions.

When conducting preseason baseline assessments, several researchers have found that among healthy college student-athletes with poorer sleep quality the night before testing, experienced an increased number of self-reported symptoms, as well as symptom severity scores due to fewer hours of sleep relative to others (Kostyun, Milewski, & Hafeez, 2015; McClure, Zuckerman, Kutscher, Gregory, & Solomon, 2014; Mihalik et al., 2013). Sleep deprivation and excessive sleepiness may lead to worsening headache, poorer cognitive function, and declines in balance performance (Degache et al., 2016), which may hinder the brain's ability to optimally perform everyday activities (Duclos, Beauregard, Bottari, Ouellet, & Gosselin, 2015; Duclos et al., 2014; Mihalik et al., 2013). Excessive sleepiness may increase daytime napping, thus affecting overall nighttime sleep quality (Ponsford, Parcell, Sinclair, Roper, & Rajaratnam, 2013).

Few studies exist on the effects of sleep immediately following concussion. Recent research examining sleep duration post-injury compared to baseline sleep duration has identified associations between shorter sleep duration and 1) increased symptom severity and 2) poorer cognitive function (Hoffman et al., 2017). Concussed individuals who slept less acutely following injury self-reported greater symptom severity scores until they were deemed asymptomatic (Hoffman et al., 2017). Additionally, concussed individuals with shorter sleep duration experienced a slower reaction time even once asymptomatic compared to individuals with no sleep change compared to baseline and those who slept longer post-injury. Sleep may be a factor that affects concussion recovery, including the days to symptom resolution, days to neurocognitive deficit resolution, and days to balance deficit resolution. Individuals with poor sleep quality following concussion may experience persistent symptoms, however, the relationship between sleep and concussion recovery remains unclear. The ability to identify the influence of sleep on concussion recovery is important to determine the utility of providing treatment recommendations based on sleep hygiene to facilitate concussion recovery.

Sleep disturbances are commonly identified by clinicians using subjective sleep questionnaires. The Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds Iii, Monk, Berman, & Kupfer, 1989) and the Epworth Sleepiness Scale (ESS) (Johns, 1991), have been widely used to evaluate sleep disturbances across a range of age groups (Gosselin et al., 2009; Mantua, Mahan, Henry, & Spencer, 2015; Schmidt et al., 2015; Williams, Lazic, & Ogilvie, 2008). The Pittsburgh Sleep Quality is a reliable and valid subjective sleep assessment (Buysse et al., 1989) that assesses seven sleep components: duration of sleep, sleep disturbances, sleep onset latency, day dysfunction, sleep efficiency, overall sleep quality, and use of sleeping medication (Buysse et al., 1989). Global scores are used to categorize individuals as having good or poor (>5) sleep quality. The Epworth Sleepiness Scale (ESS) identifies a subject's habitual “likelihood of dozing or falling asleep” in common situations of daily living (Johns, 1991; Mondal, Gjevre, Taylor-Gjevre, & J. Lim, 2013). By utilizing subjective measures such as the

PSQI and ESS as a mean to characterize the degree of sleep disturbances, it may be possible to identify relationships between sleep quality and concussion recovery.

Objective measures such as polysomnography (gold standard) and actigraphy have been utilized to evaluate sleep disturbances. Through the use of wrist-worn accelerometers, actigraphy is a valid and useful tool compared to polysomnography to detect sleep-wake disturbances, and is commonly used to assist in determining multi-day sleep patterns through continuous recordings for 24-hour periods (Ancoli-Israel et al., 2003; Sadeh, Hauri, Kripke, & Lavie, 1995). It has a sensitivity of >90% when measuring sleep duration relative to polysomnography amongst healthy individuals (Jean-Louis, Kripke, Mason, Elliott, & Youngstedt, 2001). Individuals can be evaluated in their natural sleeping environment, thus eliminating laboratory effects that have been suspected of altering routine sleep patterns (Ancoli-Israel et al., 2003). Surprisingly, despite the prevalence of sleep disturbances identified post-concussion, literature on actigraphy in concussed college students is currently limited.

Statement of the Problem

Sleep is necessary in the maintenance of many cognitive, physical, and psychological functions (Chiu, Chen, Chen, Chuang, & Tsai, 2013; Mah et al., 2011) and may serve as a key factor in brain injury recovery. A growing body of literature is examining sleep-wake disturbances following concussion in college students (Chiu et al., 2013; Gosselin et al., 2009; Raikes & Schaefer, 2016), but the relationship between sleep and concussion is not well understood. Current concussion consensus recommendations broadly address acute rest (within 24-48 hours) following concussion (McCrory et al., 2017), but it is unknown if sleep could be considered in this category as beneficial to concussion recovery. Studies have primarily been retrospective in nature, with a few small sample studies addressing prospective sleep acutely following concussion. Sleep may be an important missing piece in concussion management, since abnormalities in sleep components such as duration, quality, and efficiency may negatively impact symptom severity.

Statement of Purpose

The overall purpose of this study is to determine the relationship between sleep, as measured by objective and subjective measures, and symptom recovery.

Aims and Hypotheses

Aim 1: Concussed vs. Non-Concussed Individuals

1a. To describe and compare sleep, *as measured by actigraphy*, between concussed and non-concussed individuals throughout symptom recovery.

1b. To describe and compare sleep, *as measured by subjective sleep questionnaires*, between concussed and non-concussed individuals throughout symptom recovery.

H1a-b: Concussed participants will experience greater sleep disturbances, based on actigraphy and subjective sleep questionnaires, throughout symptom recovery compared to non-concussed participants.

Actigraphy

Independent Variables:

- Group:
  - Concussed
  - Non-Concussed
- Days across recovery
  - 72 hours post-injury
  - Mid-point of recovery

    - Within 48 hours of recovery

Dependent Variables:

- Sleep onset latency (min.)
- Sleep efficiency (%)
- Total sleep time (min.)
- Wake after sleep onset (%)
- Number of awakenings per hour throughout the night

<u>Subjective Sleep Questionnaires</u>

Independent Variable:

- Group:
    - Concussed
    - Non-Concussed

Dependent Variables:

- Pittsburgh Sleep Quality Index (PSQI) global scores
- Epworth Sleepiness Scale (ESS) total scores
- SCAT3 Sleep Cluster (drowsiness and trouble falling asleep)

Aim 2: Concussed Individuals

2a. To determine the relationship between sleep disturbances, *as measured by actigraphy*, and days to symptom recovery.

2b. To determine the relationship between sleep disturbances, *as measured by subjective sleep questionnaires*, and days to symptom recovery.

H1a-b: Concussed individuals who experience greater sleep disturbances, based on actigraphy and subjective sleep questionnaires, will take longer to recover.

<u>Actigraphy</u>

Independent Variables:

- Sleep onset latency (min.)
- Sleep efficiency (%)
- Total sleep time (min.)
- Wake after sleep onset (%)
- Number of awakenings per hour throughout the night

Dependent Variable:

- Days to symptom recovery

<u>Subjective Sleep Questionnaires</u>

Independent Variables:

- Pittsburgh Sleep Quality Index (PSQI) global scores
    - Since concussion
- Epworth Sleepiness Scale (ESS) total scores
    - Since concussion
- SCAT3 Sleep Cluster (drowsiness and trouble falling asleep)

Dependent Variable:

- Days to symptom recovery

Operational Definitions

Days to symptom recovery: operationally defined as the number of days from the date of injury to symptom resolution confirmed by clinical evaluation. Symptom recovery was evaluated by comparing self-reported symptom severity to baseline proxy symptom severity scores (captured at follow-up evaluation) that are typically experienced on a regular basis (>3 times per week).

Actigraphy: wrist-worn accelerometry device used to capture objective sleep continuously. Sleep parameters include: sleep onset latency, sleep efficiency, total sleep time, wake after sleep onset, and number of awakenings.

Subjective sleep assessments: questionnaires such as the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale that include self-rated questions to determine sleep quality.

Pittsburgh Sleep Quality Index: subjective sleep assessment that measures duration of sleep, sleep disturbances, sleep onset latency, day dysfunction, sleep efficiency, overall sleep quality, and use of sleeping medication (Buysse et al., 1989).

Epworth Sleepiness Scale: subjective sleep assessment that measures fatigue based on the likelihood of dozing off during common daily activities.

Sleep (objectively): based on immobility using wrist-worn accelerometry. Measures include sleep onset latency, sleep efficiency, total sleep time, wake after sleep onset, and number of awakenings per hour throughout the night.

Sleep (subjectively): based on self-reported quality of sleep. Higher scores indicate poor sleep quality, whereas lower scores indicate good sleep quality. Measures include duration of sleep, sleep disturbances, sleep onset latency, day dysfunction and excessive sleepiness, sleep efficiency, use of sleep medications.

Limitations

Due to numerous exclusion factors, we were limited to a small sample of 20 concussed and 20 non-concussed college-aged students. The use of actigraphy is low-cost and convenient for longitudinal studies, however, early termination (13.3%) of actigraphy monitoring was a problem in our study, which is a common limitation across the literature. Two participants lost the watch and approximately 13% recorded less than 5 nights of data (either from early recovery or participants discontinued to wear the watch). Despite multiple reminders, several concussed participants failed to complete the daily symptoms checklist throughout the duration of symptom recovery, therefore we were unable to define symptom recovery using the final day of self-reported symptoms. For our first aim, we excluded two concussed participants due to missing data at the end of recovery time-point. We also lost one participant in our second aim due to non-compliance with a follow-up evaluation within 48 hours of self-reporting symptom recovery despite several means of communication. Lastly, our subjective data were collected retrospectively, and may have been subjected to recall bias.

Significance of the Study

Clinicians are gradually recognizing sleep disturbances as more than a post-concussion symptom. Sleep disturbances may negatively affect brain recovery; therefore, our study may help clinicians develop a deeper understanding of the relationship between sleep and concussion recovery. It will not only inform clinical best practices but may guide clinicians in the development of individualized interventions to mitigate negative effects from sleep disturbances after brain injury. Understanding the relationship between sleep and concussion recovery would have a significant impact on clinical concussion management as sleep is not accounted for in the current assessment battery and may be a critical variable in treatment. This study is a novel approach to concussion research and is the first of its kind to follow individuals throughout the duration of symptom recovery.

CHAPTER 2

REVIEW OF LITERATURE

Understanding the effects of concussions continues to be ambiguous for healthcare professionals; therefore, management decisions are primarily based on clinical judgment (McCrory et al., 2017). Currently, concussions are managed with physical and cognitive rest until symptoms resolve, where the initial period of rest has been found to provide some benefit (McCrory et al., 2017). The cornerstone in concussion management focuses on minimizing activities that would exacerbate these symptoms. However, it is unclear what type of rest is influential and beneficial to concussion recovery. We seek to determine whether sleep influences the days to concussion recovery. The purpose of this review of literature is to further explore the 1) epidemiology of sport-related concussion, 2) concussion recovery, 3) functions of sleep, and 4) sleep assessments.

Epidemiology of Sport-Related Concussion

Sports-related concussions continue to be a nationwide concern. Approximately 1.6 to 3.8 million sports-related concussions occur each year, and can potentially result in acute and long-term consequences (Langlois et al., 2006). Sports are a major cause of concussions between the ages of 9-22 years, where participation is most prevalent (Zemek, Osmond, Barrowman, & Pediatric Emergency Research Canada Concussion, 2013). Understanding the epidemiology of concussion rates and risk is important to clinicians in order to promote safety and guide safe return-to-play decisions.

Earlier research found that overall concussion rates in young adults accounted for approximately 2.5 concussions per 10,000 athlete exposures (1 exposure=1 athlete participating in 1 NCAA-sanctioned practice or competition) (Gessel, Collins, & Dick, 2007; Marar, McIlvain, Fields, & Comstock, 2012). Concussion rates account for the number of concussions divided by the total amount of time the athletes are at risk. However, a recent study has shown that this rate has increased to 4.5 concussions per 10,000 athlete exposures, with larger competition concussion injury rates (12.8) compared to practice rates (2.6) (Zuckerman et al., 2015). Based on national estimates, it is not believed that the rate of concussion incidence has increased; rather it may be attributed to an increase in concussion awareness and reporting (Zuckerman et al., 2015).

The epidemiology of sport-related concussion incidence has gradually increased over the past several years. In a study examining injury data between 2009 to 2014 from the National Collegiate Athletic Association Injury Surveillance Program, concussions represented 6.2% of all sport-related injuries from 25 sports (Zuckerman et al., 2015). Several factors have been explored to determine the predisposition of concussion: sport and gender. Based on differences in sport, the highest concussion incidence occur from participation in men's wrestling , followed by men's ice hockey and women's ice hockey and men's football (Zuckerman et al., 2015) and Kerr et al. 2015. Among gender comparable sports, females have higher concussion rates than their male counterparts (Castile, Collins, McIlvain, & Comstock, 2012; Gessel et al., 2007; Marar et al., 2012), as well as higher rates of recurrent concussions (Castile et al., 2012). Evidence supports that females may be at greater risk of concussions than males, which may be attributed to a reporting bias due to cultural norms (Dick, 2009). Additional research has examined potential structural components, where women may be at greater risk of concussion due to greater head-neck segment peak angular acceleration and displacement compared to males (Tierney et al., 2008). In a study by Tierney et al., females were able to initiate earlier cervical neck muscle activity during unknown and known external force application tasks compared to males. However, they exhibited less isometric strength (49%), neck girth (30%), and head mass (43%) (Tierney et al., 2008), resulting in greater head and neck rotational acceleration following an external force. Gender differences in isometric strength, neck girth, and head mass could mean that females have a greater disposition to concussions in the event of a direct or indirect blow to the head during sport participation. The most common causes of sport-related concussion involve player-to-player contact, player-to-surface contact, and player-equipment contact (Marar et al., 2012). The most common mechanism of injury in collegiate athletics results from player-to-player contact (Zuckerman et al., 2015), with the following sports contributing the greatest percentage of all diagnosed sport-related concussions: 1) football (36.1%), 2) men's ice hockey (13.4%), and 3) women's soccer (8.1%). Player-equipment contact accounts for 32.7% of concussions in women's lacrosse and 20.0% in field hockey (Zuckerman et al., 2015). It is important to consider several types of contact mechanisms to guide preventative measures.

Historically, injury rates have been explored to identify the frequency of concussions across various groups: 1) games vs. practice and 2) males vs. females. However, recent literature is emphasizing concussion risk versus rates to account for varying exposures. Researchers examine the percentage of concussion risk, which calculates the probability that a concussion will occur within a designated group (i.e. sports team) over time (i.e. single season) (Kerr et al., 2017). For example, if a risk of concussion in football over one season is 2%, then it would be expected that 2 players out of a roster of 100 may sustain a concussion in one season. By identifying risk over a season, clinicians may be able to better quantify concussion incidence to policymakers and administrators, especially when advocating for concussion prevention programs (Kerr et al., 2017). However, clinicians must be aware that a true risk may be underestimated, where some athletes may participate only in practices, or others may have been exposed to external factors that removed them from participation during the season (i.e. non-concussion related injury).

Concussion Recovery

Evaluation Process

Due to the lack of a single definitive assessment available for diagnosing concussion, clinicians often use a thorough, multi-dimensional concussion assessment battery, which commonly includes a symptomology, neurocognitive, and postural stability evaluation (Broglio et al., 2014; McCrory et al., 2017) . Baseline evaluations may be useful in order to establish comparative individualized scores in an uninjured state in the event that an athlete later sustains a concussion (Broglio et al., 2014), however, recent international guidelines has determined that baselines are no longer necessary in order to interpret scores post-concussion (McCrory et al., 2017). Evaluating sport-related concussions can be challenging, therefore, diagnosis should be made through the use of a clinical examination, with support from each measure within the concussion assessment battery.

Symptomology

Symptom evaluations play a large role in concussion assessment and clinical management post-injury. Various symptom checklists have been used by physicians and healthcare professionals in assessment, with three most commonly used: Graded Symptom Checklist (Guskiewicz et al., 2004), Post-Concussion Symptom Scale (Lovell et al., 2006), and the symptom evaluation portion of the Sport Concussion Assessment Tool (newest: version 5)

(McCrory et al., 2017). Self-reported symptoms that are often reported following concussion include: headache, dizziness, nausea, vomiting, feeling like in a fog, feeling slowed down, trouble falling asleep, sleeping more than usual, fatigue, drowsiness, sensitivity to light or noise, balance problems, and ringing in the ears (Guskiewicz et al., 2004). Most symptom checklists are graded on a 7-point Likert scale ranging from 0 to 6. Zero indicates that the individual is not currently experiencing that symptom, and a score of 6 indicates that the symptom is currently severe. Symptom severity scores are calculated by adding each graded self-reported symptom for a combined severity score (higher scores = worse severity). Symptomology assessments are often categorized into four symptom clusters (Iverson et al., 2015; Kontos, Elbin, et al., 2012; Lau, Collins, & Lovell, 2012): cognitive (i.e. feeling like in a fog), somatic (i.e. headache), emotional (i.e. irritability), and sleep (i.e. trouble falling asleep) If signs/symptoms from any of the symptom clusters exist, a concussion should be suspected and undergo further evaluation (McCrory et al., 2017).

Symptom evaluations provide good sensitivity to concussive injuries, but solely utilizing it for concussion management is not appropriate since individuals may not appropriately report symptoms in order to return to full athletic participation sooner (Broglio et al., 2014). An additional challenge for clinicians utilizing graded symptom checklists is that several symptoms may be non-concussive in nature, so other differential diagnoses should be considered in addition to concussion during evaluation post-injury. Medical history (i.e. history of multiple concussions (Register-Mihalik, Mihalik, & Guskiewicz, 2009) or poor sleep quality (Mihalik et al., 2013; Silverberg, Berkner, Atkins, Zafonte, & Iverson, 2016; Sullivan, Berndt, Edmed, Smith, & Allan, 2016) should be taken into account when assessing symptomology, as individuals may typically experience concussion-like symptoms in absence of injury (Asken et al., 2017).

Neurocognition

Neurocognitive testing has previously been considered a vital component within the multi-dimensional concussion assessment battery (McCrory et al., 2017). The Automated Neuropsychological Assessment Metrics (ANAM), CNS Vital Signs, and Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) are examples of common computerized clinical concussion assessments used to assess cognitive function (Broglio et al., 2014). Neurocognitive tests are composed of multiple domains, which primarily include verbal and visual memory, concentration/attention, executive function, reaction time, and processing speed (Johnson, Kegel, & Collins, 2011). Cognitive domains most commonly affected by concussion include attention and processing speed (Nelson et al., 2016).

Many clinicians utilize neurocognitive testing to aid in return-to-play decisions, and similar to symptom assessments, should not be the sole basis for recovery management Studies have shown variable sensitivity and specificity from these tests. In a study comparing performance following concussion across different computerized neurocognitive tests, the overall sensitivity rate within 24 hours following concussion (47.6% (ANAM) and 67.8% (ImPACT)) significantly decreased for each neurocognitive measure past eight days post-injury (Nelson et al., 2016). False-positive rates ranged across different neurocognitive tests: (20.8-26.7% (ANAM) and 29.6-42.7% (ImPACT) (Nelson et al., 2016). Consistent with a recent review of literature, test-retest reliability values over clinically-relevant time intervals for computerized neurocognitive tests are relatively low (Nelson et al., 2016; Resch et al., 2013), which may be concerning as many clinicians tend to rely on cognitive testing when making clinical decisions due to ease of administration and rapid scoring. Clinicians should be aware that despite the benefits of information gained using computerized neurocognitive testing, there are several state factors that could negatively affect the testing results (i.e. fatigue, time of day of testing, attention, motivation, etc). Additionally, environmental testing conditions (group testing vs. individual testing and quiet vs. loud) could also influence testing performance. Clinicians should recognize the limitations with neurocognitive testing and control for external factors related to poor test performance.

Previous research showed that cognitive scores typically recovered within 1-week post-injury (Echemendia, Putukian, Mackin, Julian, & Shoss, 2001). However, the recent international consensus statement on concussions shows that most cognitive deficits recover within two weeks post-concussion (McCrory et al., 2017). Over the past decade, research has examined individual variability in clinical outcomes instead of previously examined group findings and found that many individuals take longer than 10 days to recover, which may explain why cognitive deficits appear to take longer to return to normal function (McCrory et al., 2017). Neurocognitive testing is no longer required for all individuals post-injury (McCrory et al., 2017), however, it still serves as one of several useful tools for clinicians to determine when an individual is clinically recovered.

Postural Stability

In addition to cognitive deficits, concussions can significantly affect the motor domain of neurologic function in the brain (Broglio et al., 2014; McCrory et al., 2013). Diffuse changes within motor control areas can affect balance and stability post-injury. Two assessments that are most often used to measure postural stability are the Sensory Organization Test (SOT) performed on the NeuroCom Smart Balance Master System (NeuroCom International, Inc, Clackamas, OR) and the Balance Error Scoring System (BESS). The SOT disrupts the sensory system by altering the somatosensory, visual, and vestibular information received during six various visual, surface, and sway-referenced conditions (Guskiewicz, Ross, & Marshall, 2001). Sway-referencing refers to the tilting motion of the base of support and the visual surround parts of the instrument. Vertical ground reaction forces are measured as a result of the body's center of pressure movement during each condition. Clinicians are able to obtain information on the sway path in order to detect balance impairments post-concussion (Guskiewicz et al., 2001). Identification of changes within postural control using the SOT following concussion continues to attract attention within concussion research due to the precision with objectively measuring center of pressure. Researchers have also explored non-linear dynamics to examine center of pressure oscillations over time (Cavanaugh et al., 2005). However, there is limited clinical applicability as the SOT is not widely available to clinicians due to the high expense and lack of portability.

The BESS test is more applicable clinically, and is often used during sideline concussion assessments. It does not require the use of a force plate measure to quantitatively assess postural stability, is cost-effective. The BESS test has been thoroughly examined across a wide range of populations (Bell, Guskiewicz, Clark, & Padua, 2011) and validated against the Sensory Organization Test using concussed athletes (Guskiewicz et al., 2001). Studies have reported interrater reliability ranges for BESS score totals: ICC of 0.57 to 0.85 (Bell et al., 2011). Test-retest reliability was considered moderate for young adults (generalizability coefficient: 0.64). However, there are many limitations associated with the BESS: 1) low sensitivity (unable to detect balance deficits >7 days post-injury) and 2) low interrater reliability (Bell et al., 2011). Individuals undergo six different conditions similar to the SOT, however, evaluators assess the number of errors that are committed during each trial (Guskiewicz et al., 2001).

Typical Recovery Curves

Concussion recovery varies amongst individuals, but the majority of young adult athletes recover within 10-14 days (McCrory et al., 2017). Over the past decade, there has been growing evidence that athletes are taking longer to achieve clinical recovery (Iverson et al., 2017). Previous literature was primarily based on group findings, whereas research is now focusing on individual variability. According to a review by Iverson et. al, symptoms, neurocognitive deficits, and balance performance is shown to improve within the first two weeks of injury (Iverson et al., 2017). The rate of concussion recovery has been found to vary amongst athletes, thus clinicians must understand the factors that may influence recovery time in order to determine the best management plan.

Factors That Influence Recovery

Numerous modifying factors within an individual's past medical history may influence concussion recovery. Modifying factors such as migraines, mental health disorders, multiple concussions, attention-deficit hyperactive disorders (ADHD), learning disabilities, and sleeping disorders (McCrory et al., 2017) may be indicative of persistent symptoms, and may influence how clinicians manage concussions. However, establishing a time of recovery has been complicated for healthcare professionals due to the complex nature with concussion variability (McCrory et al., 2017).

Individuals with a history of multiple concussions, including repeated concussions within a short time frame, may require a more conservative approach with respect to return to athletic participation (Broglio et al., 2014). Additionally, clinicians should also be aware of the premorbid neurocognitive impairments associated with modifying factors. Cognitive deficits following concussion, such as slowed processing and difficulties with executive function, are common symptoms shared by individuals with ADHD and a learning disability (Yeates et al., 2005). In a study by Kontos et al., individuals with a history of depression experienced an increase in depression scores up to 14 days post-injury, as well as a decrease in reaction time and visual memory (Kontos, Covassin, Elbin, & Parker, 2012). Depression may be associated with sleep disorders. One study found a strong positive relationship between sleep disturbances in concussed individuals and depression, which preliminarily supports depression as a covariate of insomnia (Mollayeva, Mollayeva, Shapiro, Cassidy, & Colantonio, 2016). Knowledge of this medical history may aid clinicians in developing an appropriate diagnosis and treatment plan for individuals with potential for persistent symptoms.

Functions of Sleep

Sleep Modulation

Circadian rhythm and sleep inertia may modulate cognition, including reaction time, sustained visual attention, memory, mood, motivation, and alertness (Achermann & Borbély, 1994). Cognition is significantly regulated by circadian rhythm processes (alternation between sleep and wakefulness) and sleep inertia (disorientation upon awakening). Earlier studies suggest that neural control within the forebrain and brainstem regions contribute to sleep-wake cycles, particularly the suprachiasmatic nucleus in the anterior hypothalamus (Rosenwasser, 2009). However, it has been determined that circadian rhythms are more broadly controlled throughout a more complex network of neuronal pathways within the central nervous system, as well as peripheral tissues (Rosenwasser, 2009). Sleep is in fact not considered a passive process, rather an active cycle that involves several regions of the brain.

Circadian Rhythm

The regular alternation between sleep and wakefulness is regulated by two mechanisms acting within a 24-hour cycle: the homeostatic process and circadian timing process. (Borbély, 1982; Schmidt, Collette, Cajochen, & Peigneux, 2007). This daily rhythmicity, in the absence of surrounding environmental time cues, is considered the most fundamental of daytime rhythms

(University of California & Society, 1993). It has been speculated that the circadian clock controls the homeostatic process in which sleepiness increases in proportion to the time awake, resulting in sleep onset. The influence of circadian rhythm disruption on human sleep has been determined through sleep deprivation experiments in which alertness continues to increase in the morning despite having the subjects remain awake all night without sleep (University of California & Society, 1993). For those subjects that experienced severe sleep deprivation over several days, it was difficult to sleep during the afternoon and evening hours that coincided with the "awake" aspect of their circadian cycles. Objective measures such as wrist-worn accelerometers (i.e. actigraphy) have been utilized to identify significant circadian phase advancement across age groups (Morgenthaler et al., 2007).

Sleep Inertia

Sleep inertia refers to a period of decreased performance or disorientation immediately after awakening from sleep relative to pre-sleep status (Tassi & Muzet, 2000). This physiological delay occurs as a result of transitioning from a state of sleep to one of full alertness (Tassi & Muzet, 2000). Jewett et al. found that alertness and cognitive performance could be impaired for longer than two hours after awakening due to sleep inertia (Jewett et al., 1999). Abrupt awakening during a slow wave, deep non-rapid eye movement cycle has been found to produce greater sleep inertia, especially in those experiencing sleep deprivation (Tassi & Muzet, 2000). Sleep inertia is dependent on several factors: 1) prior sleep duration, 2) sleep stage prior to awakening, and 3) sleep deprivation. Naps have been recommended to maintain psychomotor performance during activities that require extended periods of wakefulness, (Mulrine, Signal, Berg, & Gander, 2012), and can ultimately reduce sleepiness and enhance short-term memory and mood (Takahashi, 2003; Tietzel & Lack, 2002). However, naps may cause short-term drowsiness and impaired cognitive and behavioral performance due to sleep inertia depending on the length of the nap (Hofer-Tinguely et al., 2005). Conflicting discussions on the length of time that naps should be taken to achieve benefits are common, however, several studies have supported naps from 10 minutes, up to 60 minutes as having positive effects on increasing alertness and decreasing sleepiness (Lumley, Roehrs, Zorick, Lamphere, & Roth, 1986; Mulrine et al., 2012; Tietzel & Lack, 2002).

Resting and Sleep Interventions

Recent studies have shown that nap lengths affect cognitive performance and alertness; however, it is still unclear whether general rest would provide positive benefits. In a study using habitual nappers and non-nappers, Bertelson et al. found that resting in bed without falling asleep was just as beneficial as napping (Bertelson, 1980). Additionally, in an early study by Dais et al., both napping and resting improved mood in participants regardless of whether they took frequent naps (Daiss, Bertelson, & Benjamin, 1986). This may suggest that the period of relaxation during napping or resting may play a vital role in providing mood benefits. However, conflicting results from earlier studies showed that cognitive performance was not affected by naps or resting (Bertelson, 1980; Daiss et al., 1986). With these conflicting results over the decades, it may be challenging for clinicians to recommend adequate sleep interventions. Presently, studies have supported afternoon naps to decrease daytime sleepiness and increase cognitive performance in the general population (Lumley et al., 1986; Mulrine et al., 2012; Tassi & Muzet, 2000; Tietzel & Lack, 2002). The National Sleep Foundation recommends that healthy adults get between seven and nine hours of sleep per night to prevent performance deficits; however, athletes typically obtain slightly less than the average adult population (Leeder, Glaister, Pizzoferro, Dawson, & Pedlar, 2012), which may be attributed to training schedules in-season compared to out-of-season. Presently, there is limited research regarding sleep interventions over extended periods of time, which may be important to consider in regards to effects on athletic performance. One study by Mah et al. implemented a sleep program to increase sleep duration in collegiate basketball players (Mah et al., 2011). Results of the sleep extension program showed significant improvements in reaction time, daytime sleepiness, and mood (Mah et al., 2011). However, it is unknown whether improvements were attributed to longer nighttime sleeping or an increase in frequency and/or duration of naps/rests.

Athletic performance was improved utilizing a sleep extension program in collegiate athletes (Mah et al., 2011). Further research is needed to determine whether sleep intervention programs may provide benefits to participants who experience sleep disturbances following concussion; however, appropriate clinical sleep measures need to be considered to evaluate sleep quality.

Clinical Sleep Measures

Multiple methods have been utilized by clinicians to identify sleep disturbances, such as polysomnography, clinical interviews, subjective sleep questionnaires, sleep diaries, and actigraphy. Polysomnography is considered the gold standard for assessing sleep, but is not practical for longitudinal studies. For clinical studies, subjective sleep assessment (sleep logs and questionnaires) and objective sleep measures (actigraphy) have been found to be useful to detect sleep quality over time (Lockley, Skene, & Arendt, 1999). These measures are not without limitations. Polysomnography requires individuals to sleep in a research laboratory, which may change habitual sleep patterns. Sleep questionnaires may be difficult for individuals to complete based on their interpretation of their sleep patterns, as well as their recall accuracy in the event of cognitive impairment. Actigraphy monitors are cost-effective and are useful to estimate total sleep time, sleep efficiency, and the total minutes awake after initial sleep onset (Henricks et al., 2011). However, since actigraphy devices score sleep based on movement; it may be difficult to differentiate if individuals are lying awake motionless or if they are restless sleepers (Sadeh et al., 1995). Despite these limitations, while used together, these assessments provide valid measures that can be used to detect various sleep disturbances, which can provide pertinent information to guide clinicians in identifying the presence of potential sleep disturbances (Sadeh, 2011)

Subjective Sleep Questionnaires

Several self-report questionnaires are available to clinicians to evaluate sleep disturbances; however, the Pittsburgh Sleep Quality Index (PSQI), and the Epworth Sleepiness Scale (ESS) are most commonly used to identify potential sleep disturbances across a wide range of age groups, from children to older adults. The Pittsburgh Sleep Quality Index is one of the most commonly used generic measure in clinical and research settings in a variety of populations (Mollayeva, Thurairajah, et al., 2016), and the Epworth Sleepiness Scale has been beneficial in identifying daytime sleepiness and fatigue-related items (Johns, 1991; Mondal et al., 2013).

Pittsburgh Sleep Quality Index – (Appendix Ia & Ib)

The Pittsburgh Sleep Quality Index (PSQI) is a reliable and valid subjective sleep quality assessment (Buysse et al., 1989). The PSQI was developed in order to 1) provide a reliable, valid, and standardized measure of sleep quality; (2) discriminate between “good” and “poor” sleepers; 3) provide a simple index for clinicians and researchers to interpret; and 4) provide a brief, clinically useful assessment of a variety of sleep disturbances (Buysse et al., 1989). A global score >5 yielded a sensitivity of 89.6% and specificity of 86.5% in identifying poor sleep quality (Buysse et al., 1989) as compared to polysomnography.

The PSQI is used to assess sleep quality during the previous month. This time frame was selected in order to account for sleep quality between current inventories that assess only the previous night's sleep and surveys that assess difficulties over the previous year and beyond (Buysse et al., 1989). Questionnaires that assess for the previous night's sleep are able to account for day-to-day changes in sleep; however, they do not capture the frequency or duration of sleep disturbances. Longer periods of assessment have been validated in providing greater accuracy in assessing sleep over time.

The PSQI is composed of 19 self-rated questions, which are grouped into seven constructs: duration of sleep, sleep disturbances, sleep onset latency, day dysfunction, sleep efficiency, overall sleep quality, and use of sleeping medication (Buysse et al., 1989). The responses are coded on a scale of 0-3 for each construct, and are used to determine a combined global score of 0-21. Global scores >5 are associated with poor sleep quality. Global scores provide an advantage of giving a single overall assessment of sleep quality for simple calculation and comparison purposes. For example, a PSQI global score greater than 5 indicates that a subject is having severe difficulties in at least two areas, or moderate difficulties in more than three areas (Buysse et al., 1989). The PSQI has been used in earlier studies examining middle-aged patients with excessive sleepiness disorders, as well as disorders with initiating and maintaining sleep (Buysse et al., 1989). The PSQI is gradually becoming implemented into studies assessing sleep following concussion in young adults (Dietch et al., 2016; Gosselin et al., 2009; Schmidt et al., 2015). With this information, clinicians may be able to identify particular areas that require further investigation.

<u>Epworth Sleepiness Scale – (Appendix IIa & IIb)</u>

The Epworth Sleepiness Scale (ESS) was developed based on eight common, low-level stimulating situations that may cause daytime sleepiness: 1) sitting and reading, 2) watching TV, 3) sitting inactive in a public place, 4) sitting as a passenger in a car for an hour without a break, 5) lying down to rest in the afternoon, 6) sitting and talking to someone, 7) sitting quietly after a lunch, and 8) stopped in traffic in a car for a few minutes. The questionnaire consists of 8 self-rated items, each scored from 0-3, which measure a subject's habitual “likelihood of dozing or falling asleep” in common situations of daily living (Johns, 1991; Mondal et al., 2013). Scores of 0-1 indicate minimal chances of dozing off, and 2-3 indicate a greater chance of dozing off. ESS total scores range from 0–24. Values greater than 10 indicate significant sleepiness. This questionnaire was developed with the notion that daily routines vary from person-to-person, therefore it assesses for the likelihood of dozing off as opposed to the frequency of falling asleep during a particular activity. Internal consistency by Cronbach’s alpha was good (0.73-0.86), which is appropriate for group comparisons (Kendzerska, Smith, Brignardello-Petersen, Leung, & Tomlinson, 2014).

Objective Sleep Measures

<u>Actigraphy</u>

Actigraphy is an activity-based sleep monitoring tool commonly used in clinical sleep medicine (Sadeh, 2011). It has been proven useful in identifying individuals with circadian phase advancement (Morgenthaler et al., 2007). Through the use of wrist-worn accelerometers, actigraphy is a valid and reliable sleep assessment tool that is used to assist in determining multi-day sleep patterns through continuous recordings for 24-hour periods (Ancoli-Israel et al., 2003; Sadeh, 2011; Sadeh et al., 1995). Validation studies have shown 91%-93% in overall agreement for sleep-wake scoring (de Souza et al., 2003; Sadeh, Sharkey, & Carskadon, 1994) and 91.4%-96.5% agreement rates (0.79-0.94 correlations: sleep duration) in adults (age 20-30 years) in comparison with polysomnography. In a study by de Souza et al, high sensitivity in detecting various sleep-wake patterns was found in two common actigraphy scoring algorithms (Sadeh: 97%, Cole: 99%), but low specificity in detecting wakefulness (Sadeh: 44%, Cole: 34%) compared to polysomnography (de Souza et al., 2003). Actigraphy assesses several sleep parameters including sleep onset latency (time it takes to fall asleep), total sleep time, sleep efficiency (ratio of the total sleep time and total time spent in bed), wake after sleep onset (total number of minutes awake after initial sleep onset), number of awakenings, and average awakening length. Actigraphy devices are cost effective and unobtrusive in comparison to traditional nocturnal polysomnography and can record for multiple days and nights (Jean-Louis et al., 2001). Patients can be evaluated in their natural sleeping environment, thus eliminating laboratory effects that have been suspected of altering routine sleep patterns (Ancoli-Israel et al., 2003). Actigraphy provides more accurate information in conjunction with subjective sleep logs, which have been shown to moderately correlate with polysomnography and actigraphy with respect to sleep-wake patterns (Lichstein et al., 2006).

Even though actigraphy was found to be valid for assessing sleep duration and sleep-wake activity, research shows that it is less reliable for more specific measures such as sleep efficiency and latency (Ancoli-Israel et al., 2003). One study identified a discrepancy between the sleep estimates reported on sleep logs and those determined by the actigraphy, with a large range in the number of awakenings during the night (Wilson, Watson, & Currie, 1998). Investigators found that the total sleep time was greater, and sleep onset latency was less on actigraphy data compared to sleep logs (Wilson et al., 1998). The reliability of sleep onset latency using actigraphy compared to polysomnography has elicited controversial findings with overestimation in the onset of sleep in older individuals with sleep disorders, but have significantly correlated with polysomnography in another study (de Souza et al., 2003). Lockley et al (1999) found that in 66% of individuals, actigraphy overestimates night sleep duration (Lockley et al., 1999), compared to 56% reported by Hauri and Wisbey (1992). Overall error in night sleep duration was 60 minutes compared to 49 minutes (Hauri & Wisbey, 1992). A comprehensive approach of subjective sleep measures and actigraphy has been recommended to improve consistency when determining sleep quality (Sadeh, 2011).

Inter-instrument reliability has been investigated for numerous actigraphy accelerometers. Previous research has shown favorable validity and reliability of these accelerometers (Jean-Louis et al., 2001; Sadeh et al., 1994). In November 2014, ActiGraph released the GT9X Link (ActiGraph, Pensacola; FL, USA). The GT9X Link is a lightweight, (14 g) tri-axial accelerometer that can detect body position and movement during sleep and physical activity. The accelerometer samples data at a rate of 30-100Hz, which can be stored within the 4-gigabyte memory up to 180 days. This range allows researchers to select the rate of samples collected based on their research preference. Recently published literature on the validity of ActiGraph GT9X Link device compared to other accelerometers during sleep and physical activity revealed a high agreement on all sleep outcome measures (sensitivity: 89.18%, specificity: 93.82%) using Sadeh's algorithm.

Summary of Rationale for the Study

Sport-related concussion is a major public health concern worldwide (Kelly, 1999). Immediate concussion-related cognitive deficits and physical symptoms are commonly recognized, but the medical community is now becoming increasingly aware of the significance of sleep disturbances post-injury (Gosselin et al., 2009; McCrory et al., 2017). As many as 70% of concussed athletes report short and long-term sleep problems, fatigue, daytime sleepiness, and vigilance disturbances following concussion (Gosselin et al., 2009; Parcell et al., 2006). Few studies exist examining sleep acutely following concussion, however there is currently no literature that has prospectively examined sleep objectively and subjectively throughout the duration of symptom recovery. There is a greater need for understanding the role of sleep on concussion recovery in order for clinicians to determine the clinical utility of incorporating sleep assessments into concussion evaluations.

CHAPTER 3

METHODS

Participants

University students (n=149) between the ages of 18 and 23 years were evaluated and diagnosed with a concussion by members of the sports medicine team or the University Health Center (UHC), between August 2016 and November 2017. Concussion diagnosis was based on clinical judgement as defined in the 5th Consensus Statement on Concussion in Sport (McCrory et al., 2017). Once diagnosed, individuals were referred to the Concussion Research Laboratory to undergo a comprehensive concussion battery. Five varsity student-athletes and 15 university students were diagnosed with a concussion, referred within 72 hours post-injury (strict adherence was necessary to capture adequate acute actigraphy data), and agreed to participate.

Non-Concussed Control Group

Non-concussed control participants (n=20) were recruited and matched based on age (±1 year), sex, self-reported physical activity level (identified using International Physical Activity Questionnaire – Short Form categories: high, moderate, low, and sedentary) (Dinger, Behrens, & Han, 2006), and previous month total sleep quality (scores within ±1) using the Pittsburgh Sleep Quality Index global scores (see Appendix Ia & Ib). Interest in study participation was obtained throughout the course of the study using word of mouth and tear-off flyers. A running list of interested non-concussed individuals was created to aid in ease of participant recruitment since matching was time-sensitive. Inclusion criteria for the non-concussed group consisted of no previous history of concussion within one year of assessment. To minimize potential stress related to the academic calendar (i.e. end of the semester exams), (Ahrberg, Dresler, Niedermaier, Steiger, & Genzel, 2012; Lund, Reider, Whiting, & Prichard, 2010), instrumentation of non-concussed participants was matched to the same time frame within the academic semester (defined by dividing the semester into quarters) that their match sustained a concussion. For example, a concussion sustained in August would fall in the first quarter of the semester – the participant's matched control would be instrumented at the same time or during the first quarter of the subsequent semester (i.e. January of the spring semester). Non-concussed participants were instrumented with the ActiGraph wrist-worn accelerometer on the same day of the week as the concussed participant and were asked to wear it for the same length of time that the concussed participant wore the accelerometer. For example, if a concussed participant was issued the accelerometer on a Friday, then the non-concussed participant was also required to begin wearing the device on a Friday to control for sleep variability that may occur on weekends compared to weekdays (Lund et al., 2010).

Sleep quality was determined using PSQI global cutoff scores (Buysse et al., 1989). Using the following criteria for sleep quality: good sleep quality (scores ≤ 5) and poor sleep quality (scores >5), a concussed participant with a global score of 4 was matched to a non-concussed participant with a similar global score (± 1) as long as the non-concussed participant's score did not fall outside of the good sleep quality category (Buysse et al., 1989). In cases where a score of +1 would exceed the cutoff and place a non-concussed participant into another category, we opted to only use the score of -1 as a match.

Exclusion criteria was established for concussed and non-concussed individuals to control for confounding factors: history of concussion (≥3), chronic headaches, migraines, meningitis or any other brain infection, seizure disorder, diabetes, sleep disorder, balance disorder, psychiatric disorder, learning disorder, attention deficit hyperactivity disorder (ADHD), autism, depression, bipolar, schizophrenia, moderate/severe traumatic brain injury, brain surgery, stroke, heart disease, substance abuse, and use of prescription medications that may influence sleep (i.e. antidepressants, amphetamines, diphenhydramine (Benadryl), benzodiazepines) (Saper, Scammell, & Lu, 2005), (Figure 3.1). Medications that participants commonly self-reported included acetaminophen for headaches post-concussion and seasonal allergy medications (i.e. Zyrtec). All participants signed an informed consent form approved by the university's Institutional Review Board.

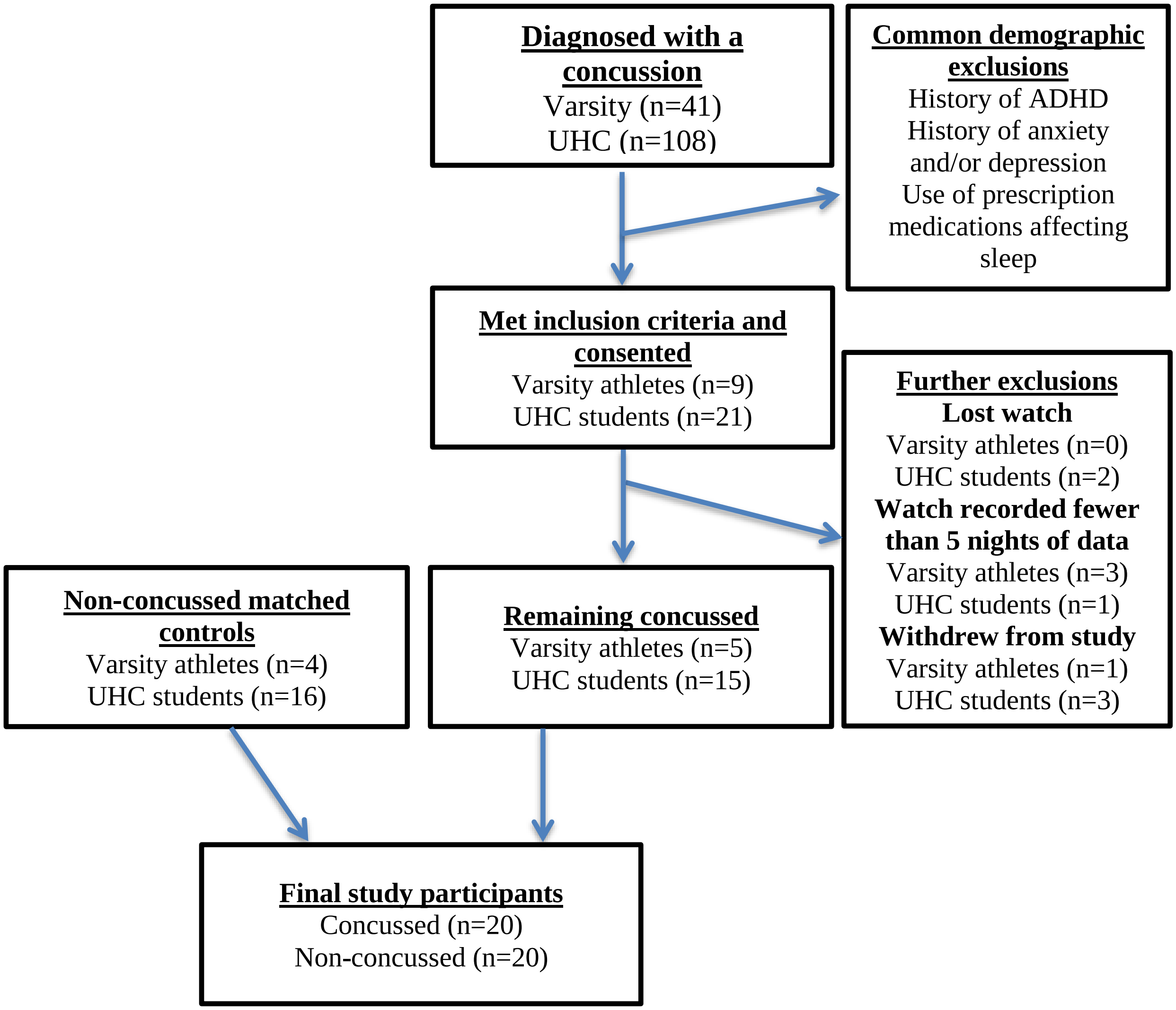

Figure 3.1. Participant selection flow chart.

Clinical Evaluation - Symptoms

Participants completed a demographic form and a graded symptoms checklist (Sport Concussion Assessment Tool, Version 3 – SCAT3; Appendix IIIb), which is a 22-item list of symptoms commonly associated with concussions. Participants rated the presence/absence of the symptom on a 0 to 6 Likert scale based on how they currently felt, with 0 indicating the symptom was not currently present, 1 and 2 indicating mild, 3 and 4 indicating moderate, and 5 and 6 indicating severe symptoms. Total symptom severity scores ranged from 0-132. Concussed individuals completed the SCAT3 at the first visit (within 72 hours post-concussion), daily thereafter, and 2) at the second visit (symptom recovery). Non-concussed participants completed the same measures as concussed participants for consistency across testing procedures (Table 3.1). All participants also completed an additional graded symptoms checklist, using modified instructions of the SCAT3 (Appendix IIIa), at the second visit to recall symptoms that are "typically experienced" (>3 times per week) in order to establish a retrospective baseline proxy.

Symptom severity progression following concussion was tracked daily using the SCAT3 graded symptoms checklist. Administration of the SCAT3 varied amongst participants depending on the limitations of daily access to a healthcare professional. Based on the current recommended clinical management protocol for sport-related concussion, varsity athletes were monitored daily throughout concussion recovery (McCrory et al., 2017). Varsity athletes completed the SCAT3 symptoms checklist daily using an interview format with a member of the sports medicine staff. Concussion management through the University Health Center does not include daily monitoring, therefore, university students completed a self-directed symptom evaluation, using the same SCAT3 symptom checklist except as an online symptom Qualtrics survey (Qualtrics, Provo, UT), administered daily to track symptom recovery.

Concussed participants were asked to complete the SCAT3 until they experienced symptom recovery, which was operationally defined as the number of days from the date of injury to symptom resolution determined by clinical evaluation. A member of the sports medicine team tracked daily symptom progression for varsity athletes. Since university students were not directly assessed daily by a healthcare professional, they were provided with written instructions to contact the Concussion Research Laboratory once they experienced symptom resolution. Symptoms were tracked daily by one trained investigator [NLH] via the online symptom Qualtrics survey to verify their self-reported symptom assessment. If university students did not complete the online symptom Qualtrics survey daily throughout recovery (~67% of students), the investigator contacted the participant with reminders via email. If university students still did not complete the daily symptom checklist despite reminders, the investigator communicated with participants via phone and/or email to determine the status of their symptoms and to schedule a follow-up evaluation.

Once participants self-reported subjective symptom resolution (either via the SCAT3 or direct email to the investigator), they were scheduled within 24-48 hours for a follow-up evaluation (2nd visit), where they underwent a clinical evaluation using the same testing procedures during the first time-point. Symptom recovery was determined by comparing SCAT3 symptom severity at the follow-up evaluation to baseline proxy symptom severity scores (using modified instructions of the SCAT3 captured immediately following the current symptom report) that are typically experienced on a regular basis (>3 times per week. Reliable change criteria for SCAT3 symptom severity performance was used to determine that a change in symptom scores between the follow-up evaluation and baseline proxy scores did not exceed 2.97 (95% CI) when determining symptom recovery (Chin, Nelson, Barr, McCrory, & McCrea, 2016).

Table 3.1. Clinical Measures and Sleep Assessments at Various Time-Points

	Non-Concussed				Concussed		
	Identify Match	1st Visit	Daily	2nd Visit	1st Visit (within 72 Hours)	Daily	2nd Visit (symptom recovery)
Clinical Measures							
SCAT3 Graded Symptoms Checklist		X	X	X[b]	X	X	X[b]
Sleep Measures							
Actigraphy			X	X		X	X
Sleep Log			X	X		X	X
PSQI & ESS (previous month)	X[a]						
PSQI (x2)[c]							X[c]
ESS (x2)[c]							X[c]

Note. [a] Non-concussed individuals interested in the study were asked to complete the PSQI prior to being scheduled for the first time-point to determine if they were a match. [b]Concussed participants were required to complete two graded symptoms checklists at the follow-up time-point: one based on how they currently felt and then one on how they recalled feeling prior to concussion. [c]Concussed participants were first required to complete the PSQI and ESS forms pertaining to sleep since they sustained their concussion and then completed the same forms pertaining to sleep quality during the month prior to concussion.

Sleep Instruments

Objective Sleep Measure

Participants were issued an ActiGraph GT9X Link, a light-weight (14g; 3.5 x 3.5 x 1cm) tri-axial wrist-worn accelerometer, at their first visit to capture objective sleep continuously for 24-hour periods. Sleep timing and duration can be estimated from actigraphy and is a valid proxy for these sleep outcomes in healthy and concussed individuals (Wickwire et al., 2016). A validated computer-based algorithm for young adults was used to analyze the sampled movements captured by the accelerometers in order to determine sleep/wake parameters (Sadeh, 2011). The ActiGraph GT9X Link device can record acceleration data at a wide sampling rate of 30-100Hz. A sampling rate of 30 Hz was selected for this study based on the needs of capturing sleep and wake activity. The ActiGraph GT9X Link measures acceleration in a dynamic range of ±8G. Data were downloaded and processed using ActiLife Software (ActiGraph, version 6.13.3). Concussed participants were instrumented with ActiGraph GT9X Link within 72 hours post-injury, and were instructed to wear it continuously on their non-dominant wrist until they experienced symptom resolution based on their self-reported SCAT3 symptom severity score (Appendix-IIIa&b). Non-concussed participants were instructed to wear the device in the same way and for the same duration of time comparable to their matched concussed participant. The actigraphy sleep parameters include: sleep onset latency (amount of time to transition from awake to sleep), sleep efficiency (percentage of the number of minutes of sleep divided by the number of minutes in bed), total sleep time, wake after sleep onset (total minutes awake after sleep onset), and number of awakenings.

Sleep Log

All participants were asked to keep a daily sleep log (Appendix IV – modified version of National Sleep Foundation sleep diary), which includes subjective information pertaining to their wake and bed times, how easily they fell asleep, and how many times they woke up (including the minutes), and whether they took a nap during the day. Participants were instructed to record the time and reasons they removed the watch at any point. Subjective information collected from the diary was used to assist with determining sleep onset and wake time intervals each night for calculating actigraphy sleep onset latency, sleep efficiency, total sleep time, and wake after sleep onset. Sleep diaries have demonstrated moderate correlations with actigraphy (Lichstein et al., 2006).

Subjective Sleep Measures

Concussed participants completed two versions (original and with modified instructions) of each subjective sleep quality questionnaire to address sleep: 1) since concussion and 2) on a typical basis prior to concussion. The modified version of the questionnaires used the same questions as the original version, but participants rated their sleep quality on the nights since they sustained their concussion only. Non-concussed participants completed the original versions of subjective sleep quality questionnaires. To our knowledge, the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale are the only subjective questionnaires in recent literature to be validated against objective sleep measures in concussed individuals (Wickwire et al., 2016).

The Pittsburgh Sleep Quality Index (PSQI – Appendix I) is a subjective sleep quality assessment supported by evidence of reliability and validity (Buysse et al., 1989). The PSQI is commonly used in clinical and research settings (Mollayeva, Thurairajah, et al., 2016) and has been widely used to distinguish between good and poor sleepers (Buysse et al., 1989). It has established adequate psychometric properties for young adults (Berger, Obeid, Timmons, & DeMatteo, 2017; Dietch et al., 2016) and has been validated against objective measures in patients with traumatic brain injury (Buysse et al., 1989; Fichtenberg, Putnam, Mann, Zafonte, & Millard, 2001). The PSQI is composed of 19 self-rated questions, which are grouped into seven sleep components: duration of sleep, sleep disturbances, sleep onset latency, day dysfunction, sleep efficiency, overall sleep quality, and use of sleeping medication (Buysse et al., 1989). Each sleep component was answered based on sleep since concussion and the month prior to concussion:

1. *Subjective sleep quality* is answered based on how the participant would rate their overall sleep quality.

2. *Sleep onset latency* is assessed by asking the participant to report how long (in minutes) it takes him/her to fall asleep on average. Participants also report the number of times that he/she could not get to sleep within 30 minutes of going to bed.
3. *Sleep duration* is determined by asking the participant to report on average how many hours of actual sleep that they got at night.
4. *Sleep efficiency* is determined based on the questions of total number of hours asleep and the total number of hours in bed. This value was represented as a percentage.
5. *Sleep disturbances* is determined based on the following situations that could contribute to a participant having difficulties sleeping: waking up in the middle of the night or early morning, having to get up to use the bathroom, could not breathe comfortably, coughing or snoring loudly, feeling too cold or too hot, having bad dreams, having pain, or any other reported disturbances.
6. *Use of sleep medications* is determined based on how often the participant took medicine (prescribed or "over the counter") to help with sleep.
7. *Day dysfunction* is assessed by asking the participant how frequently they reported having trouble staying awake while driving, eating meals, or engaging in social activity, as well as how much difficulty they had with keeping up enthusiasm completing tasks.

Pittsburgh Sleep Quality Index global scores ranged from 0-21. A cutoff score of >5 has been used to identify clinically meaningful sleep disturbances in a wide variety of populations (Buysse et al., 1989). In this study, we chose to use a cutoff global score of >8 which has been suggested for identifying poorer sleep quality and insomnia following concussion (Fichtenberg et al., 2001). The PSQI demonstrates internal consistency, as indicated by Cronbach's alpha, ranging between 0.70-0.83 (Mollayeva, Thurairajah, et al., 2016).

The Epworth Sleepiness Scale (ESS – Appendix II) consists of 8 self-rated items, each scored from 0-3, which measure a subject's habitual "likelihood of dozing or falling asleep" in common situations of daily living (i.e. watching TV, sitting, talking) (Johns, 1991; Mondal et al., 2013). This questionnaire was used to assess for the likelihood of falling asleep since the participant sustained their concussion as well as prior to concussion. Scores of 0-1 indicate minimal chances of dozing off, and 2-3 indicate a greater chance of dozing off. ESS total scores range from 0–24. A total score of >10 indicates clinically meaningful subjective assessment of excessive sleepiness (Johns, 1991). ESS demonstrates good internal consistency, as indicated by Cronbach's alpha, ranging between 0.73-0.86 (Kendzerska et al., 2014).

Data Reduction

Objective Sleep Measure

ActiGraph raw activity scores were retrieved from the accelerometer using ActiLife6 software and converted to sleep-wake scores utilizing the Sadeh algorithm: (Sadeh, Sharkey, & Carskadon, 1994), which is appropriate for our sample between ages 18-23 years. Activity count data were collected at 30 Hz and automatically compressed and filtered through a band pass width of 0.25 to 2-3 Hz using the Sadeh algorithm (Sadeh, 2011). Filtered activity counts were summed over 60-second epochs. Sleep onset was defined as the first 10 consecutive immobile minutes, which has been found to be an optimal sleep onset setting for the majority of actigraphy sleep outcomes in a clinical sample with co-existing insomnia when compared to polysomnography outcomes (Kapella, Vispute, Zhu, & Herdegen, 2017).

The ActiGraph GT9X Link contains a wear-time sensor that detects when the accelerometer was removed, which allowed us to exclude non-wear time periods from data analysis when calculating sleep-wake measures. One trained investigator [NLH] was responsible for manually identifying the sleep periods per night using the participant's daily sleep log. We recognized that cognitive impairment throughout symptom recovery may have interfered with the accuracy of self-reported bed times and wake times, therefore, we also used inclinometer data (position of the participant each night captured from the tri-axial accelerometer) to identify when participants transitioned from standing or sitting to lying down each night. In the event that the information from the sleep log contradicted the inclinometer data, we used the inclinometer data to determine the sleep onset and sleep offset.

The following sleep-wake score measures were obtained using the following calculations:

- *Sleep onset latency:* The amount of time (minutes) it takes to transition from an "awake" state to a "sleep" state. Greater transitioning time is considered poor sleep.
- *Sleep efficiency* (%): Percentage of the total number of minutes of sleep divided by the total number of minutes in bed. Greater percentages are considered better sleep.
- *Total sleep time* (TST): The total number of minutes scored as "asleep"; used to calculate sleep efficiency. Greater number of minutes scored "asleep" is considered better sleep.
- *Wake after sleep onset*: Total minutes awake throughout the night after initially falling asleep. Greater minutes awake after sleep onset is considered poor sleep.
- *Awakenings*: Number of awakenings after initially falling asleep. Greater awakenings after sleep onset is considered poor sleep.

Due to the variation in sleep duration each night amongst participants, two actigraphy sleep outcome measures were normalized to control for the extent to which an individual was awake in relation to the total time in bed: 1) wake after sleep onset and 2) number of awakenings. Wake after sleep onset was normalized by dividing the total minutes awake throughout the night after initially falling asleep by the total time in bed each night and multiplying by 100 to be represented as a percentage. Number of awakenings was expressed as the number of awakenings per hour of the total time in bed. All other sleep measures were not influenced by the total sleep period variability.

Objective Sleep Measures throughout Recovery

Day-to-Day Comparisons

To avoid masking the variability that may be evident in concussed individuals post-injury, each actigraphy sleep outcome measure was analyzed day-by-day throughout recovery. Since the days for participant recruitment post-injury and length of recovery varied, we provided a visual representation to demonstrate the fluctuations in sample size per day.

To account for unavailable data in non-concussed participants who were matched to concussed participants with symptoms that persisted past the average recovery (>14 days post-injury (McCrory et al., 2017), we replicated the sequence of data captured within the first days where participants were instrumented with the accelerometer. For example, if sleep data in non-concussed participants were available from days 1-7, but were missing from days 14-21, we replicated the available data from days 1-7 and matched with the concussed data from days 14-21. Data from a previous prospective study supports that sleep variability was adequately captured in participants over 5 days, therefore this method was suitable to analyze data for non-concussed participants who were required to wear the accelerometer for longer periods of time (Raikes & Schaefer, 2016).

Scatterplots

Three time-points were selected to examine objective sleep outcomes across recovery: 1) 48-72 hours post-injury, 2) mid-point, and 3) within 48 hours of symptom recovery. In order to calculate the mid-point of recovery based on even versus odd days to symptom recovery, we used the following criteria: even days: middle three days within recovery were averaged; odd days to symptom recovery: middle two nights were averaged. The average of two days prior to symptom recovery was selected to examine sleep during the final days of watch wear-time. The average of sleep outcome means at 48-72 hours post-concussion were utilized to represent acute sleep post-injury. Continuous wear-time longitudinally became challenging in participants with recoveries longer than 7 days, therefore by taking the average of the days around the mid-point and symptom recovery, we were able to account for days where participants may not have data available.

Subjective Sleep Measures

PSQI Scoring

1. *Subjective sleep quality:* scored using a 0-3 Likert scale; (0) very good sleep quality, (1) fairly good sleep quality, (2) fairly bad sleep quality, (3) very bad sleep quality. Minimum score = 0 (better), maximum score = 3 (worse).
2. *Sleep onset latency*: The sum of the minutes and frequency were calculated using the following scoring system: 0=0, 1-2=1, 3-4=2, and 5-6=3. Minimum score = 0 (better), maximum score = 3 (worse).

3. *Sleep duration*: Scoring: >7 hours (0), 6-7 hours (1), 5-6 hours (2), and <5 hours (3). Minimum score = 0 (better), maximum score = 3 (worse).
4. *Sleep efficiency*: Calculated based on the total number of hours asleep divided by the total number of hours in bed (multiplied by 100). If a participant's sleep efficiency was >85%, they received a score of 0; 75%-84%=1, 65%-74%=2, and <65%=3. Minimum score = 0 (better), maximum score = 3 (worse).
5. *Sleep disturbances*: The score from each factor was summed to determine the final score for sleep disturbances: 0=0, 1-9=1, 10-18=2, and 19-27=3. Minimum score = 0 (better), maximum score = 3 (worse).
6. *Use of sleep medications*: The following scores were used based on how often the participant took sleep medicine: not since they sustained a concussion (0), less than once since concussion (1), once or twice since concussion (2), three or more times since concussion (3). Minimum score = 0 (better), maximum score = 3 (worse).
7. *Day dysfunction*: The sum of the scores reported from difficulty staying awake and keeping up enthusiasm determined the score for day dysfunction: 0=0, 1-2=1, 3-4=2, and 5-6=3. Minimum score = 0 (better), maximum score = 3 (worse).
8. *Global scores:* Total responses were coded on a scale of 0-3 for each component and are used to determine a combined global score of 0-21. Global scores were calculated by adding the final scores from the seven categories together. Total scores greater than 5 indicated poor sleep quality. Minimum score = 0 (better), maximum score = 21 (worse). Totals less than or equal to 5 indicated good sleep quality.

ESS Scoring

Total scores were determined by calculating the sum of all common situations. Values >10 indicated significant sleepiness (Johns, 1991).

Sleep Cluster Symptoms

In order to examine the association of SCAT3 sleep cluster symptoms on concussed and non-concussed individuals, as well as recovery length, we extracted the total symptom severity scores reported for sleep symptoms only: 1) drowsiness and 2) trouble falling asleep from the comprehensive list of 22 symptoms. Although fatigue is often considered a symptom related to sleep disturbances (Asken et al., 2017), we focused on symptoms that target sleep directly.

Statistical Analysis

To address aim 1 using concussed and non-concussed participants, separate 2 (group) x 3 (time-point) mixed model ANOVAs were used to compare actigraphy sleep outcomes, [sleep onset latency (SOL), normalized wake after sleep onset (WASO), sleep efficiency (SE), total sleep time (TST), and normalized number of awakenings] between groups across recovery time-points. The three time-points represented sleep at: 1) 48-72 hours post-injury, 2) mid-point of recovery, and 3) within 48 hours of the end of recovery. Line charts were used to visually examine the trajectory of each actigraphy sleep outcome means between groups from days 2-7 (most continuous data available) post-injury due to the variability in days to symptom recovery. Independent samples t-tests were conducted to determine differences between subjective sleep quality scores (PSQI and ESS) between concussed and non-concussed participants (concussed: since concussion; non-concussed: previous month). Descriptive statistics were used to describe patterns within individual subjective sleep components (PSQI and ESS) between concussed and non-concussed participants. Independent samples t-tests were also conducted to compare self-reported sleep habits and SCAT3 sleep cluster symptom severity between groups.

To address aim 2 using only concussed participants, Pearson's r correlations were conducted to determine the relationship between individual actigraphy sleep outcome measures (sleep onset latency (SOL), wake after sleep onset (WASO), sleep efficiency, total sleep time (TST), and number of awakenings) and days to symptom recovery at three time-points across recovery: 48-72 hours post-injury, mid-point of recovery, and within 48 hours of the end of recovery. Pearson's r correlations were conducted for each sleep outcome a second time, except with persistent symptoms (>30+ days, n=3) removed. Scatterplots were used to visually examine the relationship of each actigraphy sleep outcome measure at the three time-points across recovery and identify potential influential subsets.

Spearman's rho correlations were used, based on non-normally distributed data, to determine the relationship between subjective sleep quality scores (PSQI global scores and ESS total scores: since concussion) and the number of days to symptom recovery. Subsequent Spearman's rho correlations were conducted a second time between subjective sleep quality scores and days to symptom recovery, except with persistent symptoms (>30+ days, n=3) removed. Spearman's rho correlation analysis was also conducted to evaluate the relationship between the self-reported sleep symptoms cluster (drowsiness and trouble falling asleep) and days to symptom recovery. Strength of correlations were determined using the following criteria: weak = 0.30, moderate = 0.50, strong = 0.70 (Cohen, 1992). Statistical analyses were conducted using IBM SPSS Statistics (Version 24.0, IBM Corp., Armonk, NY), with alpha level set a priori at 0.05. A summary of statistical analysis methods is provided in Table 3.2.

Table 3.2. Statistical Analysis Methods

	Objective	Measures	Variables	Statistical Method
Aim 1: Concussed and Non-Concussed	a. To describe and compare sleep, as measured by actigraphy, throughout symptom recovery.	-Actigraphy	IV: -Group: concussed and non-concussed -Days across recovery (48-72 hours post-injury, mid-point of recovery, end of recovery DV: - sleep onset latency, sleep efficiency, total sleep time, wake after sleep onset, and number of awakenings	-2 (group) x 3 (time-point) mixed model ANOVAs -Descriptive statistics
Aim 1: Concussed and Non-Concussed	b. To describe and compare sleep, as measured by subjective sleep questionnaires, throughout symptom recovery.	-Pittsburgh Sleep Quality Index -Epworth Sleepiness Scale	IV: -Group: concussed and non-concussed DV: -PSQI global scores -ESS total scores	-Independent samples t-tests -Descriptive statistics
Aim 2: Concussed	a. To determine the relationship between sleep disturbances, as measured by actigraphy, and days to symptom recovery.	Actigraphy	IV: sleep onset latency, sleep efficiency, total sleep time, wake after sleep onset, and number of awakenings DV: -Days to symptom recovery	-Pearson's r correlations
Aim 2: Concussed	b. To determine the relationship between sleep, as measured by subjective sleep questionnaires, and symptom recovery.	-Pittsburgh Sleep Quality Index -Epworth Sleepiness Scale -SCAT3 graded symptom checklist	IV: -PSQI global scores: since concussion -ESS total scores: since concussion -SCAT3 sleep cluster (drowsiness and trouble falling asleep) DV: -Days to symptom recovery	Spearman's rho correlations

Project Timeline

Sept 2016	Oct 2016	Nov 2016	Dec 2016	Jan-May 2017	June-Aug 2017	Sept-Oct 2017	Nov-Dec 2017	Jan 2018	Feb 2018	Mar 2018	Apr 2018
Prospectus Proposal											
	Modify IRB										
	Recruitment & Data Collection										
								Data Analysis			
								Manuscript Writing			
										Dissertation Defense	

CHAPTER 4

DIFFERENCES IN SLEEP BETWEEN CONCUSSED AND NON-CONCUSSED COLLEGE STUDENTS: A MATCHED CASE-CONTROL STUDY[1]

[1]Hoffman NL, O'Connor PJ, Schmidt MD, Lynall RJ, Schmidt JD. To be submitted to *SLEEP*.

Abstract

Study Objectives: To describe and compare sleep between concussed and non-concussed individuals using actigraphy and subjective sleep questionnaires.

Methods: Twenty college students (20.0±1.5 years) were diagnosed with a concussion. Twenty non-concussed controls (20.6±1.4 years) were matched on age, sex, physical activity level, and sleep quality. A validated wrist-worn ActiGraph GT9X Link was provided during initial evaluation (within 72 hours of injury for concussed group) and worn day and night until symptom resolution (duration matched for non-concussed group). Groups completed the Sport Concussion Assessment Tool,V3 (SCAT3), Pittsburgh Sleep Quality Index (PSQI), and Epworth Sleepiness Scale (ESS). Separate 2x3 mixed-model ANOVAs were conducted to compare actigraphy sleep outcomes (sleep onset latency, wake after sleep onset, total sleep time, sleep efficiency, number of awakenings) between groups across recovery time-points (48-72 hours post-injury, mid-point, end of recovery). Independent samples t-tests compared PSQI global and ESS total scores, and sleep symptom severity between groups (α=0.05).

Results: Concussed individuals had longer sleep onset latencies (11.6±9.1min) compared with non-concussed individuals (7.3±3.9min, p=0.006). At 48-72 hours post-injury, concussed individuals took longer to fall asleep (15.8±11.6min) compared to non-concussed individuals (5.8±2.6min, p=0.002), but did not differ at other time-points or other actigraphy sleep outcomes. Concussed individuals experienced poorer sleep quality (concussed:7.8±3.0, non-concussed:4.2±1.8, p<0.001), excessive daytime sleepiness (concussed:12.6±5.3, non-concussed:8.5±4.4, p=0.011), and worse sleep-related symptom severity (concussed:6.8±4.4, non-concussed:1.7±2.5, p<0.001) compared to non-concussed individuals.

Conclusions: Concussed individuals may take longer to fall asleep and experience poorer sleep quality, excessive daytime sleepiness, and worse sleep symptoms compared to non-concussed individuals. These preliminary findings may guide clinicians to screen for individuals with sleep difficulties post-concussion and manage appropriately.

Keywords: Actigraphy, Sleep, Symptom recovery, Concussion

Statement of Significance: Sleep disturbances may negatively affect brain recovery; therefore, our study may help clinicians develop a deeper understanding of the relationship between sleep and concussion recovery. Our study informs clinical best practices, but may also guide clinicians to screen for sleep disturbances to mitigate negative effects from sleep disturbances after concussion. This study is a novel approach to studying post-concussion sleep and is the first of its kind to follow individuals throughout the duration of symptom recovery.

Introduction

Sleep disturbances are a common complaint following concussion, where as many as 70% of concussed individuals report sleep disturbances, fatigue, daytime sleepiness, or vigilance disturbances (Gosselin et al., 2009; Makley et al., 2008). Furthermore, insomnia (characterized by difficulties falling or staying asleep) is frequently reported in 30-60% of individuals across varying severities of traumatic brain injury (TBI)(Ouellet, Beaulieu-Bonneau, & Morin, 2006), with greater reports in individuals with concussion (Jaffee, 2015). A meta-analysis examining individuals across the TBI spectrum found that 853 (out of n=1706) experienced significantly greater sleep disturbances post-injury compared to healthy individuals (Mathias & Alvaro, 2012). Despite this evidence, sleep is not commonly assessed or considered when managing concussion recovery. Sleep may be an important missing piece in concussion management, since abnormalities in sleep components such as duration and quality may negatively impact symptom severity post-injury (Hoffman et al., 2017). Targeting sleep may be critical in establishing treatment to improve outcomes to assist with recovery following concussion (Wickwire et al., 2016).

Traditionally, sleep disturbances have been identified as a post-concussive symptom, however, sleep may have a more active role throughout recovery post-injury. It is well known that concussions and sleep are much intertwined, yet the mechanisms of how one influences the other is not clear. To our knowledge, direct comparison of sleep in concussed individuals throughout entire duration of recovery compared to healthy individuals has yet to be examined. What is known from recent research is that shorter sleep duration is related to worse sleep symptom severity in healthy individuals (McClure, Zuckerman, Kutscher, Gregory, & Solomon, 2013; Mihalik et al., 2013). Conversely, better sleep provides many benefits to healthy individuals. Research on the effects of increasing the number of hours of sleep in young adults demonstrated a significant improvement in areas such as reaction time, daytime alertness, and mood (Kamdar et al., 2004; Mah et al., 2011), and may also show the opposite effect in those with poor sleep quality following concussion (Jaffee, 2015).

Few studies exist on the effect of concussion on sleep immediately following injury through full recovery. Recent research examining self-reported sleep duration post-concussion compared to baseline sleep duration identified associations between shorter sleep duration with increased symptom severity and poorer cognitive function (Hoffman et al., 2017). Concussed individuals who slept less acutely following injury self-reported greater symptom severity scores until they were deemed asymptomatic (Hoffman et al., 2017).

Standardized subjective sleep questionnaires are commonly used to examine sleep in concussed and non-concussed individuals. The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and the Epworth Sleepiness Scale (ESS) (Johns, 1991), have been validated to evaluate sleep disturbances in a wide range of age groups, including college-aged individuals (Gosselin et al., 2009; Schmidt et al., 2015; Williams et al., 2008). By utilizing subjective measures as a mean to characterize the degree of sleep disturbances, researchers identified clinically significant sleep disturbances in concussed compared to non-concussed young adults . A comprehensive approach of subjective and objective sleep assessments is being recommended by researchers (Sadeh, 2011) to address individual sleep variability, especially post-concussion. Objective measures, such as ActiGraph wrist-worn accelerometers, are becoming more widely used since they assist in determining multi-day sleep-wake patterns through continuous recordings for 24-hour periods over longer periods of time compared to polysomnography (gold standard) (Ancoli-Israel et al., 2003; Sadeh, 2011; Sadeh et al., 1995). Surprisingly, despite the prevalence of sleep disturbances identified post-concussion, researchers have only used actigraphy to target sleep during the initial days following concussion or over various time points throughout recovery (Chiu et al., 2013; Raikes & Schaefer, 2016). Sleep has yet to be described daily across concussion recovery. The overall purpose of this study was to describe and compare sleep throughout the duration of recovery between concussed and non-concussed individuals using actigraphy and subjective sleep questionnaires.

Methods

Participants

University students (n=149) between the ages of 18 and 23 years were evaluated and diagnosed with a concussion by members of the sports medicine team or the University Health Center (UHC), between August 2016 and November 2017. Concussion diagnosis was based on clinical assessment as defined in the 5^{th} Consensus Statement on Concussion in Sport (McCrory et al., 2017). Once diagnosed, individuals were referred to the Concussion Research Laboratory to undergo a comprehensive concussion battery. Five varsity student-athletes and 15 university students were diagnosed with a concussion, referred within 72 hours post-injury (strict adherence was necessary to capture adequate acute actigraphy data), and agreed to participate.

Non-Concussed Control Group

Non-concussed control participants (n=20) were recruited and matched based on age (±1 year), sex, self-reported physical activity level (identified using International Physical Activity Questionnaire – Short Form categories: high, moderate, low, and sedentary) (Dinger et al., 2006), and previous month total sleep quality (scores within ±1) using the Pittsburgh Sleep Quality Index global scores (see Appendix Ia & Ib). Inclusion criteria for the non-concussed group consisted of no previous history of concussion within one year of assessment. To minimize potential stress related to the academic calendar (i.e. end of the semester exams), (Ahrberg et al., 2012; Lund et al., 2010), instrumentation of non-concussed participants was matched to the same time frame within the academic semester (defined by dividing the semester into quarters) that their match sustained a concussion. For example, a concussion sustained in August would fall in the first quarter of the semester – the participant's matched control would be instrumented at the same time or during the first quarter of the subsequent semester (i.e. January of the spring semester). Non-concussed participants were instrumented with the ActiGraph wrist-worn accelerometer on the same day of the week as the concussed participant and were asked to wear it for the same length of time that the concussed participant wore the accelerometer. For example, if a concussed participant was issued the accelerometer on a Friday, then the non-concussed participant was also required to begin wearing the device on a Friday to control for sleep variability that may occur on weekends compared to weekdays (Lund et al., 2010).

Exclusion criteria obtained from demographic forms for concussed and non-concussed individuals included: history of concussion (≥3), chronic headaches, migraines, meningitis or any other brain infection, seizure disorder, diabetes, sleep disorder, balance disorder, psychiatric disorder, learning disorder, attention deficit hyperactivity disorder (ADHD), autism, depression, bipolar, schizophrenia, moderate/severe traumatic brain injury, brain surgery, stroke, heart disease, substance abuse, and use of prescription medications that may influence sleep (i.e. antidepressants, amphetamines, diphenhydramine (Benadryl), benzodiazepines) (Saper et al., 2005), (Figure 4.1). Medications that participants commonly self-reported included acetaminophen for headaches post-concussion and seasonal allergy medications (i.e. Zyrtec). All participants signed an informed consent form approved by the University's Institutional Review Board.

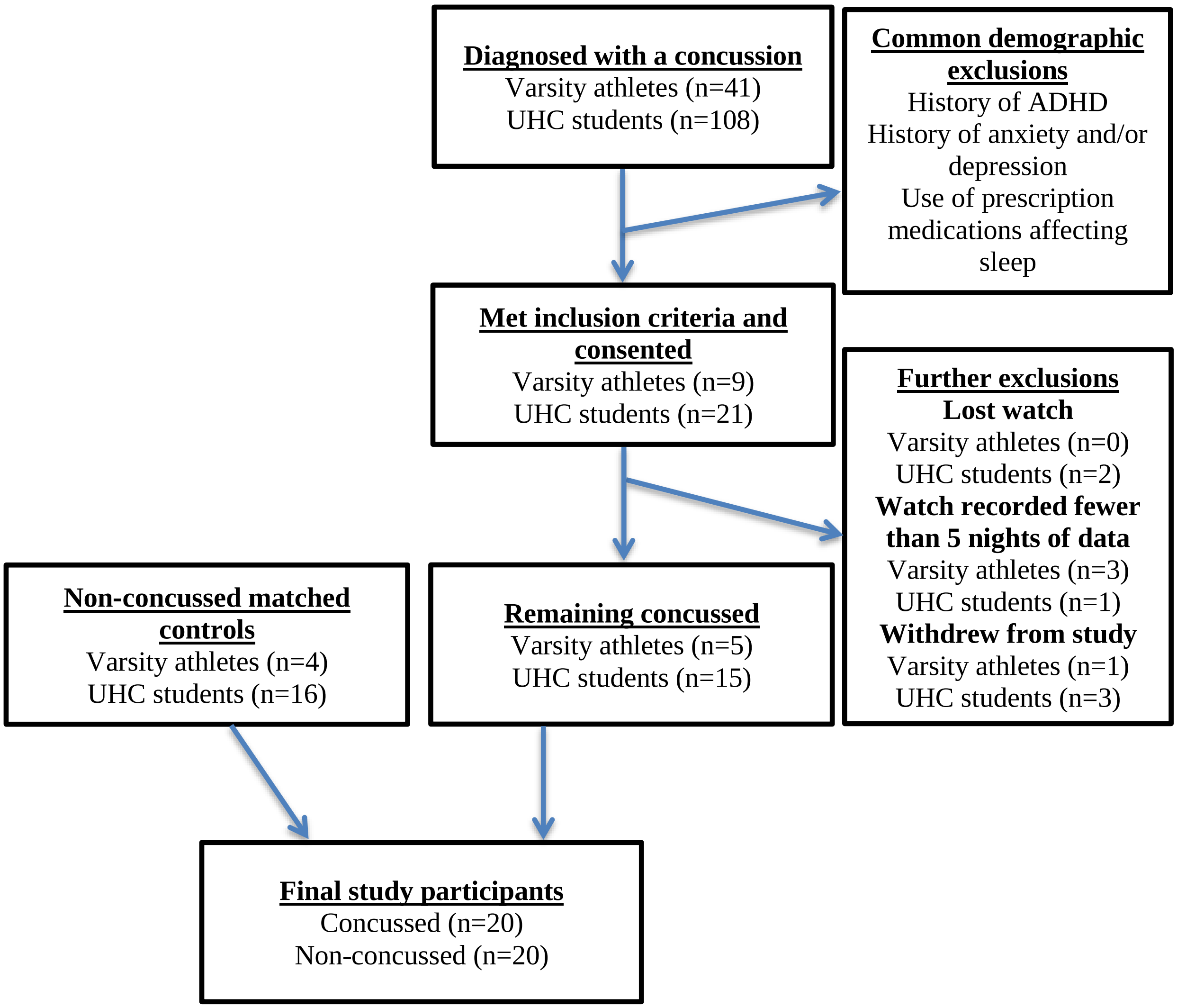

Figure 4.1. Participant selection flow chart.

Clinical Evaluation - Symptoms

Participants completed a demographic form and a graded symptoms checklist (Sport Concussion Assessment Tool, Version 3 – SCAT3; Appendix IIIb), which is a 22-item list of symptoms commonly associated with concussions. Participants rated the presence/absence of the symptom on a 0 to 6 Likert scale based on how they currently felt, with 0 indicating the symptom was not currently present, 1 and 2 indicating mild, 3 and 4 indicating moderate, and 5 and 6 indicating severe symptoms. Total symptom severity scores ranged from 0-132. Concussed individuals completed the SCAT3 at the first visit (within 72 hours post-concussion), daily thereafter, and 2) at the second visit (symptom recovery). Non-concussed participants completed the same measures as concussed participants for consistency across testing procedures (Table 4.1). All participants also completed an additional graded symptoms checklist, using modified instructions of the SCAT3 (Appendix IIIa), at the second visit to recall symptoms that are "typically experienced" (>3 times per week) in order to establish a retrospective baseline proxy.

Symptom severity progression following concussion was tracked daily using the SCAT3 graded symptoms checklist. Administration of the SCAT3 varied amongst participants depending on the limitations of daily access to a healthcare professional. Based on the current recommended clinical management protocol for sport-related concussion, varsity athletes were monitored daily throughout concussion recovery (McCrory et al., 2017). Varsity athletes completed the SCAT3 symptoms checklist daily using an interview format with a member of the sports medicine staff. Concussion management through the University Health Center does not include daily monitoring, therefore, university students completed a self-directed symptom evaluation, using the same SCAT3 symptom checklist except as an online symptom Qualtrics survey (Qualtrics, Provo, UT), administered daily to track symptom recovery.

Concussed participants were asked to complete the SCAT3 until they experienced symptom recovery, which was operationally defined as the number of days from the date of injury to symptom resolution determined by clinical evaluation. A member of the sports medicine team tracked daily symptom progression for varsity athletes. Since university students were not directly assessed daily by a healthcare professional, they were provided with written instructions to contact the Concussion Research Laboratory once they experienced symptom resolution. Symptoms were tracked daily by one trained investigator [NLH] via the online symptom Qualtrics survey to verify their self-reported symptom assessment. If university students did not complete the online symptom Qualtrics survey daily throughout recovery (~67% of students), the investigator contacted the participant with reminders via email. If university students still did not complete the daily symptom checklist despite reminders, the investigator communicated with participants via phone and/or email to determine the status of their symptoms and to schedule a follow-up evaluation.

Once participants self-reported subjective symptom resolution (either via the SCAT3 or direct email to the investigator), they were scheduled within 24-48 hours for a follow-up evaluation (2^{nd} visit), where they underwent a clinical evaluation using the same testing procedures during the first time-point. Symptom recovery was determined by comparing SCAT3 symptom severity at the follow-up evaluation to baseline proxy symptom severity scores (using modified instructions of the SCAT3 captured immediately following the current symptom report) that are typically experienced on a regular basis (>3 times per week. Reliable change criteria for SCAT3 symptom severity performance was used to determine that a change in symptom scores between the follow-up evaluation and baseline proxy scores did not exceed 2.97 (95% CI) when determining symptom recovery (Chin et al., 2016).

Table 4.1. Sleep Assessments at Various Time-Points

	Non-Concussed				Concussed		
	Identify Match	1st Visit	Daily	2nd Visit	1st Visit (within 72 hours)	Daily	2nd Visit (symptom recovery)
Sleep Measures							
SCAT3 Graded Symptoms Checklist		X	X	X[b]	X	X	X[b]
Actigraphy			X	X		X	X
Sleep Log			X	X		X	X
PSQI & ESS (previous month)	X[a]						
PSQI (x2)[c]							X[c]
ESS (x2)[c]							X[c]

Note. [a]Non-concussed individuals interested in the study were asked to complete the PSQI prior to being scheduled for the first time-point to match on sleep quality. [b]Concussed participants were required to complete two graded symptoms checklists at the follow-up time-point: one based on how they currently felt and then one on how they recalled feeling prior to concussion. [c]Concussed participants were first required to complete the PSQI and ESS forms pertaining to sleep since they sustained their concussion and then completed the same forms pertaining to sleep quality during the month prior to concussion.

Sleep Instruments

Objective Sleep Measure

Participants were issued an ActiGraph GT9X Link, a light-weight (14g; 3.5 x 3.5 x 1cm) tri-axial wrist-worn accelerometer, at their first visit to capture objective sleep continuously for 24-hour periods. Sleep timing and duration can be estimated from actigraphy and is a valid proxy for these sleep outcomes in healthy and concussed individuals (Wickwire et al., 2016). A validated computer-based algorithm for young adults was used to analyze the sampled movements captured by the accelerometers in order to determine sleep/wake parameters (Sadeh, 2011). The ActiGraph GT9X Link device can record acceleration data at a wide sampling rate of 30-100Hz. A sampling rate of 30 Hz was selected for this study based on the needs of capturing sleep and wake activity. The ActiGraph GT9X Link measures acceleration in a dynamic range of ±8G. Data were downloaded and processed using ActiLife Software (ActiGraph, version 6.13.3).

Concussed participants were instrumented with ActiGraph GT9X Link within 72 hours post-injury and were instructed to wear it continuously on their non-dominant wrist until they experienced symptom resolution based on their self-reported SCAT3 symptom severity score (Appendix-IIIa&b). Non-concussed participants were instructed to wear the device in the same way and for the same duration of time comparable to their matched concussed participant. The actigraphy sleep parameters include: sleep onset latency (amount of time to transition from awake to sleep), sleep efficiency (percentage of the number of minutes of sleep divided by the number of minutes in bed), total sleep time, wake after sleep onset (total minutes awake after sleep onset), and number of awakenings.

Sleep Log

All participants were asked to keep a daily sleep log (Appendix IV – modified version of National Sleep Foundation sleep diary), which includes subjective information pertaining to their wake and bed times, how easily they fell asleep, and how many times they woke up (including the minutes), and frequencies of naps during the day. Participants were instructed to record the time and reasons they removed the watch at any point. Subjective information collected from the diary was used to assist with identifying sleep onset and wake time intervals each night for calculating actigraphy sleep onset latency, sleep efficiency, total sleep time, wake after sleep onset, and number of awakenings. Sleep diaries have demonstrated moderate correlations with actigraphy (Lichstein et al., 2006).

Subjective Sleep Measures

Concussed participants completed two versions (original and with modified instructions) of each subjective sleep quality questionnaire to address sleep: 1) since concussion and 2) on a typical basis prior to injury. The modified version of the questionnaires used the same questions as the original version, but participants rated their sleep quality on the nights since they sustained their concussion only. Non-concussed participants completed the original versions of subjective sleep quality questionnaires. To our knowledge, the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale are the only subjective questionnaires in recent literature to be validated against objective sleep measures in concussed individuals (Wickwire et al., 2016).

The Pittsburgh Sleep Quality Index (PSQI – Appendix I) is a subjective sleep quality assessment supported by evidence of reliability and validity (Buysse et al., 1989). The PSQI is commonly used in clinical and research settings (Mollayeva, Thurairajah, et al., 2016) and has been widely used to distinguish between good and poor sleepers (Buysse et al., 1989). It has established adequate psychometric properties for young adults (Berger et al., 2017; Dietch et al., 2016) and has been validated against objective measures in patients with traumatic brain injury (Buysse et al., 1989; Fichtenberg et al., 2001). The PSQI is composed of 19 self-rated questions, which are grouped into seven sleep components: duration of sleep, sleep disturbances, sleep onset latency, day dysfunction, sleep efficiency, overall sleep quality, and use of sleeping medication (Buysse et al., 1989). Pittsburgh Sleep Quality Index global scores ranged from 0-21. A cutoff score of >5 has been used to identify clinically meaningful sleep disturbances in a wide variety of populations (Buysse et al., 1989). In this study, we chose to use a cutoff global score of >8 which has been suggested for identifying poorer sleep quality and insomnia following concussion (Fichtenberg et al., 2001). The PSQI demonstrates internal consistency, as indicated by Cronbach's alpha, ranging between 0.70-0.83 (Mollayeva, Thurairajah, et al., 2016).

The Epworth Sleepiness Scale (ESS – Appendix II) consists of 8 self-rated items, each scored from 0-3, which measure a subject's habitual "likelihood of dozing or falling asleep" in common situations of daily living (i.e. watching TV, sitting, talking) (Johns, 1991). This questionnaire was used to assess for the likelihood of falling asleep since the participant sustained their concussion as well as prior to concussion. Scores of 0-1 indicate minimal chances of dozing off, and 2-3 indicate a greater chance of dozing off. ESS total scores range from 0–24. A total score of >10 indicates clinically meaningful subjective assessment of excessive sleepiness (Johns, 1991). ESS demonstrates good internal consistency, as indicated by Cronbach's alpha, ranging between 0.73-0.86 (Kendzerska et al., 2014).

Data Reduction

Objective Sleep Measure

ActiGraph raw activity scores were retrieved from the accelerometer using ActiLife6 software and converted to sleep-wake scores utilizing the Sadeh algorithm: (Sadeh et al., 1994), which is appropriate for our sample between ages 18-23 years. Activity count data were collected at 30 Hz and automatically compressed and filtered through a band pass width of 0.25 to 2-3 Hz using the Sadeh algorithm (Sadeh, 2011). Filtered activity counts were summed over 60-second epochs. Sleep onset was defined as the first 10 consecutive immobile minutes, which has been found to be an optimal sleep onset setting for the majority of actigraphy sleep outcomes in a clinical sample with co-existing insomnia when compared to polysomnography outcomes (Kapella et al., 2017).

The ActiGraph GT9X Link contains a wear-time sensor that detects when the accelerometer was removed, which allowed us to exclude non-wear time periods from data analysis when calculating sleep-wake measures. One trained investigator [NLH] was responsible for manually identifying the sleep periods per night using the participant's daily sleep log. We recognized that cognitive impairment throughout symptom recovery may have interfered with the accuracy of self-reported bed times and wake times, therefore, we also used inclinometer data (position of the participant each night captured from the tri-axial accelerometer) to identify when participants transitioned from standing or sitting to lying down each night. In the event that the information from the sleep log contradicted the inclinometer data, we used the inclinometer data to determine the sleep onset and sleep offset.

Wake after sleep onset and frequency of awakenings were normalized to the total time in bed each night to control for variations in sleep duration. Wake after sleep onset was normalized by dividing the total minutes awake throughout the night after initially falling asleep by the total time in bed each night and multiplying by 100; represented as a percentage. Number of awakenings was expressed as the number of awakenings per hour throughout the total time in bed. All other sleep measures were not influenced by the total sleep period variability.

Three time-points were selected to examine objective sleep outcomes across recovery: 1) 48-72 hours post-injury, 2) mid-point, and 3) within 48 hours of symptom recovery. In order to calculate the mid-point of recovery based on even versus odd days to symptom recovery, we used the following criteria: odd days: middle three nights within recovery were averaged; even days to symptom recovery: middle two nights were averaged. The average of two days prior to symptom recovery was selected to examine sleep during the final days of watch wear-time. The average of sleep outcome means at 48-72 hours post-concussion were utilized to represent acute sleep post-injury. Continuous wear-time longitudinally became challenging in participants with recoveries longer than 7 days, therefore by taking the average of the days around the mid-point and end of recovery, we were able to account for days where participants may not have data available (mid-point: n=3, end: n=6).

<u>**Subjective Sleep Measures**</u>

PSQI Scoring

Global scores: Total responses were coded on a scale of 0-3 for each sleep component and were used to determine a combined global score of 0-21 (Buysse et al., 1989). Global scores were calculated by adding the sub-scores from the seven components together. Total scores greater than 8 indicated poor sleep quality. Totals less than or equal to 5 indicated good sleep quality. Minimum score = 0 (better), maximum score = 21 (worse).

ESS Scoring

Responses were coded on a scale of 0-3 for each situation where individuals were likely to fall asleep (0=would never doze, 3=high chance of dozing) (Johns, 1991). Total scores were then determined by calculating the sum of all common situations of daily living. Values greater than 10 indicated significant sleepiness.

Statistical Analysis

Descriptive statistics were used to display demographic information between groups (Table 4.3). We describe the trajectory of mean actigraphy sleep outcomes between groups across days 2-7 post-injury (to account for greatest representation of data among participants). Separate 2 (group) x 3 (time-point) mixed model ANOVAs were used to compare actigraphy sleep outcomes, [sleep onset latency (SOL), normalized wake after sleep onset (WASO), sleep efficiency (SE), total sleep time (TST), and normalized number of awakenings] between groups across the three recovery time points: 1) 48-72 hours post-injury, 2) mid-point of recovery, and 3) within 48 hours of the end of recovery. Independent samples t-tests were also conducted to compare subjective sleep quality scores (PSQI and ESS) between concussed and non-concussed participants (concussed: since concussion; non-concussed: previous month). Independent samples t-tests were also conducted compare self-reported sleep habits and SCAT3 sleep cluster symptom severity between groups. Statistical analyses were conducted using IBM SPSS Statistics (Version 24.0, IBM Corp., Armonk, NY), with alpha level set a priori at 0.05.

Results

Demographic information is presented in Table 4.2. There were no differences between groups based on age, height, and mass. Based on group frequencies, 60% were females and 70% of participants in each group self-reported engaging in a high level of physical activity. Days to symptom recovery ranged from 6 days to 38 days post-injury.

Table 4.2. Demographics for Concussion and Non-Concussed Individuals

Demographic Information	Concussed (n=20)	Non-Concussed (n=20)	*p*-value
Age: *M*±*SD* (years)	20.0±1.5	20.4±1.4	0.332
Sex: n (%)			
Males	8(40)	8(40)	
Females	12(60)	12(60)	
Height: *M*±*SD* (cm)	171.32±10.08	173.48±10.50	0.510
Mass: *M*±*SD* (kg)	69.81±12.25	77.84±16.51	0.089
Race: n (%)			
Asian	2(10)	1(5)	
Black	3(15)	0 (0)	
Hispanic	1(5)	0 (0)	
White	14(70)	19(95)	
Hand Dominance: n (%)			
Right	17(85)	18(90)	
Left	3(15)	2(10)	
Education: n (%)			
Freshman	8(40)	5(25)	
Sophomore	5(25)	4(20)	
Junior	1(5)	4(20)	
Senior	3(15)	5(25)	
5+	3(15)	2(10)	

Physical Activity Level: n (%)		
Moderate	6(30)	6(30)
High	14(70)	14(70)
Previous Concussions: n (%)		
0	10(50)	14(70)
1	7(35)	3(15)
2	3(15)	3(15)
Phase of Academic Semester: n(%)		
1st Quarter	4(20)	4(20)
2nd Quarter	12(60)	11(55)
3rd Quarter	3(15)	4(20)
4th Quarter	1(5)	1(5)

Note. Significance at $p<0.05$.

Actigraphy

Concussed participants (n=20) were recruited within 72 hours post-injury, (within 24 hours: n=8, within 48 hours: n=7, within 72 hours: n=5). When examining our data during the first week of recovery, 75% of pairs (concussed and non-concussed; n=15) complied with continuous wear between days 2-7 and only 1.8% of nightly sleep data were not available within the first 7 days (Figure 4.2). Self-reported reasons based on sleep logs for why data was not available often included: "watch fell off in the middle of the night" or "removed for a social function and forgot to put it back on". Table 4.3 demonstrates sample size fluctuations across the first week of recovery based on available data for each day. Approximately 26% of participants experienced symptom recovery within 10 days post-injury. Figures 4.3a-e depict mean trajectories of separate actigraphy sleep outcomes (a: SOL, b: normalized WASO, c: SE, d: TST, and e: normalized number of awakenings) across recovery.

Using a mixed model ANOVA, 18 concussed and 18 non-concussed participants had complete data across all three recovery time-points. A significant group x time-point interaction was found for SOL ($F_{2, 34}$=4.78, p=0.017). At 48-72 hours post-injury, concussed individuals took longer to fall asleep (15.8±11.6min) compared to non-concussed individuals (5.8±2.6min,

p=0.002) (Figure 4.4). Likewise, we observed a group main effect for SOL ($F_{1, 34}$ =8.73, p=0.006), such that concussed individuals took longer to fall asleep (11.6±9.1 min) compared to non-concussed individuals (7.3±3.9min). No significant group x recovery time-point interaction effects were found for normalized WASO, SE, TST, and normalized number of awakenings. No significant main effects were observed for normalized WASO, SE, TST, and normalized number of awakenings.

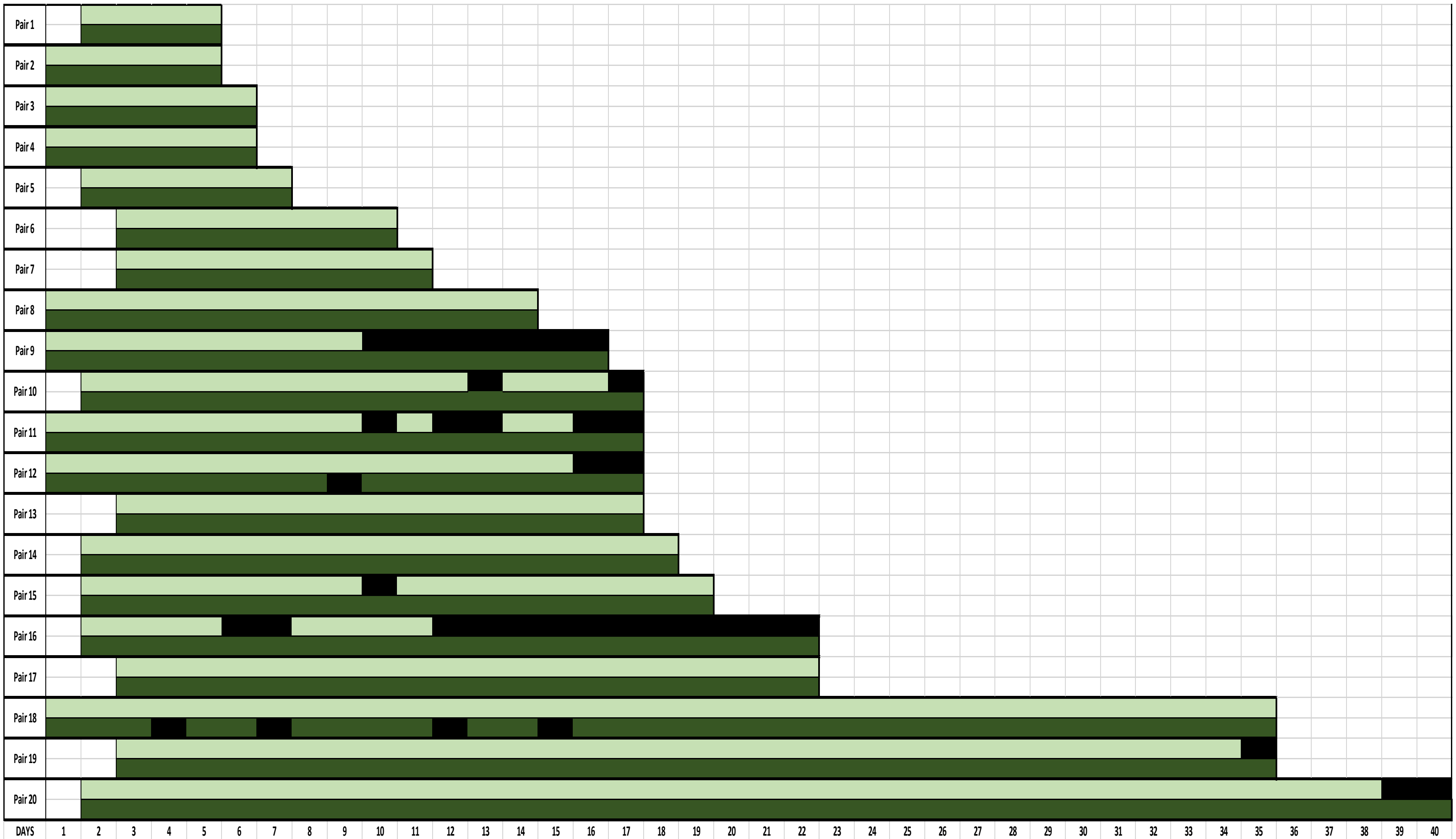

Figure 4.2. Actigraphy data representation between concussed (n=20) and non-concussed (n=20) participants. Black squares indicate unavailable data. Light green lines per pair represent concussed participants across days to symptom recovery.

Table 4.3. Variable Sample Sizes Across Recovery

Day(s) Post-Injury	Concussed (*n*)	Non-Concussed (*n*)
2	15	15
3	20	20
4	20	19
5	19	20
6	18	19
7	15	15

Note. Sample sizes varied depending on available data and/or symptom recovery.

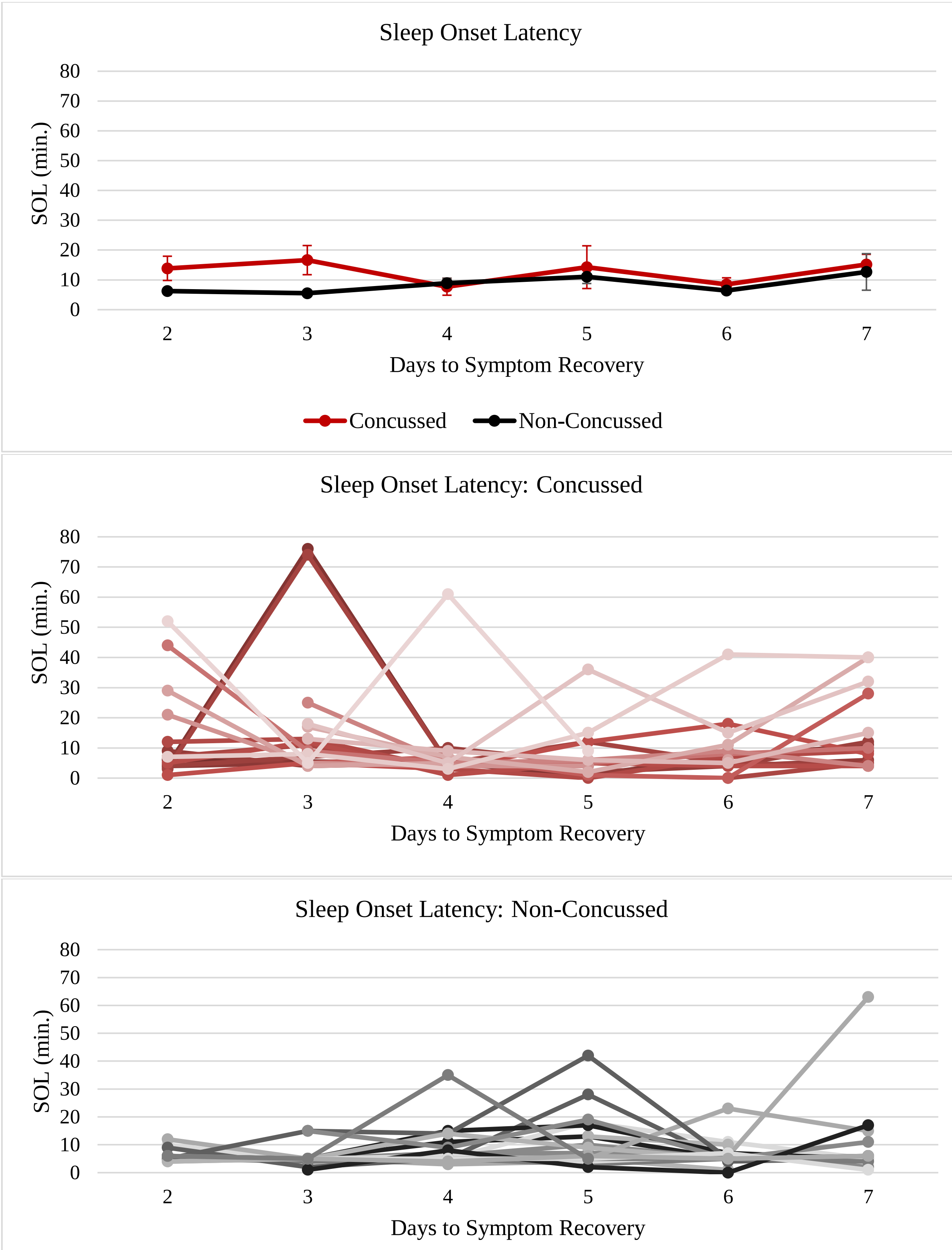

Figure 4.3a. Line chart depicting average sleep onset latency (min.) for days 2-7 between groups across symptom recovery (top). Middle and bottom charts = individual variability.

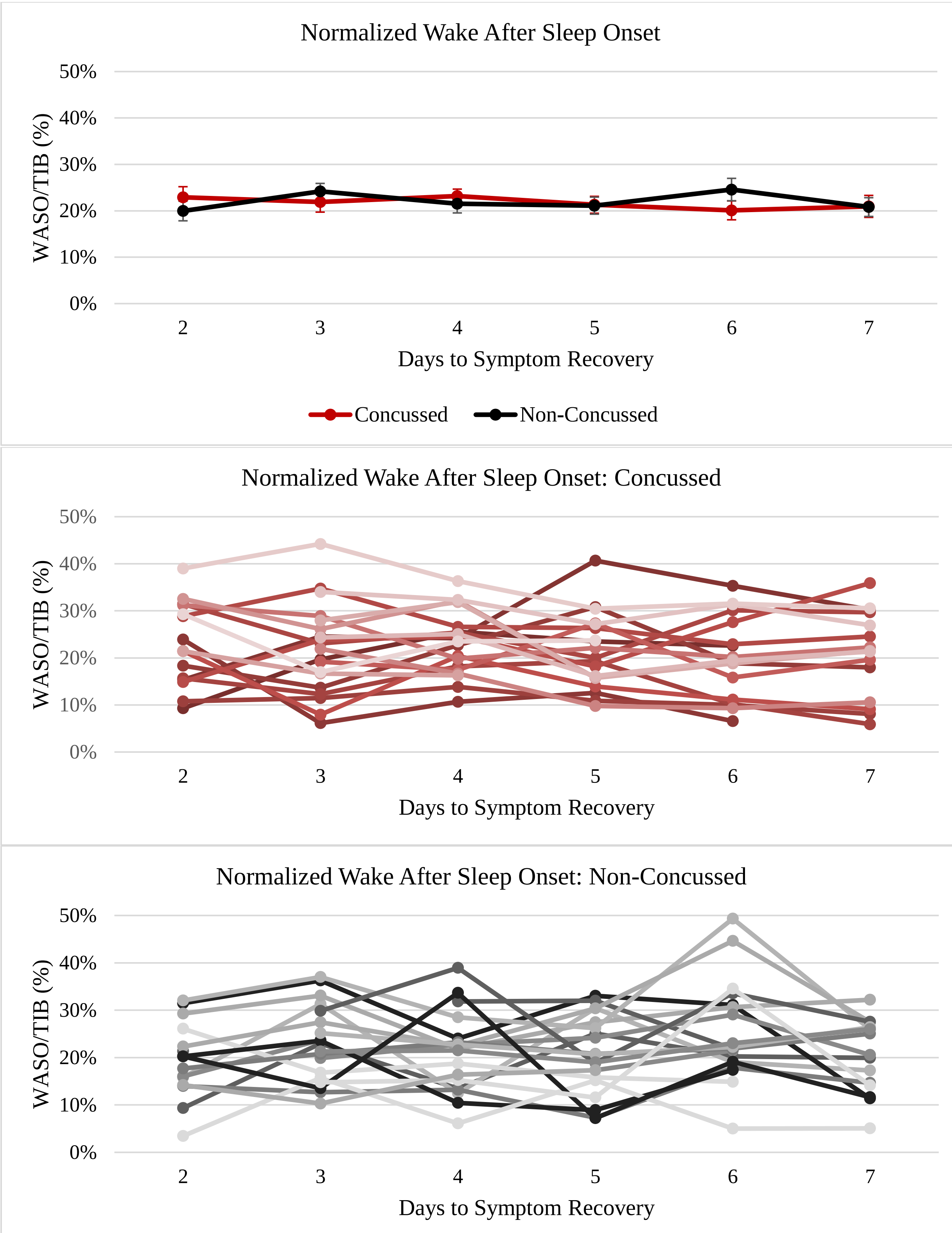

Figure 4.3b. Line chart depicting average normalized wake after sleep onset/total time in bed for days 2-7 between groups across symptom recovery (top). Middle and bottom charts = individual variability.

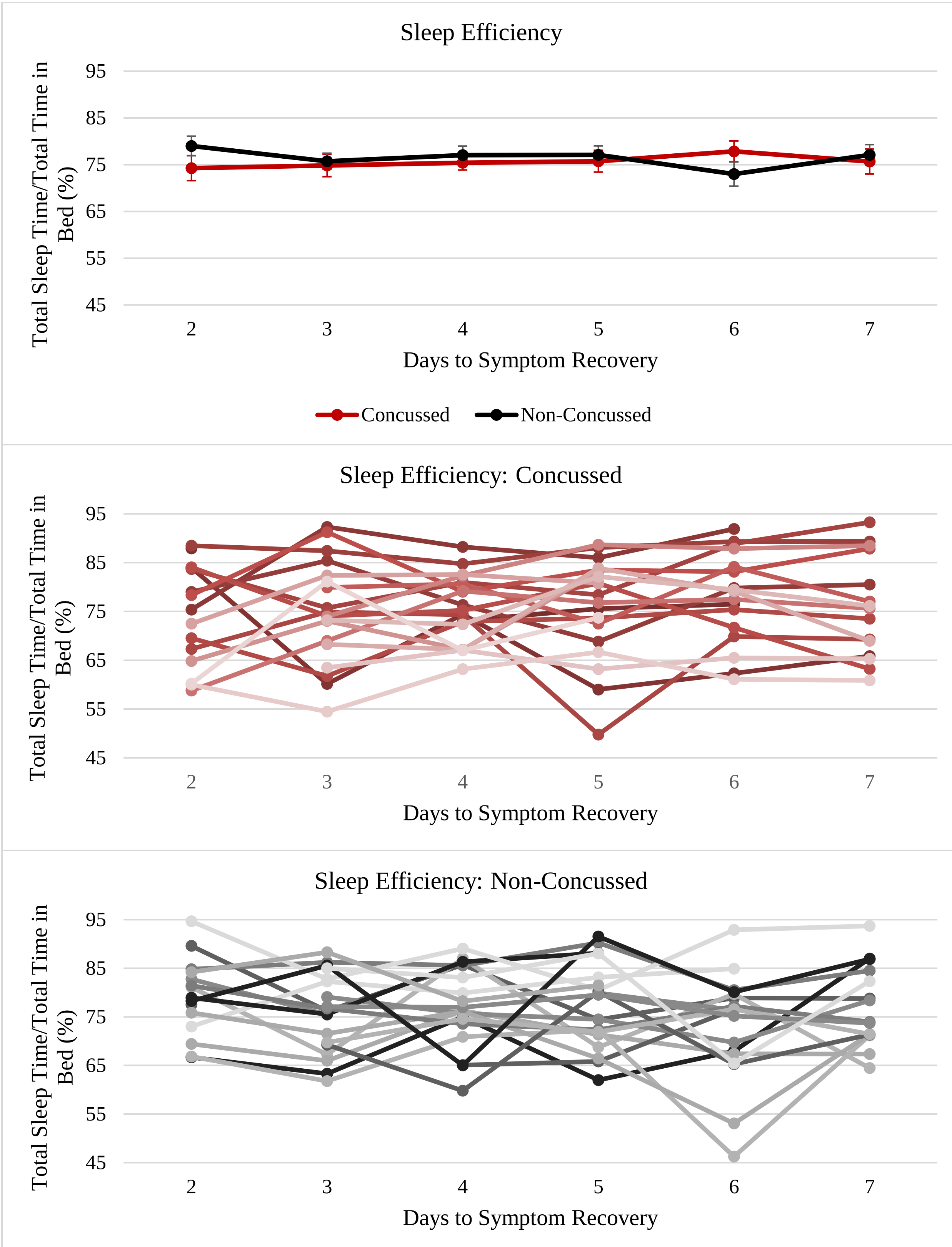

Figure 4.3c. Line chart depicting average sleep efficiency for days 2-7 between groups across symptom recovery (top). Middle and bottom charts = individual variability.

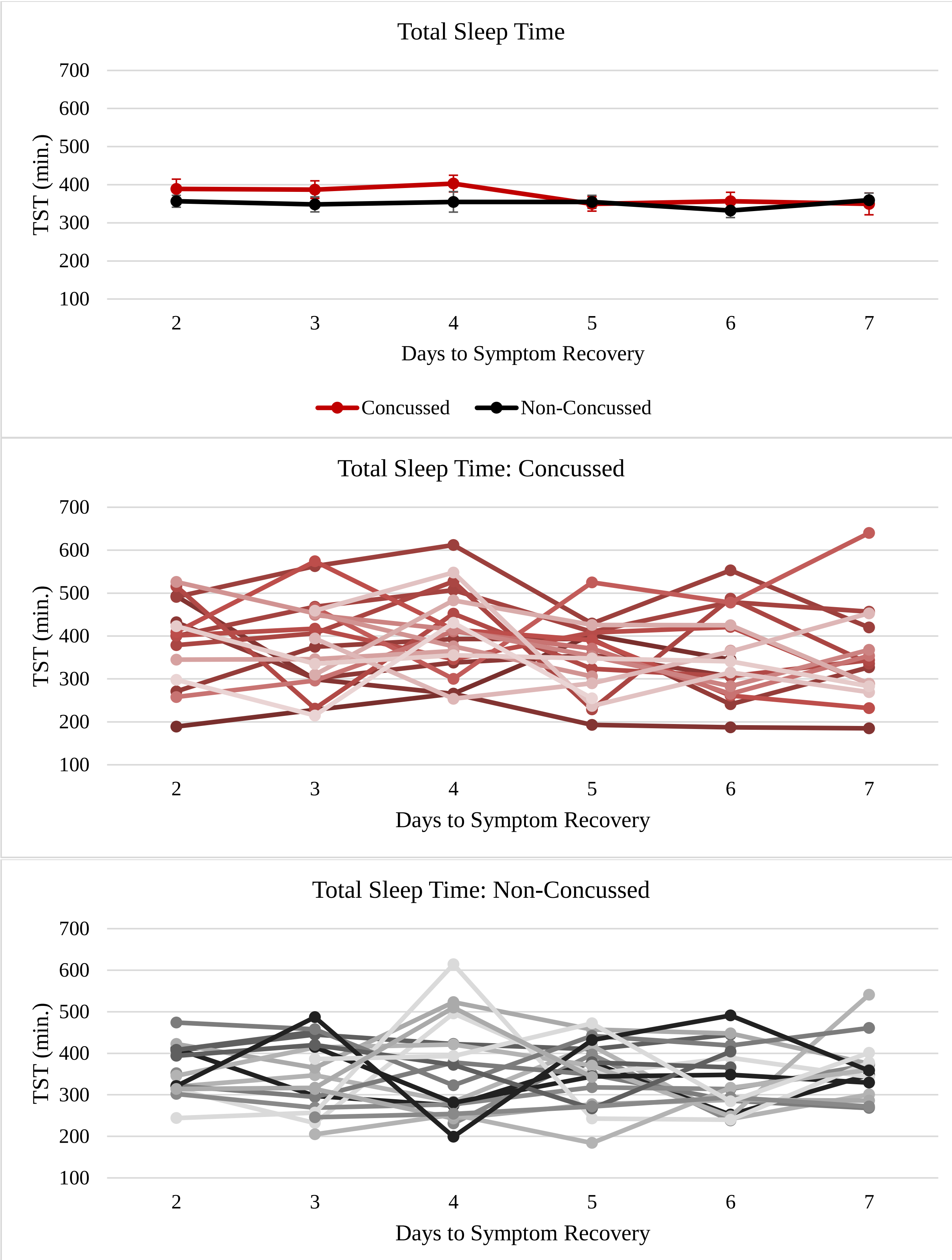

Figure 4.3d. Line chart depicting average total sleep time at night for days 2-7 between groups across symptom recovery (top). Middle and bottom charts = individual variability.

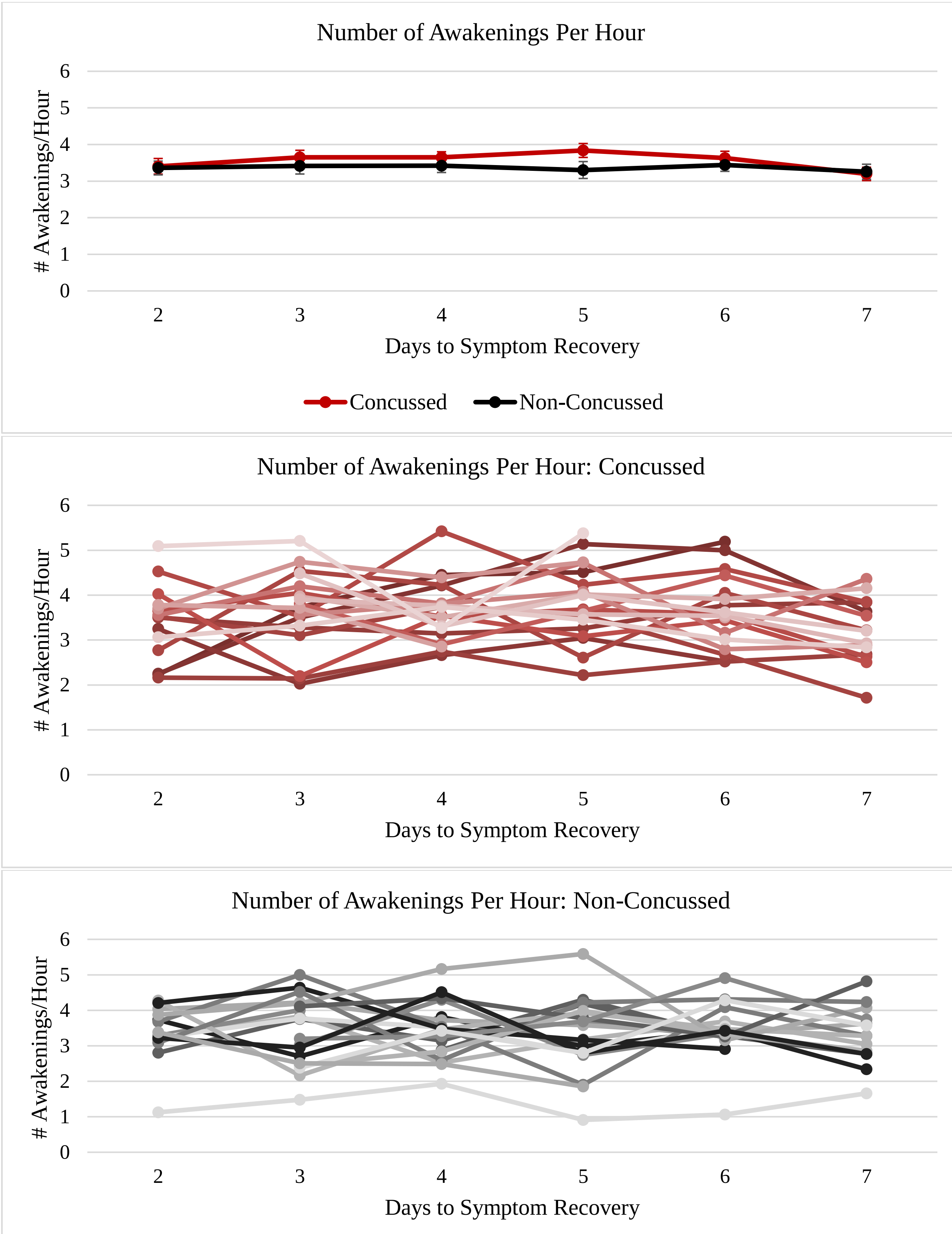

Figure 4.3e. Line chart depicting average number of awakenings/hour each night for days 2-7 between groups across symptom recovery (top). Middle and bottom charts = individual variability.

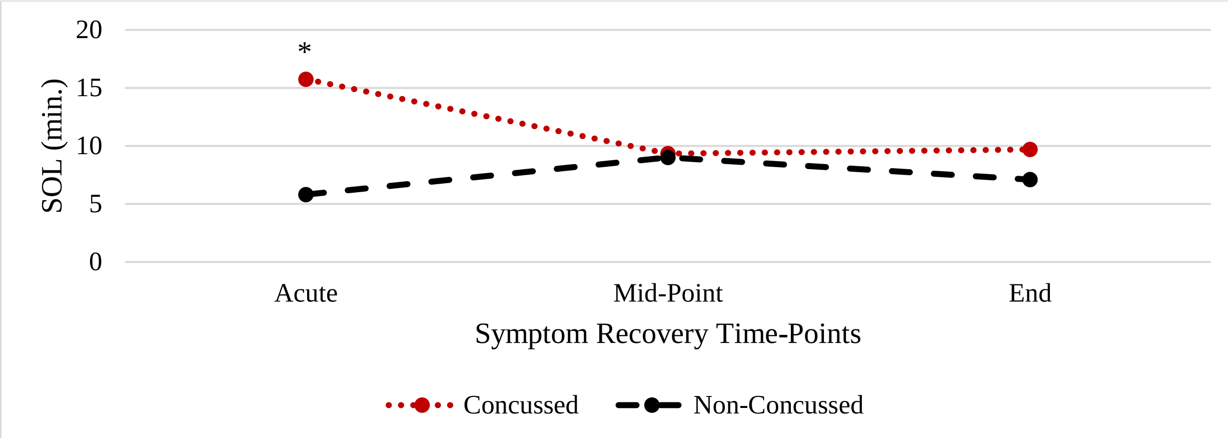

Figure 4.4. Interaction between sleep onset latency and concussed (n=18) and non-concussed (n=18) groups across symptom recovery time-points. *Significant interaction between groups and number of minutes to fall asleep at 48-72 hours (acute) post-injury ($p<0.05$).

Subjective Sleep Questionnaires

Significant differences existed in PSQI global scores between groups, where concussed individuals self-reported poorer sleep quality since concussion (7.8±3.0) compared to typical sleep quality in non-concussed individuals (4.2±1.8) ($t(38)=2.87$, $p<0.001$, $d=1.46$). Sleep components primarily contributing to differences include: sleep efficiency (concussed: 0.8±1.0, non-concussed: 0.1±0.3, $p=0.009$), sleep disturbances (concussed: 1.3±0.5, non-concussed: 1.0±0.4, $p=0.015$), use of sleep medications (concussed: 0.7±1.0, non-concussed: 0.1±0.2, $p=0.025$), and daytime dysfunction (concussed: 1.8±0.6, non-concussed: 0.9±0.9, $p<0.001$). Significant differences were observed in ESS total scores between groups, where concussed individuals self-reported a greater likelihood of falling asleep during common activities of daily living since their concussion (12.6±5.3) compared to typical daytime sleepiness in non-concussed individuals (8.5±4.4) ($t(38)=1.68$, $p=0.011$, $d=0.84$).

Individual sleep habit responses on the PSQI significantly differed in self-reported wake times, where concussed individuals woke up ~1 hour later (8:27am±1.7 hr) compared to non-concussed individuals (7:29am±0.9hr) ($t(38)=-2.22$, $p=0.035$, $d=0.48$). Self-reported bedtimes, sleep onset latency, and sleep duration did not differ between groups, but are summarized in

Table 4.4. Response frequencies and percentages for each PSQI (Table 4.5) and ESS (Table 4.6) question were further explored between concussed and non-concussed individuals. Seventy-five percent of concussed individuals reported that they woke up in the middle of the night or early morning since concussion compared to a larger percentage (85%) of non-concussed individuals. A smaller percentage of concussed participants (55%) reported that they had trouble sleeping because they had to use the bathroom, whereas 85% of non-concussed individuals reported this sleep problem. Fifty percent of concussed individuals reported that they had trouble sleeping following concussion due to “other reasons”, however, few participants provided the reason on the PSQI questionnaire. With respect to daytime sleepiness, 30% of concussed individuals stated that they were somewhat likely to fall asleep while sitting inactive in a public place compared to 10% of non-concussed individuals. Additionally, 100% of concussed individuals reported some degree of likelihood of falling asleep while sitting and reading compared to 90% of non-concussed individuals. The majority of concussed (95%) and non-concussed (100%) individuals reported that they were likely to doze off or fall asleep when lying down to rest in the afternoon.

Sleep Symptom Cluster

The SCAT3 graded symptom checklist was used to explore sleep disturbances between concussed (captured within 72 hours of concussion) and non-concussed individuals (captured during initial visit) based on how they currently felt on the sleep-related symptoms cluster (drowsiness and trouble falling asleep). Significant differences existed between concussed and non-concussed individuals, where concussed participants self-reported a higher severity of sleep-related symptoms (4.4±3.2) within 72 hours of concussion compared to non-concussed individuals (0.8±1.4) at the first visit ($t(38)$=0.9.28, p<0.001, d=1.44).

Table 4.4. Sleep Habits in Concussed and Non-Concussed Individuals using PSQI and ESS

Sleep Characteristics	Concussed (since concussion)	Non-Concussed (previous month)	*p*-value	*d*
Pittsburgh Sleep Quality Index: *M*±*SD*				
Bedtime (hh:mm±hour)	00:03±1.5	23:45±1.0	0.465	0.23
Sleep onset latency (min.)	24.3±17.5	17.4±10.0	0.135	0.48
Wake up time (hh:mm±hour)	08:27±1.7	07:29±0.9	0.035*	0.70
Sleep duration (hour)	7.3±1.4	7.2±1.1	0.756	0.08
Global score	7.8±3.0	4.2±1.8	<0.001**	1.46
Individual PSQI scores				
Sleep quality	1.2±0.8	0.9±0.6	0.189	0.42
Sleep latency	1.4±1.0	1.0±0.9	0.181	0.42
Sleep duration	0.8±0.6	0.6±0.8	0.373	0.28
Sleep efficiency	0.8±1.0	0.1±0.3	0.009*	0.94
Sleep disturbances	1.3±0.5	1.0±0.4	0.015*	0.66
Use of sleep medications	0.7±1.0	0.1±0.2	0.025*	0.83
Day dysfunction	1.8±0.6	0.9±0.9	<0.001**	1.18
Epworth Sleepiness Scale: *M*±*SD*				
Total score	12.6±5.3	8.5±4.4	0.011*	0.84
Total Sleep Cluster Symptom Severity	4.4±3.2	0.8±1.4	<0.001**	1.44
[a]Average nap frequency during recovery: n (%)				
None	4(22.2)	4(20)		
Once per week	5(27.8)	5(25)		
Twice per week	2(11.1)	5(25)		
3+ times per week	7(38.9)	6(30)		

Note. PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale. Large effect size for Cohen's *d* >0.80. Sleep cluster symptoms include: drowsiness and trouble falling asleep.
[a]Missing concussed napping frequency (n=2).
*Significance at $p<0.05$. **Significance at $p<0.001$.

Table 4.5. Percentages of Self-reported PSQI Sleep Disturbances in Concussed and Non-Concussed Participants

	No trouble		< Once/week		1-2 times/week		3+ times/week	
Individual Questions	C	NC	C	NC	C	NC	C	NC
Pittsburgh Sleep Quality Index: (%)								
Sleep disturbances: How often have you had trouble sleeping because you:								
Wake up in the middle of the night or early morning	25%	15%	15%	30%	30%	30%	30%	25%
Have to get up to use the bathroom	45%	15%	20%	35%	30%	30%	5%	20%
Cannot breathe comfortably	85%	90%	10%	5%	5%	5%	0%	0%
Cough or snore loudly	80%	90%	10%	5%	0%	5%	10%	0%
Feel too cold	75%	80%	15%	15%	10%	5%	0%	0%
Feel too hot	50%	40%	15%	45%	20%	10%	15%	5%
Had bad dreams	50%	60%	15%	35%	20%	5%	15%	0%
Have pain	50%	0%	20%	0%	25%	0%	5%	0%
Other reason(s)	35%	90%	20%	5%	30%	5%	15%	0%

Note. C=concussed, NC=non-concussed. Concussed participants were asked to complete the Pittsburgh Sleep Quality Index based on sleep since they sustained their concussion. Non-concussed participants answered based on their sleep from the previous month. Percentages sum to 100% across categories for each question.

Table 4.6. Percentages of Self-reported ESS Daytime Sleepiness in Concussed and Non-Concussed Participants

Individual Questions	Never		Slight chance		Moderate chance		High chance	
	C	NC	C	NC	C	NC	C	NC
Epworth Sleepiness Scale: (%)								
Daytime Sleepiness: How likely are you to doze off or fall asleep in the following situations?								
Sitting and reading	0%	10%	15%	45%	15%	35%	40%	40%
Watching TV	5%	10%	25%	45%	10%	60%	25%	20%
Sitting, inactive in a public place	40%	55%	10%	20%	5%	30%	30%	10%
As a passenger in a care for an hour	15%	0%	20%	45%	15%	40%	20%	15%
Lying down to rest in the afternoon	5%	0%	15%	50%	45%	15%	30%	40%
Sitting and talking to someone	65%	75%	30%	0%	5%	15%	5%	0%
Sitting quietly after a lunch	30%	40%	35%	10%	5%	45%	25%	10%
In a car, stopped for a few minutes	11%	17%	25%	10%	5%	10%	10%	0%

Note. C=concussed, NC=non-concussed. Concussed participants were asked to complete the Epworth Sleepiness Scale based on daytime sleepiness since they sustained their concussion. Non-concussed participants answered based on their daytime sleepiness from the previous month. Percentages sum to 100% across categories for each question.

Discussion

This study is the first to examine sleep continuously throughout the duration of symptom recovery using actigraphy and subjective sleep questionnaires. Overall, our results further justify that concussed individuals experience various sleep disturbances as measured by both objective and subjective sleep measures following injury and may serve as a foundation for future research assessing sleep across consecutive days post-injury. Although there was no evidence of statistically significant interactions between concussed and non-concussed groups across recovery for WASO, TST, SE, or number of awakenings, we identified that concussed individuals experienced greater difficulties falling asleep during the acute stage post-injury compared to non-concussed individuals.

Actigraphy

We instrumented concussed participants within 72 hours of concussion and captured continuous data until symptom recovery. By examining our actigraphy line charts for all sleep components across days 2 through 7 (where we had the most consistent data across consecutive days), we found that the error bars for concussed participants do not overlap with the non-concussed participants during the acute phase (days 2-3), but mostly converge throughout the first 7 days post-injury. This pattern was consistent across sleep onset latency, sleep efficiency, and total sleep time, where sleep was initially disturbed relative to the non-concussed group, but appeared to normalize over time. Normalized wake after sleep onset and number of awakenings appeared to remain consistent between groups throughout the entire symptom recovery. Day 1 was not included in our analyses due to a small recruitment sample immediately post-injury (n=8).

To our knowledge, this is the first study to identify differences in sleep onset latency between concussed and non-concussed college students across recovery. On average, concussed individuals took longer to fall asleep within 48-72 hours post-injury compared to non-concussed individuals. Longer sleep onset within 48-72 hours in concussed individuals may be explained by confounding factors not objectively analyzed in this study (i.e. timing of daytime TST measured by actigraphy). Concussed individuals may take frequent naps acutely following concussion, therefore may be at risk of having difficulties falling asleep at night (Ye, Hutton Johnson, Keane, Manasia, & Gregas, 2015). We captured frequency of daily naps per week subjectively using sleep logs (Table 4.4), but surprisingly we did not observe major differences between concussed and non-concussed individuals. It is unknown if acute difficulties falling asleep may be attributed to the timing of the naps during the day or the concussion itself.

Previous studies using wrist-worn actigraphy commonly report an underestimation in SOL (Sadeh, 2011). Interestingly, our findings demonstrate shorter SOL (~6 min.) in non-concussed individuals compared to a larger study of 108 college students, where individuals took an average of 12 minutes to fall asleep (Slater et al., 2015). Our data were captured on weekdays and weeknights, which may explain the apparent differences between studies, especially in a smaller sample of non-concussed college students (Lund, Reider, Whiting, & Prichard, 2010). Social habits on the weekends may influence individuals to fall asleep faster compared to weekdays. Further research with larger samples is needed to explore actigraphy sleep outcomes on weekdays compared to weekends in college students.

Despite a lack in statistical differences in sleep efficiency between groups, concussed participants exhibited a greater range of individual variability in sleep efficiency (54.5-88.5%) at 48 hours post-injury compared to non-concussed individuals (70-90%), where greater than 85%

is considered good sleep efficiency according to the National Sleep Foundation. There were no obvious differences in the normalized wake after sleep onset or number of awakenings per hour based on the error bars when comparing groups across recovery, which may be explained by our matching criteria based on the same day of the week and time of the semester that participants were instrumented with the wrist-worn accelerometer.

When further examining individual variation, we noted that our actigraphy values are seemingly higher in WASO and number of awakenings, and lower in sleep efficiency compared to normative values (Slater et al., 2015). Despite commonly reported overestimation of WASO using actigraphy, greater WASO in both concussed and non-concussed individuals may have been influenced by altered sleep-wake patterns one week prior the transition out of daylight savings time (Tonetti, Erbacci, Fabbri, Martoni, & Natale, 2013); possibly affecting ~13% of our total sample. Further research is warranted to investigate the variability in sleep-wake cycle alterations.

With regards to TST, our findings are consistent with other studies where no significant differences were evident in TST despite self-reports of poor sleep quality using subjective measures (Gosselin et al., 2009; Ouellet, Savard, & Morin, 2004; Raikes & Schaefer, 2016). Healthy college students typically report insufficient sleep and irregular sleep-wake patterns, with 75% of students reporting feeling tired and sleepy at least once a week (Lund et al., 2010). When further examining our day-to-day averages for total sleep time based on actigraphy, we found that concussed individuals slept for approximately 6.5 hours at 3 days following concussion, but non-concussed individuals were sleeping even less (5.8 hours). This presents an interesting finding such that concussed individuals and non-concussed individuals are experiencing similar sleep disturbances regardless of injury.

Poor sleep quality in healthy college students has been found to mostly be attributed to irregular sleep schedules and “self-imposed sleep deprivation” (Ye et al., 2015), whereas concussed individuals may be experiencing greater sleep disturbances attributed to the concussion itself (i.e. symptom burden), especially during the acute stages of concussion recovery (Hoffman et al., 2017). Future studies should consider further examination of sleep symptoms acutely in concussed and non-concussed individuals. Our study points to the need for further research to better understand the acute sleep disturbances experienced following concussion. Several preclinical human and animal models have recently been used to develop sleep therapies to target improving recovery post-injury (i.e. bright light therapy, human melatonin, dietary supplementation with branched chain amino acids in mice, aerobic exercise) (Sandsmark, Elliott, & Lim, 2017). Researchers should consider examining objective sleep within 72 hours post-injury with a larger sample in order to guide the next step of identifying the need for sleep treatment programs in concussed individuals.

Subjective Sleep Questionnaires

Overall, poorer sleep quality was prevalent in concussed individuals following concussion compared to typical sleep quality in otherwise healthy college-aged students. Thirty percent exceeded the cutoff value of 8 on the PSQI since they sustained their concussion, indicating clinically meaningful insomnia on the basis of Diagnostic and Statistical Manual of Mental Disorders, V4 (DSM-IV) criteria (Fichtenberg et al., 2001), compared to 10% in the non-concussed group. Our study is comparable to that of a similar study examining subjective sleep post-TBI with a wider age range (33.8±14.5 years), where 30% of individuals also exceeded the same global cutoff of 8 post-acutely (Fichtenberg et al., 2001). Researchers may consider using PSQI global score cutoffs of 8 in future research to screen for individuals with insomnia post-

TBI in order to develop adequate treatment approaches to aid in recovery. In order to target acute periods immediately following concussion, future studies should consider developing and validating a sleep quality questionnaire similar to the PSQI that assesses sleep in a shorter time frame in order to identify insomniacs who may be at risk of longer recoveries.

Our findings on subjective sleep-related disturbances compared to non-concussed individuals are consistent with previous research (Gosselin et al., 2009; Theadom et al., 2015; Williams et al., 2008), where poor sleep quality, greater sleep disturbances, and greater daytime sleepiness are evident post-concussion. Seventy-five percent of concussed individuals exceeded the cutoff value of 10 for excessive daytime sleepiness (Johns, 1991), compared to 25% in the non-concussed group. However, no differences existed in self-reported sleep onset latencies between concussed and non-concussed individuals. Our findings showed that 60% of concussed individuals (n=12) reported average SOL scores that exceeded a cutoff of 20 minutes (Augner, 2011), which could be clinically meaningful, as prolonged SOL greater than 20 minutes has been found to be a predictor of poor subjective sleep quality (Augner, 2011). In comparison to non-concussed individuals, these findings were not surprising considering that research has shown that greater sleep difficulties including insufficient sleep and irregular sleep-wake patterns are also commonly found in healthy college-aged individuals (Lund et al., 2010).

We also found no differences in total sleep time per night between concussed and non-concussed individuals, which is consistent with the literature in college-aged individuals (Gosselin et al., 2009). Consistent with our findings, a survey examining sleep patterns found that healthy college students self-report sleeping an average of 7 hours per night (Lund et al., 2010). Approximately 30% of our concussed and 30% of our non-concussed individuals reported sleeping less than 7 hours per night. In a study that examined sleep duration in healthy individuals, those who slept less than 7 hours per night exhibited more severe symptom cluster scores during baseline concussion testing (clusters: somatic, cognitive, emotional, and sleep) (McClure et al., 2014), which is comparable to our sleep symptom cluster findings where concussed individuals self-reported more severe sleep symptoms compared to non-concussed individuals.

Sleep Cluster Symptoms

Subjective complaints of sleep disturbances are becoming more commonly investigated through the use of graded symptoms checklists to describe sleep problems (Covassin, Elbin, Harris, Parker, & Kontos, 2012; Kostyun, 2015; Tkachenko, Singh, Hasanaj, Serrano, & Kothare, 2016; Towns, Silva, & Belanger, 2015). We administered the SCAT3 and found that concussed individuals experienced a higher severity of drowsiness and trouble falling asleep compared to non-concussed individuals. One recent study administered the SCAT3 assessment tool to individuals 2 days to 3 years after concussion, where approximately 31% of concussed individuals reported sleep complaints (i.e. drowsiness and trouble falling asleep) (Tkachenko et al., 2016). Studies have shown that sleep-related symptoms are often described as having a debilitating effect on an individual's quality of life (Fichtenberg et al., 2001; Ouellet et al., 2004; Zeitzer, Friedman, & O'Hara, 2009). The SCAT3 graded symptoms checklist is easy to administer and may reveal clinical sleep deficiencies early following concussion. Many clinicians have the ability to evaluate sleep-related symptoms by using graded symptom checklists, which may help in developing treatment plans to mitigate the negative effects of symptom burden post-concussion.

Limitations

Due to numerous exclusion factors and the challenges of quick report and referral post-injury, we were limited to a small sample of 20 concussed and 20 non-concussed college-aged students. The use of actigraphy is low-cost and convenient for longitudinal studies, however, early termination (13.3%) of actigraphy monitoring was a limitation in our study, which is common across the literature (Wickwire et al., 2016). Two participants lost the watch and approximately 13% recorded less than 5 nights of data (either from early recovery or participants discontinued to wear the watch). Despite multiple reminders, several concussed participants failed to complete the daily symptoms checklist throughout the duration of symptom recovery, therefore we were unable to define symptom recovery using the final day of self-reported symptoms. We also lost one participant due to non-compliance with a follow-up evaluation within 48 hours of self-reporting symptom recovery despite several means of communication. When calculating pre-injury average bedtime information, it is important to note that data were collected retrospectively, and may have been subjected to recall bias.

Conclusion

This prospective study is the first to examine sleep throughout recovery between concussed and non-concussed individuals. By controlling for numerous comorbid conditions that have been found to worsen sleep, we were able to focus on confound-free sleep objectively and subjectively within individual days to further elucidate the relationship with symptom recovery. Generally, by using actigraphy we were able to objectively identify that concussed individuals experienced greater difficulties falling asleep compared to non-concussed individuals during the acute phase (48-72 hours) post-injury. This may be clinically meaningful to identify individuals who may be at risk of insomnia early post-injury in order to manage appropriately. Additionally, we were able to add to the growing body of literature that concussed samples self-report poorer overall sleep quality, greater daytime sleepiness, and worse sleep-related symptoms compared to non-concussed individuals. Perception of sleep quality may be just as important to capture other areas of sleep disturbances that are not identified in objective measurements throughout recovery.

Our findings provide preliminary information to guide researchers to the next step on examining the day-to-day variability in sleep acutely following concussion, followed by possible sleep interventions on sleep onset latency acutely (i.e. providing sleep hygiene education during the early stages). Sleep and concussion recovery remains an area that needs a multi-dimensional approach in order to identify causality of sleep on recovery.

CHAPTER 5

DETERMINING THE RELATIONSHIP BETWEEN POST-CONCUSSION SLEEP AND SYMPTOM RECOVERY USING ACTIGRAPHY AND SUBJECTIVE QUESTIONNAIRES[1]

[1]Hoffman NL, O'Connor PJ, Schmidt MD, Lynall RJ, Schmidt JD. To be submitted to the *American Journal of Sports Medicine*.

Abstract

Background: Sleep-wake disturbances are commonly reported following concussion, but how sleep variability influences concussion recovery has not been examined.

Purpose: To determine the relationship between sleep, as measured by actigraphy and subjective sleep questionnaires, and days to symptom recovery.

Study Design: Cross-Sectional Study.

Methods: Nineteen students (age: 20.0±1.5 years) were diagnosed with a concussion, and asked to complete a demographic form and graded symptoms checklist within 72 hours post-injury and within 24-48 hours of symptom recovery. Participants were instrumented with a validated wrist-worn ActiGraph GT9X Link device during the initial evaluation to wear continuously until symptom recovery. Modified instructions on the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale were given at symptom recovery to assess recalled sleep quality since concussion. Pearson's correlations were conducted to determine the relationship between days to symptom recovery and actigraphy sleep outcome measures: sleep onset latency (SOL), wake after sleep onset (WASO), sleep efficiency (SE), total sleep time (TST), and number of awakenings; separately at three time-points across recovery: 48-72 hours post-injury, mid-point, and within 24-48 hours of becoming symptom-free. Spearman's rho correlations were used to determine the relationship between 1) subjective sleep quality scores (PSQI global and ESS total since concussion) and 2) sleep cluster symptom severity scores and days to symptom recovery.

Results: We observed a moderate positive relationship between normalized WASO at mid-point and days to symptom recovery (r=0.60, p=0.014) and a moderate negative relationship between SE at mid-point and days to symptom recovery (r=-0.54, p=0.030), where individuals who were awake longer each night and/or were less efficient sleeping took longer to recover. A moderate positive relationship also existed between TST towards the end of recovery and days to symptom

recovery (r=0.57, p=0.034), where concussed individuals who took longer to recover were sleeping more at the end of their recovery. No other actigraphy sleep outcomes correlated with days to symptom recovery at any of the three time-points. Individuals who self-reported poorer sleep quality (based on PSQI) since concussion took longer to experience symptom recovery (PSQI: r_s=0.70, p=0.001).

Conclusion: Greater amount of time spent awake each night and poorer sleep efficiency at mid-point of recovery, greater sleep duration towards the end of recovery, and poorer self-reported sleep quality post-injury may be associated with the number of days to symptom recovery. Actigraphy and subjective sleep questionnaires may separately provide unique information to guide future research in the next step of exploring benefits of sleep interventions to expedite recovery.

Key Terms: Sleep, Symptom recovery, Concussion, Actigraphy, Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale

What this study adds to existing knowledge: Greater amount of time spent awake each night and poorer sleep efficiency at mid-point of recovery, greater sleep duration towards the end of recovery, and poorer self-reported sleep quality post-injury may be associated with the number of days to symptom recovery.

What is known: Actigraphy is becoming a major assessment tool in sleep research to monitor sleep over longer periods of time.

Introduction

Immediate recognition of clinical symptoms, physical signs, balance performance impairment and cognitive-related deficits, continues to be a challenge for clinicians due to the complex nature of concussions (McCrory et al., 2017). The medical community widely recognizes clinical symptoms including, but not limited to, headaches, dizziness, feeling like in a fog, and increased irritability post-injury (Harmon et al., 2013; Lovell et al., 2006; McCrory et al., 2017). Physical signs (i.e. loss of consciousness and difficulties remembering events prior to and following injury), gait unsteadiness, and poor performance on cognitive-related tasks (i.e. memory and reaction time) may also be evident following concussion (McCrory et al., 2017). However, sleep disturbances are given less attention clinically despite a growing body of literature that suggests as many as 70% of concussed athletes report sleep disturbances, fatigue, daytime sleepiness, and vigilance disturbances after a concussion (Gosselin et al., 2009; Parcell et al., 2006). Post-concussion sleep disturbances are often described as having a debilitating effect on many individuals (Sullivan, Edmed, Allan, Karlsson, & Smith, 2014). Despite this evidence, sleep is not commonly assessed or considered when managing concussion recovery, which may be an important missing piece in concussion management, since abnormalities in sleep components such as duration, quality, and efficiency may negatively impact symptom severity. Sleep may be a critical variable in treatment to assist with recovery following concussion.

Traditionally, sleep disturbances have been identified as a post-concussive symptom, however, sleep may have more of an active role on recovery. Among healthy individuals, sleep has been found to be pertinent in the maintenance of cognitive functions including learning, memory formation, and neural plasticity (Carrier, 2014; Ron et al., 1980). Studies focusing on the effects of increasing the number of hours of sleep in young adults demonstrated a significant improvement in areas such as reaction time, daytime alertness, and mood (Kamdar et al., 2004; Mah et al., 2011). It is possible that improving post-concussion sleep might aid in recovery of commonly experienced neurocognitive and balance deficits.

The cognitive deficit and symptom recovery period typically takes 10-14 days, on average, among collegiate athletes (McCrory et al., 2017), with atypical persistent symptoms occurring >30 days (Leddy, Baker, Haider, Hinds, & Willer, 2017). Due to the variability of symptom presentation amongst individuals, treatment recommendations continue to be challenging (Pardini et al., 2012), especially when addressing rest and sleep. Acute cognitive and physical rest presently serves as a foundation to recovery during the initial days (24-48 hours) post-injury (McCrory et al., 2017). Rest may ease symptom severity and promote recovery (McCrory et al., 2017). However, it is unknown if the type of rest includes sleep due to limited literature within this novel area. It is unclear if clinicians should address sleep hygiene education throughout recovery in order to mitigate symptom burden when managing concussions. The importance that sleep may have on concussion recovery should be further explored, especially when determining an individual's readiness to return to physical activities and everyday tasks such as work/academics.

Few studies exist on the effects of sleep acutely following concussion (Chiu et al., 2013; Hoffman et al., 2017; Raikes & Schaefer, 2016) and none-to-date have examined sleep throughout the duration of symptom recovery. Recent research examining self-reported sleep duration post-injury compared to baseline sleep duration has identified associations between shorter sleep duration and increased symptom severity at various time-points post-injury (Hoffman et al., 2017). Concussed individuals who slept less acutely following injury self-reported greater symptom severity scores until they were deemed asymptomatic. Individuals with poor sleep quality following concussion may experience persistent symptoms, however, the relationship between sleep and concussion recovery remains unclear as sleep has not been examined prospectively throughout recovery. The purpose of this study is to determine the relationship between sleep, as measured by actigraphy and subjective sleep questionnaires, and days to symptom recovery. We hypothesize that concussed individuals with poorer sleep may take longer to recover.

Methods

Participants

University students (n=149) between the ages of 18 and 23 years were evaluated and diagnosed with a concussion by members of the sports medicine team or the University Health Center (UHC), between August 2016 and November 2017. Concussion diagnosis was based on clinical judgement as defined in the 5th Consensus Statement on Concussion in Sport (McCrory et al., 2017). Once diagnosed, individuals were referred to the Concussion Research Laboratory to undergo a comprehensive concussion battery. Five varsity student-athletes and 15 university students were diagnosed with a concussion, referred within 72 hours post-injury (strict adherence was necessary to capture adequate acute actigraphy data), and agreed to participate (Figure 5.1). As per the university's concussion management protocol, physicians instructed participants to minimize cognitive activity and refrain from physical activity until symptoms subside. They were not provided any specific information addressing how to improve their sleep habits following concussion.

Exclusion criteria included: history of concussion (≥3), chronic headaches, migraines, meningitis or any other brain infection, seizure disorder, diabetes, pre-existing sleep disorder, balance disorder, psychiatric disorder, learning disorder, attention deficit hyperactivity disorder

(ADHD), depression, bipolar, schizophrenia, moderate/severe traumatic brain injury, brain surgery, substance abuse, and use of prescription sleep medications or other medications that may influence sleep. Data from eleven participants were excluded throughout the study due to various reasons: lost watch (n=2), watch recorded fewer than 5 nights of data (n=4), withdrew (n=4), or unable to report for follow-up testing within 48 hours of experiencing symptom recovery (n=1). Our final sample included 19 concussed individuals. All participants signed an informed consent form approved by the University's Institutional Review Board.

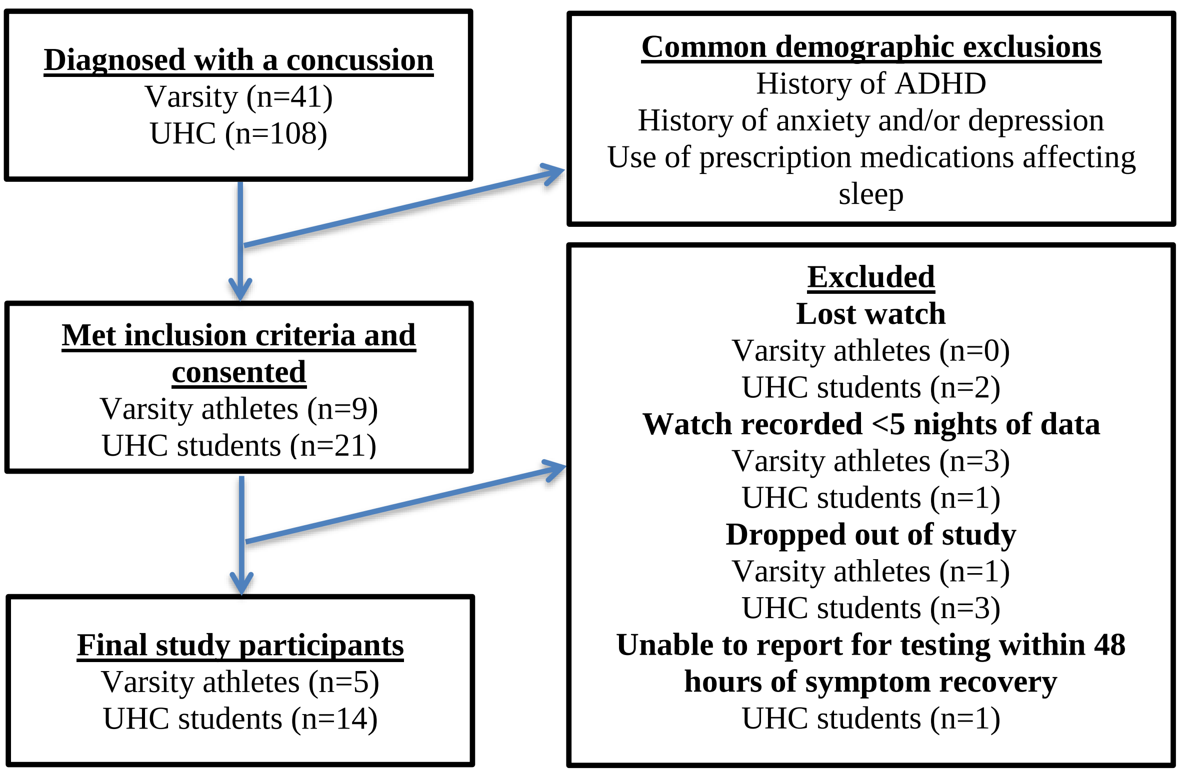

Figure 5.1. Participant selection flow chart.

Clinical Evaluation - Symptoms

Participants completed a demographic form and a graded symptoms checklist (Sport Concussion Assessment Tool, Version 3 – SCAT3; Appendix IIIb), which is a 22-item list of symptoms commonly associated with concussions. Participants rated the presence/absence of the symptom on a 0 to 6 Likert scale based on how they currently felt, with 0 indicating the symptom was not currently present, 1 and 2 indicating mild, 3 and 4 indicating moderate, and 5 and 6 indicating severe symptoms. Total symptom severity scores ranged from 0-132. Participants completed the SCAT3 at the first visit (within 72 hours post-concussion), daily thereafter, and 2) at the second visit (symptom recovery). Participants also completed an additional graded symptoms checklist, using modified instructions of the SCAT3 (Appendix IIIa), at the second visit to recall symptoms that are "typically experienced" (>3 times per week) in order to establish a retrospective baseline proxy.

Symptom severity progression following concussion was tracked daily using the SCAT3 graded symptoms checklist. Administration of the SCAT3 varied amongst participants depending on the limitations of daily access to a healthcare professional. Based on the current recommended clinical management protocol for sport-related concussion, varsity athletes were monitored daily throughout concussion recovery (McCrory et al., 2017). Varsity athletes completed the SCAT3 symptoms checklist daily using an interview format with a member of the sports medicine staff. Concussion management through the University Health Center does not include daily monitoring, therefore, university students completed a self-directed symptom evaluation, using the same SCAT3 symptom checklist except as an online symptom Qualtrics survey (Qualtrics, Provo, UT), administered daily to track symptom recovery.

Concussed participants were asked to complete the SCAT3 until they experienced symptom recovery, which was operationally defined as the number of days from the date of injury to symptom resolution determined by clinical evaluation. A member of the sports medicine team tracked daily symptom progression for varsity athletes. Since university students were not directly assessed daily by a healthcare professional, they were provided with written instructions to contact the Concussion Research Laboratory once they experienced symptom resolution. Symptoms were tracked daily by one trained investigator [NLH] via the online symptom Qualtrics survey to verify their self-reported symptom assessment. If university students did not complete the online symptom Qualtrics survey daily throughout recovery (~67% of students), the investigator contacted the participant with reminders via email. If university students still did not complete the daily symptom checklist despite reminders, the investigator communicated with participants via phone and/or email to determine the status of the symptoms and to schedule a follow-up evaluation.

Once participants self-reported subjective symptom resolution (either via the SCAT3 or direct email to the investigator), they were scheduled within 24-48 hours for a follow-up evaluation (2nd visit), where they underwent a clinical evaluation using the same testing procedures during the first time-point. Symptom recovery was determined by comparing SCAT3 symptom severity at the follow-up evaluation to baseline proxy symptom severity scores (using modified instructions of the SCAT3 captured immediately following the current symptom report) that are typically experienced on a regular basis (>3 times per week. Reliable change criteria for SCAT3 symptom severity performance was used to determine that a change in symptom scores between the follow-up evaluation and baseline proxy scores did not exceed 2.97 (95% CI) when determining symptom recovery (Chin et al., 2016).

Sleep Instruments

Objective Sleep Measure

Participants were issued an ActiGraph GT9X Link, a light-weight (14g; 3.5 x 3.5 x 1cm) tri-axial wrist-worn accelerometer, at their first visit to capture objective sleep continuously for

24-hour periods. Sleep timing and duration can be estimated from actigraphy and is a valid proxy for these sleep outcomes in healthy and concussed individuals (Wickwire et al., 2016). A validated computer-based algorithm for young adults was used to analyze the sampled movements captured by the accelerometers in order to determine sleep/wake parameters (Sadeh, 2011). The ActiGraph GT9X Link device can record acceleration data at a wide sampling rate of 30-100Hz. A sampling rate of 30 Hz was selected for this study based on the needs of capturing sleep and wake activity. The ActiGraph GT9X Link measures acceleration in a dynamic range of ±8G. Data were downloaded and processed using ActiLife Software (ActiGraph, version 6.13.3).

Participants were instrumented with ActiGraph GT9X Link within 72 hours post-injury, and were instructed to wear it continuously on their non-dominant wrist until they experienced symptom resolution based on their self-reported SCAT3 symptom severity score (Appendix-IIIa&b). The actigraphy sleep parameters include: sleep onset latency (amount of time to transition from awake to sleep), sleep efficiency (percentage of the number of minutes of sleep divided by the number of minutes in bed), total sleep time, wake after sleep onset (total minutes awake after sleep onset), and number of awakenings per hour each night.

Sleep Log

Participants were asked to keep a daily sleep log (Appendix IV – modified version of National Sleep Foundation sleep diary; sleepfoundation.org), which includes subjective information pertaining to their wake and bed times, how easily they fell asleep, and how many times they woke up (including the minutes), and whether they took a nap during the day. Participants were instructed to record the time and reasons they removed the watch at any point. Subjective information collected from the diary was used to assist with determining sleep onset and wake time intervals each night for calculating actigraphy sleep onset latency, sleep efficiency, total sleep time, and wake after sleep onset. Sleep diaries have demonstrated moderate correlations with actigraphy (Lichstein et al., 2006).

Subjective Sleep Measures

Concussed participants completed two versions (original and with modified instructions) of each subjective sleep quality questionnaire to address sleep: 1) since concussion and 2) on a typical basis prior to injury. The modified version of the questionnaires used the same questions as the original version, but participants rated their sleep quality on the nights since they sustained their concussion only. Non-concussed participants completed the original versions of subjective sleep quality questionnaires. To our knowledge, the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale are the only subjective questionnaires in recent literature to be validated against objective sleep measures in concussed individuals (Wickwire et al., 2016).

The Pittsburgh Sleep Quality Index (PSQI – Appendix I) is a subjective sleep quality assessment supported by evidence of reliability and validity (Buysse et al., 1989). The PSQI is commonly used in clinical and research settings (Mollayeva, Thurairajah, et al., 2016) and has been widely used to distinguish between good and poor sleepers (Buysse et al., 1989). It has established adequate psychometric properties for young adults (Berger et al., 2017; Dietch et al., 2016) and has been validated against objective measures in patients with traumatic brain injury (Buysse et al., 1989; Fichtenberg et al., 2001). The PSQI is composed of 19 self-rated questions, which are grouped into seven sleep components: duration of sleep, sleep disturbances, sleep onset latency, day dysfunction, sleep efficiency, overall sleep quality, and use of sleeping medication (Buysse et al., 1989). Pittsburgh Sleep Quality Index global scores ranged from 0-21. A cutoff score of >5 has been used to identify clinically meaningful sleep disturbances in a wide variety of populations (Buysse et al., 1989). In this study, we chose to use a cutoff global score of >8 which has been suggested for identifying poorer sleep quality and insomnia following concussion (Fichtenberg et al., 2001). The PSQI demonstrates internal consistency, as indicated by Cronbach's alpha, ranging between 0.70-0.83 (Mollayeva, Thurairajah, et al., 2016).

The Epworth Sleepiness Scale (ESS – Appendix II) consists of 8 self-rated items, each scored from 0-3, which measure a subject's habitual "likelihood of dozing or falling asleep" in common situations of daily living (i.e. watching TV, sitting, talking) (Johns, 1991; Mondal et al., 2013). This questionnaire was used to assess for the likelihood of falling asleep since the participant sustained their concussion as well as prior to concussion. Scores of 0-1 indicate minimal chances of dozing off, and 2-3 indicate a greater chance of dozing off. ESS total scores range from 0–24. A total score of >10 indicates clinically meaningful subjective assessment of excessive sleepiness (Johns, 1991). ESS demonstrates good internal consistency, as indicated by Cronbach's alpha, ranging between 0.73-0.86 (Kendzerska et al., 2014).

In order to examine the association of SCAT3 sleep cluster symptoms on concussed individuals and recovery length, we extracted the total symptom severity scores reported within 72 hours of concussion for sleep-related symptoms only: 1) drowsiness and 2) trouble falling asleep, from the comprehensive list of 22 symptoms. Although fatigue is often considered a symptom related to sleep disturbances (Asken et al., 2017), we focused on symptoms that target sleep directly.

Data Reduction

<u>Objective Sleep Measure</u>

ActiGraph raw activity scores were retrieved from the accelerometer using ActiLife6 software and converted to sleep-wake scores utilizing the Sadeh algorithm: (Sadeh et al., 1994), which is appropriate for our sample between ages 18-23 years. Activity scores were collected at

30 Hz and automatically compressed and filtered through a band pass width of 0.25 to 2-3 Hz using the Sadeh algorithm (Sadeh, 2011). Filtered activity counts were summed over 60-second epochs. Sleep onset was defined as the first 10 consecutive immobile minutes, which has been found to be an optimal sleep onset setting for the majority of actigraphy sleep outcomes in a clinical sample with co-existing insomnia when compared to polysomnography outcomes (Kapella et al., 2017).

The ActiGraph GT9X Link contains a wear-time sensor that detects when the accelerometer was removed, which allowed us to exclude non-wear time periods from data analysis when calculating sleep-wake measures. One trained investigator [NLH] was responsible for manually identifying the sleep periods per night using the participant's daily sleep log. We recognized that cognitive impairment throughout symptom recovery may have interfered with the accuracy of self-reported bed times and wake times, therefore, we also used inclinometer data (position of the participant each night captured from the tri-axial accelerometer) to identify when participants transitioned from standing or sitting to lying down each night. In the event that the information from the sleep log contradicted the inclinometer data, we used the inclinometer data to determine the sleep onset and sleep offset.

Wake after sleep onset and frequency of awakenings were normalized to the total time in bed each night to control for variations in sleep duration. Wake after sleep onset was normalized by dividing the total minutes awake throughout the night after initially falling asleep by the total time in bed each night and multiplying by 100; represented as a percentage. Number of awakenings was expressed as the number of awakenings per hour throughout the total time in bed. All other sleep measures were not influenced by the total sleep period variability.

Three time-points were selected to examine objective sleep outcomes across recovery: 1) 48-72 hours post-injury, 2) mid-point, and 3) within 48 hours of symptom recovery. In order to calculate the mid-point of recovery based on even versus odd days to symptom recovery, we used the following criteria: odd days: middle three nights within recovery were averaged; even days to symptom recovery: middle two nights were averaged. The average of two days prior to symptom recovery was selected to examine sleep during the final days of watch wear-time. The average of sleep outcome means at 48-72 hours post-concussion were utilized to represent acute sleep post-injury. Continuous wear-time longitudinally became challenging in participants with recoveries longer than 7 days, therefore by taking the average of the days around the mid-point and symptom recovery, we were able to account for days where participants may not have data available.

Subjective Sleep Measures

PSQI Scoring

Global scores: Total responses were coded on a scale of 0-3 for each sleep component and were used to determine a combined global score of 0-21 (Buysse et al., 1989). Global scores were calculated by adding the sub-scores from the seven components together. Total scores greater than 8 indicated poor sleep quality. Totals less than or equal to 5 indicated good sleep quality. Minimum score = 0 (better), maximum score = 21 (worse).

ESS Scoring

Responses were coded on a scale of 0-3 for each situation where individuals were likely to fall asleep (0=would never doze, 3=high chance of dozing) (Johns, 1991). Total scores were then determined by calculating the sum of all common situations of daily living. Values greater than 10 indicated significant sleepiness.

Statistical Analysis

Pearson's r correlations were conducted to determine the relationship between days to symptom recovery and individual actigraphy sleep outcome measures: sleep onset latency (SOL), wake after sleep onset (WASO), sleep efficiency (SE), total sleep time (TST), and number of awakenings separately at the three time-points across recovery: 48-72 hours post-injury (n=19), mid-point of recovery (n=19), and within 48 hours of end of recovery (n=17, two unavailable data points). Pearson's r correlations were then conducted for each sleep outcome, except with those who experienced persistent symptoms (>30+ days, n=3) removed. Scatterplots were used to visually examine the relationship of each actigraphy sleep outcome measure at the three time-points across recovery and identify potential influential subsets (Figure 5.2a-e).

Spearman's rho correlations were used, based on non-normally distributed data, to determine the relationship between subjective sleep quality scores (PSQI global scores and ESS total scores: since concussion) and the number of days to symptom recovery. Subsequent Spearman's rho correlations were conducted to assess the relationship between subjective sleep quality scores and days to symptom recovery, except with persistent symptoms (>30+ days, n=3) removed. Spearman's rho correlation analysis was also conducted to evaluate the relationship between the self-reported sleep symptoms cluster (drowsiness and trouble falling asleep) and days to symptom recovery. Strength of correlations were determined using the following criteria: weak = 0.30, moderate = 0.50, strong = 0.70 (Cohen, 1992). Statistical analyses were conducted using IBM SPSS Statistics (Version 24.0, IBM Corp., Armonk, NY), with alpha level set a priori at 0.05.

Results

Descriptive statistics and frequencies are provided to display demographic and clinical characteristics of injury for concussed participants (Tables 5.2 and 5.3, respectively).

Table 5.1 Demographics for Concussed Participants

Demographic Information	Concussed (n=19)
Age: *M*±*SD* (years)	20.0±1.5
Sex: n (%)	
Males	8(42.1)
Females	11(57.9)
Height: *M*±*SD* (cm)	171.78±10.13
Mass: *M*±*SD* (kg)	70.57±12.08
Race: n (%)	
Asian	2(10.5)
Black	3(15.8)
Hispanic	1(5.3)
White	13(68.4)
Education: *M*±*SD* (years)	
Freshman	8(42.1)
Sophomore	4(21.1)
Junior	1(5.3)
Senior	3(15.8)
5+ year	3(15.8)
Hand Dominance: n (%)	
Right	16(84.2)
Left	3(15.8)
Physical Activity Level: n (%)	
Moderate	6(31.6)
High	13(68.4)
Previous Concussions: n (%)	
0	10(52.6)
1	6(31.6)
2	3(15.8)

Note. *SD*=standard deviation.

Table 5.2 Clinical Characteristics of Injury for Concussed Participants

Characteristics	Concussed (n=19)
Recruitment Post-Injury: n (%)	
24 hours PI	8(42.1)
48 hours PI	6(31.6)
72 hours PI	5(26.3)
Symptom Recovery: *M*±*SD* (days)	17.9±10.3
Mechanism of Injury: n (%)	
Sports-related	10(52.6)
Falls	8(42.1)
Motor Vehicle Accidents	1(5.3)
Sports-related Mechanism Types: n (%)	
Player contact	6(60.0)
Apparatus contact	2(20.0)
Surface contact	2(20.0)
Head Impact Location: n (%)	
Front	2(10.5)
Left	7(36.8)
Right	6(31.6)
Back	4(21.1)
Injury Severity: n (%)	
LOC	
Yes	5(26.3)
No	14(73.7)
Retrograde Amnesia	
Yes	3(15.8)
No	16(84.2)
Post-traumatic Amnesia	
Yes	3(15.8)
No	16(84.2)
Delayed Onset of Symptoms: n (%)	
Yes	6(31.6)
No	13(68.4)
Recovery Length: n (%)	
<10 days	5(26.3)
10-14 days	3(15.8)
15-21 days	6(31.6)
22-30 days	2(10.5)
+30 days	3(15.8)

Note. *SD*=standard deviation. PI=post-injury. Sports-related mechanism types: n=10.

Actigraphy and Days to Symptom Recovery

When examining all concussed participants across three symptom recovery time-points, no significant relationships existed between SOL, normalized WASO, SE, and TST and days to symptom recovery. However, a weak positive correlation existed between number of awakenings per hour and days to symptom recovery (r=0.49, p=0.045), where concussed participants who had greater number of awakenings towards the end of recovery took longer to recover. No other actigraphy sleep outcomes correlated with days to symptom recovery at any of the three time-points.

Once we removed participants (n=3) who experienced persistent symptoms (>30+ days post-injury), we identified a moderate positive relationship between normalized WASO at the mid-point of recovery and days to symptom recovery (r=0.60, p=0.014), where individuals who were awake longer throughout the night took longer to recover. Additionally, a moderate negative relationship existed between sleep efficiency at mid-point of recovery and days to symptom recovery (r=-0.54, p=0.030), where concussed individuals who were less efficient at sleeping at night took longer to recover. A moderate positive relationship also existed between TST towards the end of recovery and days to symptom recovery (r=0.57, p=0.034), where concussed individuals who were sleeping more at the end of their recovery took longer to recover. No other actigraphy sleep outcomes correlated with days to symptom recovery at any of the three time-points.

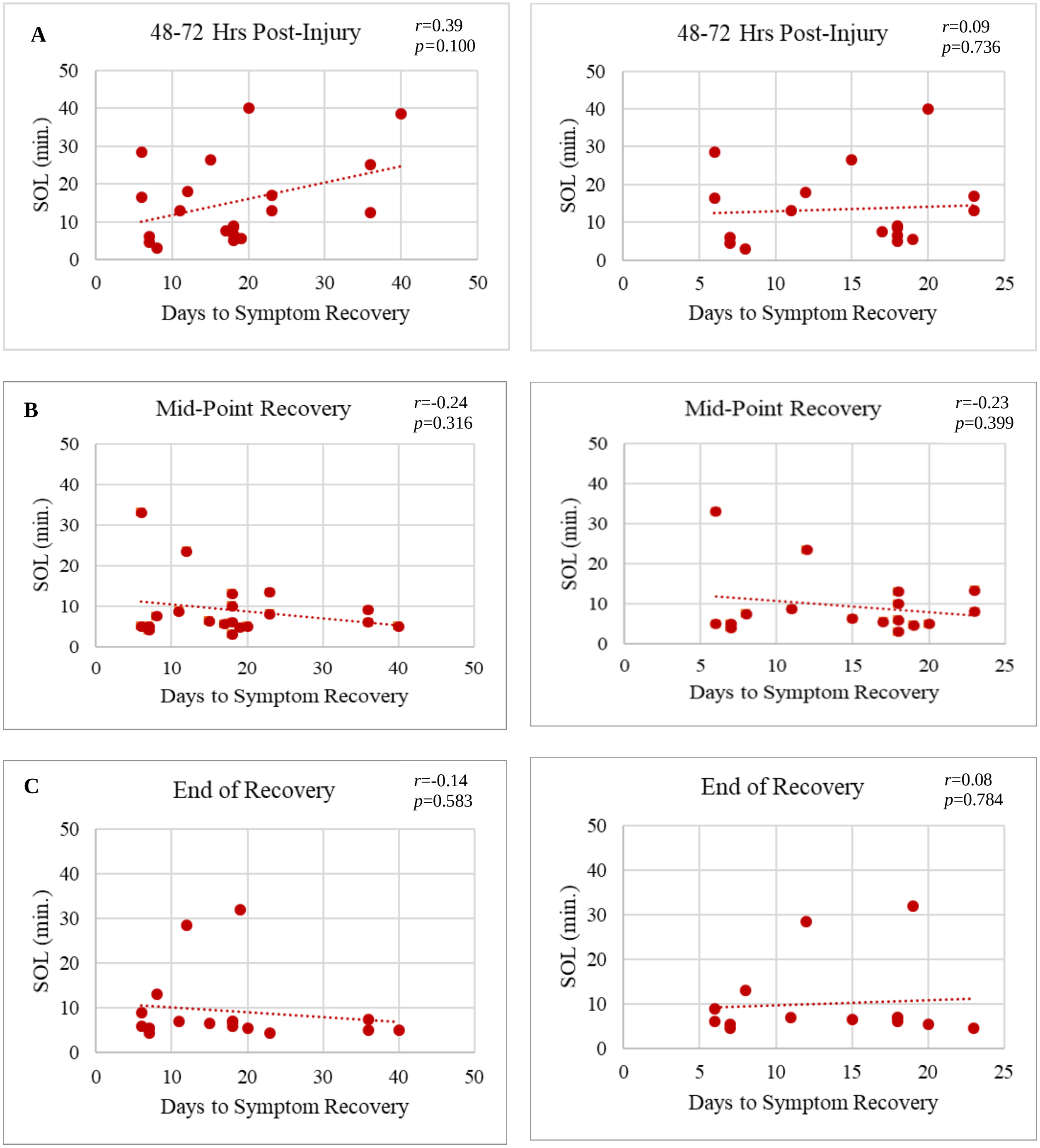

Figure 5.2a. Individual actigraphy sleep onset latency (SOL) scatterplots for three time-points (A-C) across symptom recovery (left=includes all recovery, right=excludes persistent symptoms: >30+ days).

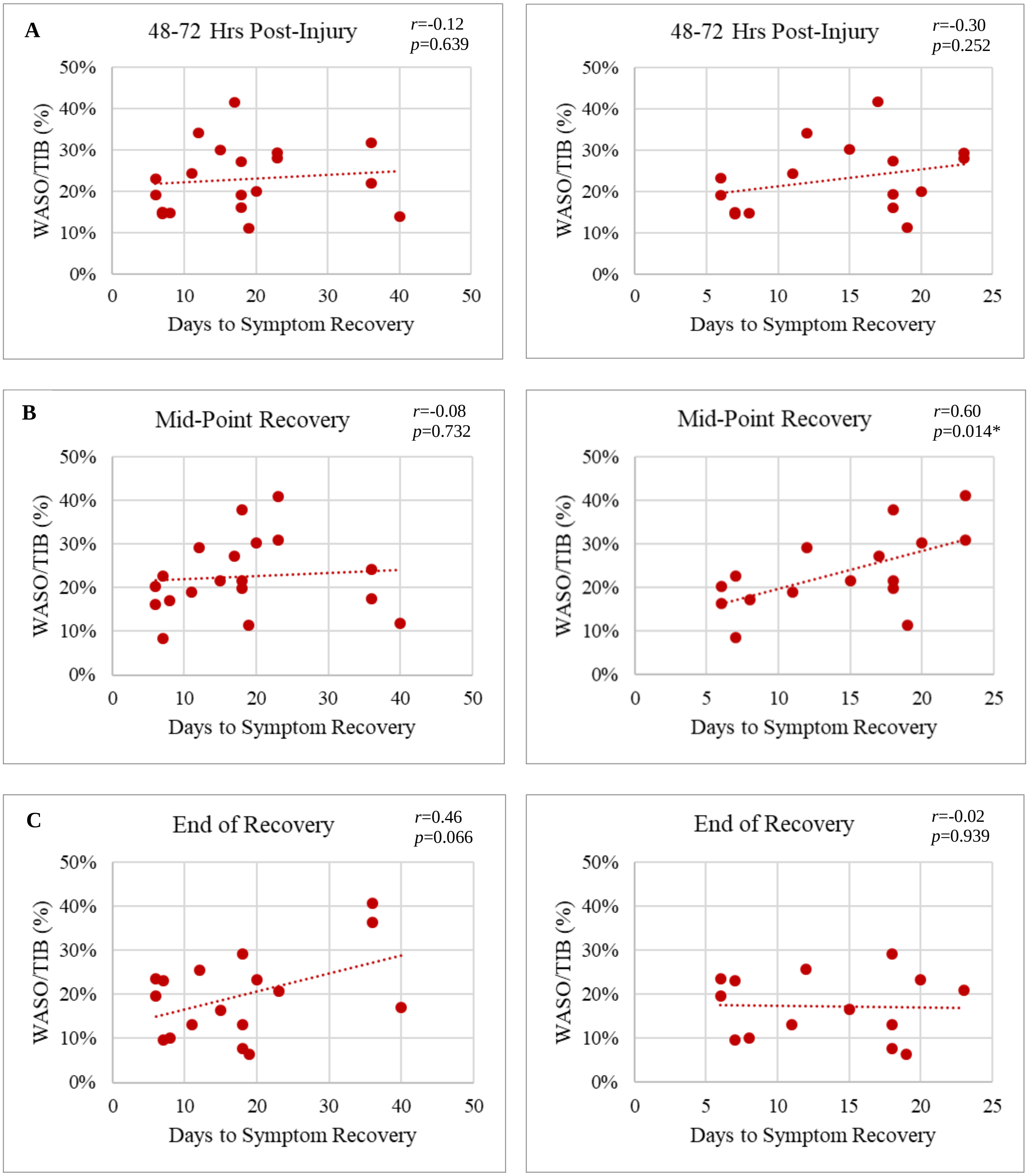

Figure 5.2b. Individual actigraphy normalized wake after sleep onset (WASO) per time in bed (TIB) scatterplots for three time-points (A-C) across symptom recovery (left=includes all recovery, right=excludes persistent symptoms: >30+ days).

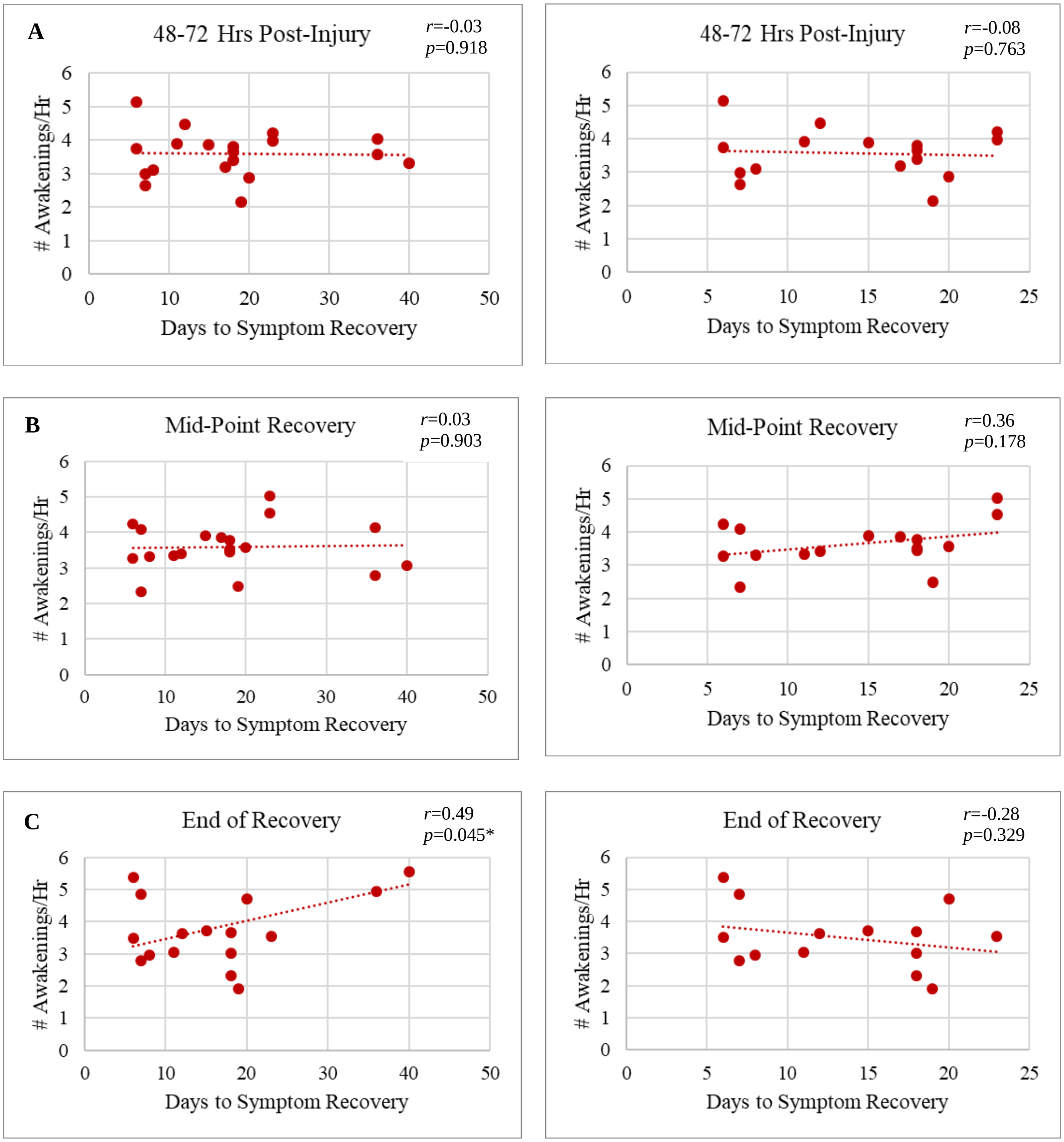

Figure 5.2c. Individual actigraphy normalized number of awakenings per hour scatterplots for three time-points (A-C) across symptom recovery (left=includes all recovery, right=excludes persistent symptoms: >30+ days).

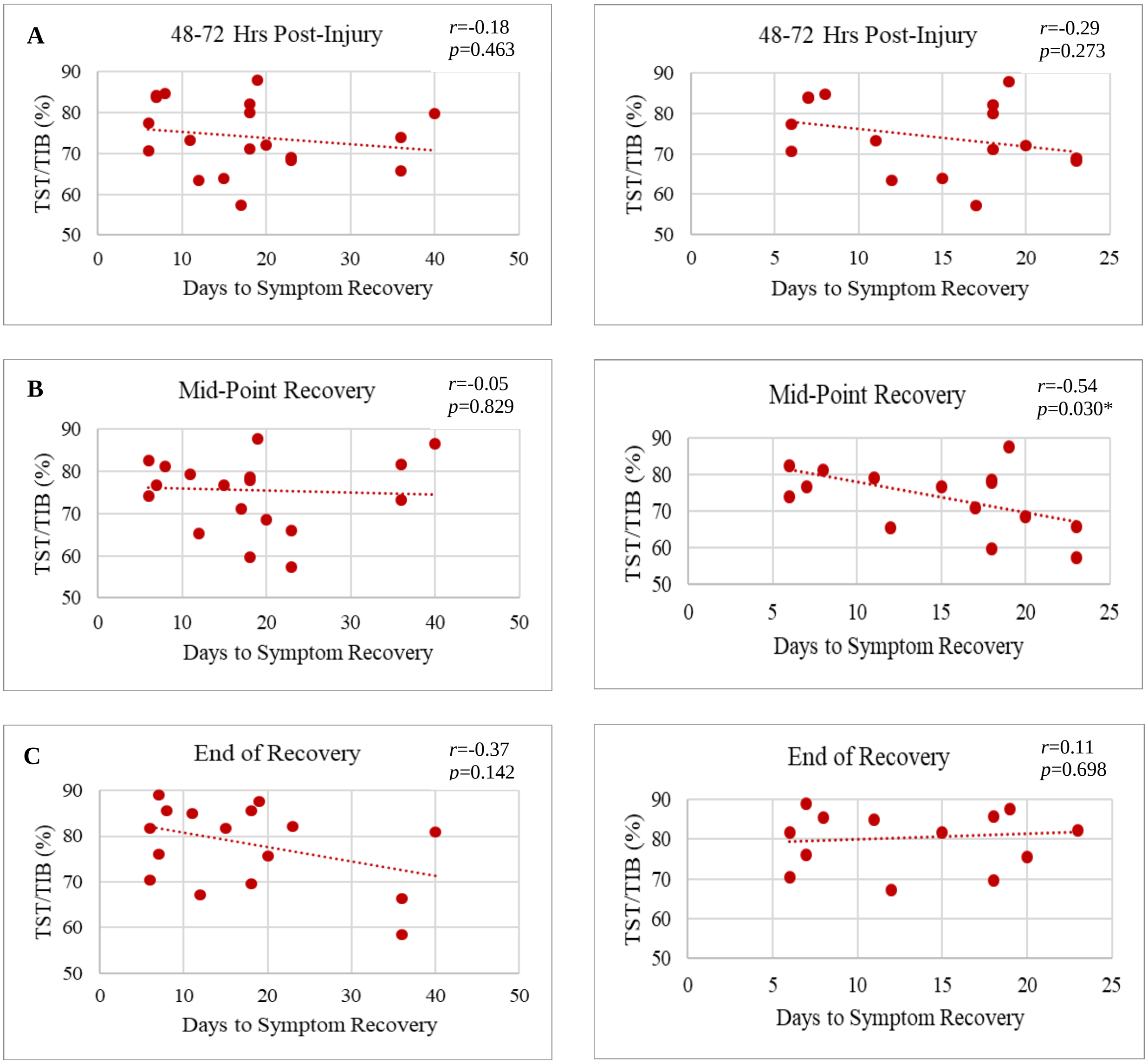

Figure 5.2d. Individual sleep efficiency (total sleep time/time in bed) scatterplots for three time-points (A-C) across symptom recovery (left=includes all recovery, right=excludes persistent symptoms: >30+ days).

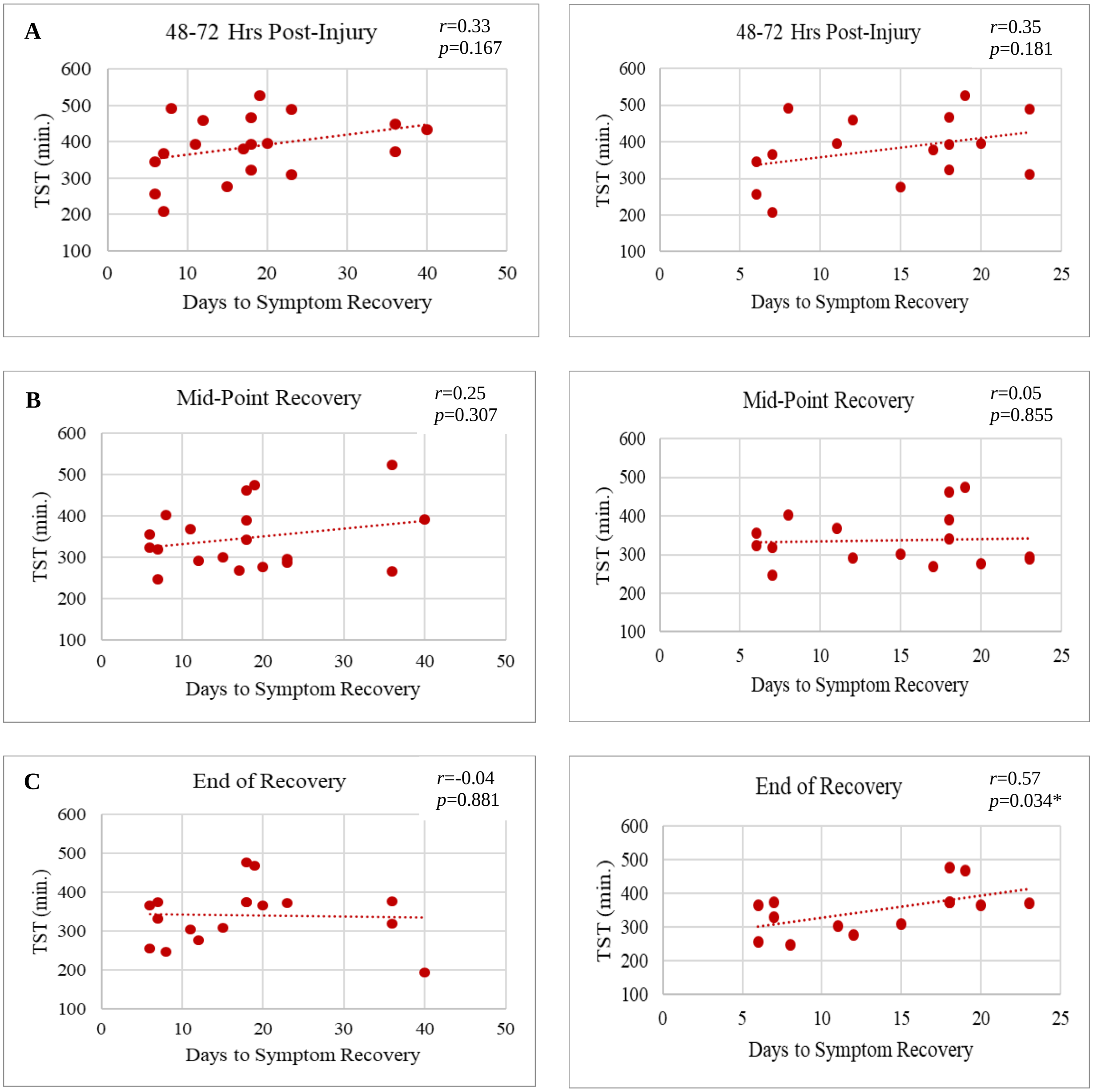

Figure 5.2e. Individual total sleep time (TST) scatterplots for three time-points (A-C) across symptom recovery (left=includes all recovery, right=excludes persistent symptoms: >30+ days).

Subjective Questionnaires, Sleep Symptoms Cluster, and Days to Symptom Recovery

A strong positive correlation existed between post-injury PSQI global scores and days to symptom recovery, where individuals with higher scores (poorer sleep quality) since concussion took longer to recover (r_s=0.70, p=0.001; Figure 5.3). No other significant relationships existed between ESS total scores since concussion and days to symptom recovery. When we removed individuals with persistent symptoms (n=3), a slightly weaker, but moderate positive correlation existed between post-injury PSQI global scores and days to symptom recovery (r_s=0.63, p=0.009), where individuals with poorer sleep quality since concussion took longer to recover. No significant relationship existed between sleep symptom severity cluster and days to symptom recovery when examining across all participants. However, when excluding individuals with persistent symptoms, a trend towards significance existed between sleep symptoms and days to symptom recovery (r_s=0.48, p=0.058) (Figure 5.4).

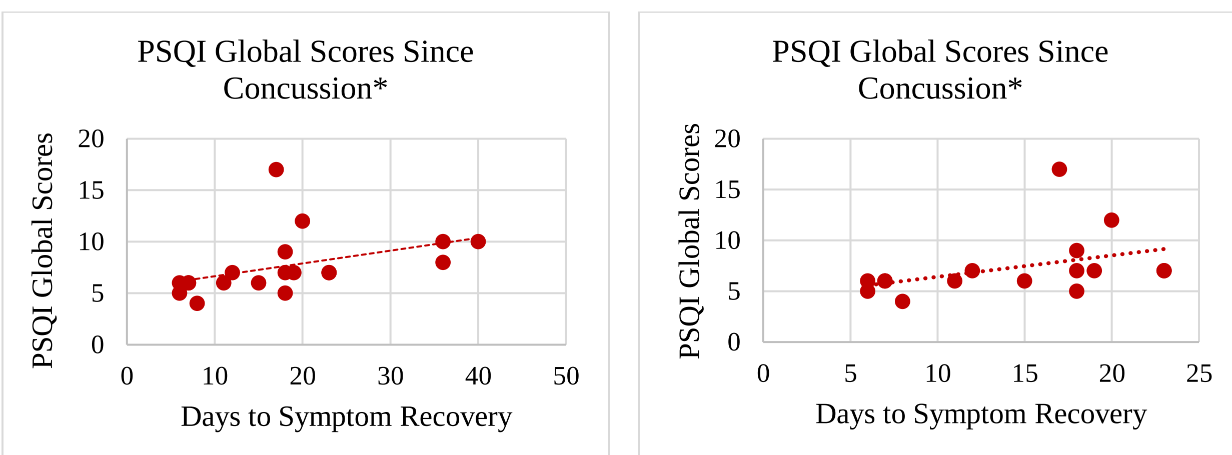

Figure 5.3. Individual PSQI global scores scatterplot across symptom recovery (left=includes all recovery, right=excludes persistent symptoms: >30+ days).
*Significance at p<0.05.

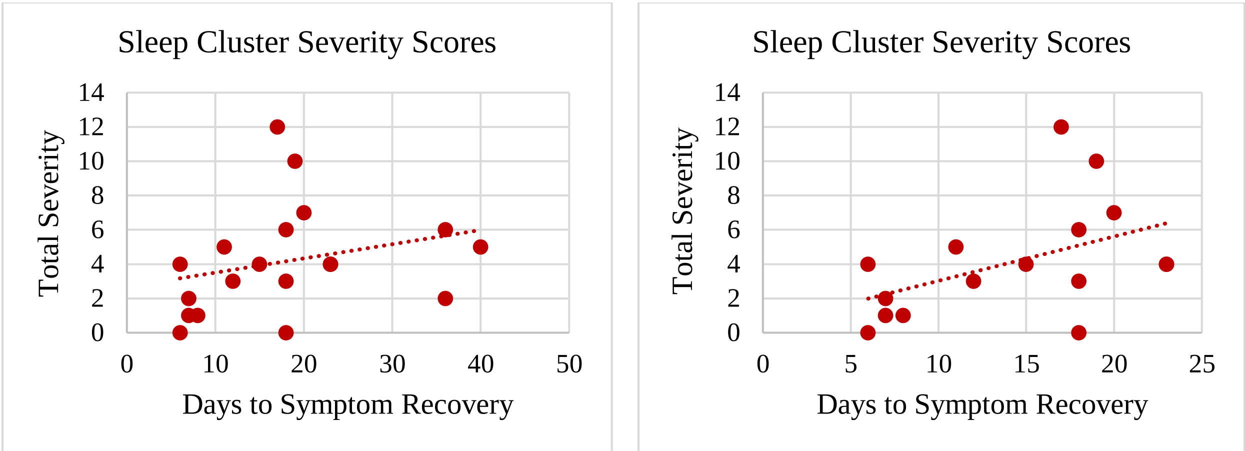

Figure 5.4. Individual sleep cluster severity scores scatterplot across symptom recovery (left=includes all recovery, right=excludes persistent symptoms: >30+ days).
*Significance at $p<0.05$.

Discussion

This prospective study is the first to examine sleep using actigraphy and subjective questionnaires throughout the course of symptom recovery following concussion in college-aged students. Our findings are consistent with recent prospective data using actigraphy to identify post-concussion sleep trajectories and disturbances at various time-points post-injury (Chiu et al., 2013; Raikes & Schaefer, 2016). Interestingly, in concussed individuals with typical symptom recovery patterns, we observed that individuals who were awake longer throughout the night and were less efficient at sleeping at the mid-point of recovery may have experienced longer recoveries. The alternate scenario could also be considered where individuals with longer recoveries experienced greater lengths of time awake at night and/or were less efficient at sleeping as a result of the concussion. Additionally, individuals who slept more towards the end of their recovery experienced longer recovery. It is more plausible that concussed individuals who took longer to recover may have experienced the need to sleep longer. We further confirm that sleep and concussion recovery are much intertwined and warrant further investigation.

Using subjective questionnaires, individuals who self-reported poorer sleep quality throughout concussion took longer to experience symptom recovery or that those with good sleep quality throughout concussion experienced symptom recovery faster. It is difficult to determine causality without further evaluation, but our study provides preliminary direction to guide further research regarding post-concussion sleep intervention strategies.

Actigraphy

Through clinical observation of our individualized scatterplots, it was evident that sleep disturbances existed acutely (within 48-72 hours) following concussion, where concussed individuals experienced greater difficulties falling asleep, prolonged sleep duration, greater awakening lengths throughout the night, poorer sleep efficiency at night, and awakening more frequently compared to other recovery time-points. Our observation is consistent with findings in a wider age range sample of concussed individuals that had examined sleep change trajectories acutely post-injury (Chiu et al., 2013). Surprisingly, there was no relationship in this study between acute sleep outcomes and the length of symptom recovery regardless of excluding individuals with prolonged symptom recoveries. When including all participants regardless of length of recovery, we also noted no relationships between sleep outcomes at mid-point and within 48 hours of recovery and the number of days to experience symptom recovery.

However, through further exploration of other recovery time-points and the length of symptom recovery, our findings in greater WASO lengths and poorer sleep efficiency at mid-point of recovery, and longer sleep duration towards the end of recovery may be explained by a lack of exercise post-injury. In our sample of college-aged individuals, ~68% of individuals were previously highly active prior to concussion. As per our concussion management protocol, concussed individuals were advised to refrain from physical and cognitive activities that may exacerbate symptom severity until symptoms subsided. In a large meta-analysis by Kredlow et. al, regular exercise has shown to have a small positive impact on sleep efficiency and total sleep time each night, but a moderate negative impact on WASO in healthy individuals across the general population (Kredlow, Capozzoli, Hearon, Calkins, & Otto, 2015). It is important to note that our study did not examine causality, therefore further examination of physical activity is warranted to determine if prolonged effects of lack of exercise would negatively influence sleep disturbances.

Our preliminary results compliments a recent pilot study by Raikes et al., where individuals slept longer immediately post-concussion (Raikes & Schaefer, 2016). Similarly, in a study by Chiu et al., approximately 70% of concussed individuals experienced longer sleep duration 24 hours post-concussion (Chiu et al., 2013). When examining TST throughout the duration of recovery, we found that concussed individuals who took longer to recover, continued to experience a need to sleep longer throughout recovery. It is well documented that sleep is considered a restorative process for brain energy and serves as a protective mechanism against cognitive tasks that may prolong recovery. However, a larger sample is needed to explore the causality and the impact of external factors for why individuals may or may not be taking longer to achieve symptom recovery. Capturing sleep data using actigraphy at 24 hours following injury is very challenging as it requires quick recognition and diagnosis. Despite these challenges, future research aimed at better capturing sleep outcomes acutely following injury is warranted based on our results.

Subjective Sleep Questionnaires

When examining the PSQI post-injury and the number of days to experience symptom recovery, we observed that individuals who had poorer subjective sleep quality since they sustained their concussion, took longer to experience symptom recovery. Poorer sleep quality following concussion is consistent with previous research using the PSQI in young adults (Gosselin et al., 2009; Schmidt et al., 2015; Williams et al., 2008). An individual's perception of the quality of sleep that they are experiencing throughout concussion may be affecting the length of symptom recovery. Our results showed that 84% of individuals exceeded the cutoff value of 5 and 30% exceeded the cutoff value of 8 on the PSQI since they sustained their concussion, which indicates clinically meaningful sleep disturbances. The average PSQI global score was 7.6±3.0 since concussion, which complements scores indicated by another study who examined concussed individuals 1-month post-injury (6.77±4.0) (Schmidt et al., 2015). Our findings highlight that this easy-to-administer subjective questionnaire was able to identify days to symptom recovery following concussion independently from the actigraphy device. However, further research is needed to not only validate this version with modified instructions, but to also determine if the PSQI can be used in a comparable manner, except with a focus on assessing sleep quality within the initial days following concussion. It should also be noted that administration of the PSQI once individuals experience symptom recovery has limited clinical value since the window for sleep intervention has passed.

Limitations

Due to numerous exclusion factors, we were limited to a small sample of 19 college-aged students. The use of actigraphy is low-cost and convenient for longitudinal studies, however, early termination (13.3%) of actigraphy monitoring was a problem in our study, which is a common limitation across the literature. Two participants lost the watch and approximately 13% recorded less than 5 nights of data (either from early recovery or participants discontinued to wear the watch). Despite multiple reminders, several concussed participants failed to complete the daily symptoms checklist throughout the duration of symptom recovery, therefore we were unable to define symptom recovery using the final day of self-reported symptoms. We also lost one participant due to non-compliance with a follow-up evaluation within 48 hours of self-reporting symptom recovery despite several means of communication. When calculating pre-injury average bedtime information, it is important to note that data were collected retrospectively, and may have been subjected to recall bias. Future studies are needed to extend sleep analyses further out through return to athletic participation and return to academics.

Conclusion

This prospective study is the first to examine sleep past the acute period of concussion and daily throughout symptom recovery. By controlling for numerous confounding conditions that have been found to worsen sleep, we were able to focus more on sleep objectively and subjectively to further elucidate the relationship with symptom recovery. Using actigraphy, we were able to identify a relationship between mid-point WASO and SE and recovery, highlighting two plausible scenarios: 1) individuals who experienced a greater percentage of time awake at night and/or were less efficient at sleeping at the mid-point of recovery experienced a longer recovery or 2) individuals with longer recoveries experienced a greater percentage of time awake at night and/or were less efficient at sleeping due to the concussion itself. Easy-to-administer subjective questionnaires such as the PSQI and the SCAT3 also revealed relationships between 1) poor sleep quality post-injury and days to symptom recovery. When examining sleep, the use of objective and subjective measures may be considered to further explore effects of sleep on concussion recovery. Our findings provide preliminary information to guide researchers to the next step on determining whether clinicians should identify those who are at risk of experiencing persistent awakening lengths, poor sleep efficiency, and the need for more sleep later in recovery. Addressing sleep habit interventions subacutely that may influence persistent poor sleep disturbances affecting WASO, SE, and TST may potentially expedite the recovery process (i.e. providing sleep hygiene education acutely post-injury, addressing the use of technology in bed, etc.). A self-care intervention addressing areas such as exercise, establishing some routine, and environmental factors (noise and light) may be considered to address poor sleep quality throughout recovery. Online interventions have been used to improve overall sleep by using cognitive behavior principles to include (relaxation training, cognitive therapy (how to identify thoughts to disrupt falling asleep), and mindfulness meditation (to assist with falling asleep) (Theadom et al., 2017). Sleep and concussion recovery remains an area that needs a multi-dimensional approach in order to identify causality of sleep on recovery.

CHAPTER 6

STUDY SUMMARIES

This prospective study is the first to examine sleep throughout recovery. By controlling for numerous confounding conditions that have been found to worsen sleep, we were able to focus more on sleep objectively and subjectively within individual days to describe post-concussion sleep disturbances and to further elucidate the relationship with symptom recovery. We objectively identified that concussed individuals experienced greater difficulties falling asleep compared to non-concussed individuals. Using actigraphy, we were able to identify a relationship between mid-point WASO and SE and recovery, highlighting two plausible scenarios: 1) individuals who experienced a greater percentage of time awake at night and/or were less efficient at sleeping at the mid-point of recovery experienced a longer recovery or 2) individuals with longer recoveries experienced a greater percentage of time awake at night and/or were less efficient at sleeping due to the concussion itself. We added to the growing body of literature that concussed individuals experience poorer overall sleep quality, greater daytime sleepiness, and worse sleep-related symptoms compared to non-concussed individuals. Perception of sleep quality may be just as important as objectively capturing sleep throughout recovery. Easy-to-administer subjective questionnaires such as the PSQI revealed relationships between 1) poor sleep quality and days to symptom recovery. When examining sleep, the use of objective and subjective measures may be considered to further explore effects of sleep on concussion recovery.

Our findings provide preliminary information to guide researchers to the next step on examining the day-to-day variability in sleep following concussion, followed by possible sleep interventions on length of awakenings each night, sleep efficiency, and total sleep time (i.e. providing sleep hygiene education during the early stages). Researchers should consider whether intervening on sleep would potentially expedite the recovery process (i.e. providing sleep hygiene education acutely post-injury, addressing the use of technology in bed, etc.). A self-care intervention addressing areas such as exercise, establishing a routine, and examine environmental factors (noise and light) may be considered to address poor sleep quality and decrease sleep symptoms acutely following concussion. Online interventions have been used to improve overall sleep by using cognitive behavior principles to include (relaxation training, cognitive therapy (how to identify thoughts to disrupt falling asleep) (Theadom et al., 2017), and mindfulness meditation (to assist with falling asleep). Sleep and concussion recovery remains an area that needs a multi-dimensional approach in order to identify causality of sleep on recovery.

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APPENDIX - Ia

PITTSBURGH SLEEP QUALITY INDEX: POST-INJURY

INSTRUCTIONS:
The following questions relate to your sleep habits since you sustained your concussion only. Your answers should indicate the most accurate reply for the majority of days and nights. Please answer all questions.

---

1. Since you sustained your concussion, what time have you usually gone to bed at night?

   BED TIME _____________

2. Since you sustained your concussion, how long (in minutes) has it usually taken you to fall asleep each night?

   NUMBER OF MINUTES ________________

3. Since you sustained your concussion, what time have you usually gotten up in the morning?

   GETTING UP TIME _________________

4. Since you sustained your concussion, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT ______________

For each of the remaining questions, check the one best response. Please answer all questions.

5. Since you sustained your concussion, how often have you had trouble sleeping because you:

a) Cannot get to sleep within 30 minutes

Not since concussion_____	Less than once a week_______	Once or twice a week______	Three or more times a week_______

b) Wake up in the middle of the night or early morning

Not since concussion ______ Less than once a week _______ Once or twice a week_______ Three or more times a week________

c) Have to get up to use the bathroom

Not since concussion________ Less than once a week________ Once or twice a week_______ Three or more times a week________________
_____

d) Cannot breathe comfortably

Not since concussion________ Less than once a week________ Once or twice a week_______ Three or more times a week______________

e) Cough or snore loudly

Not since concussion ________ Less than once a week________ Once or twice a week_______ Three or more times a week________

f) Feel too cold

Not since concussion________ Less than once a week________ Once or twice a week_______ Three or more times a week________

g) Feel too hot

Not since concussion ________ Less than once a week________ Once or twice a week_______ Three or more times a week__________

h) Had bad dreams

Not since concussion ________ Less than once a week________ Once or twice a week_______ Three or more times a week__________

i) Have pain

Not since concussion________ Less than once a week________ Once or twice a week_______ Three or more times a week__________

j) Other reason(s): ____

How often since you sustained your concussion have you had trouble sleeping because of this other reason?

Not since concussion_______	Less than once a week_______	Once or twice a week______	Three or more times a week________

6. Since you sustained your concussion, how would you rate your sleep quality overall?

Very good _____________

Fairly good _____________

Fairly bad _____________

Very bad _____________

7. Since you sustained your concussion, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not since concussion _______	Less than once a week_______	Once or twice a week______	Three or more times a week________

8. Since you sustained your concussion, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not since concussion _______	Less than once a week_______	Once or twice a week______	Three or more times a week________

9. Since you sustained your concussion, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all ___________

Only a very slight problem ___________

Somewhat of a problem ___________

A very big problem ___________

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.

APPENDIX - Ib

PITTSBURGH SLEEP QUALITY INDEX: BASELINE

INSTRUCTIONS:

The following questions relate to your sleep habits <u>during the past month only</u>. Your answers should indicate the most accurate reply for the <u>majority</u> of days and nights.
Please answer all questions.

---

1. During the past month, what time have you usually gone to bed at night?

BED TIME _____________

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES ________________

3. During the past month, what time have you usually gotten up in the morning?

GETTING UP TIME _________________

4. During the past month, how many hours of <u>actual</u> <u>sleep</u> did you get at night? (This may be different than the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT ______________

For each of the remaining questions, check the one best response. Please answer <u>all</u> questions.

5. During the past month, how often have you had trouble sleeping because you:

a) Cannot get to sleep within 30 minutes

Not during past month _____	Less than once a week_____	Once or twice a week______	Three or more times a week_______

b) Wake up in the middle of the night or early morning

Not during past month _____	Less than once a week ____	Once or twice a week_____	Three or more times a week______

c) Have to get up to use the bathroom

Not during past month_______	Less than once a week_______	Once or twice a week______	Three or more times a week_______

d) Cannot breathe comfortably

Not during past month ______	Less than once a week______	Once or twice a week______	Three or more times a week_______

e) Cough or snore loudly

Not during past month_______	Less than once a week______	Once or twice a week______	Three or more times a week_______

f) Feel too cold

Not during past month_______	Less than once a week_______	Once or twice a week______	Three or more times a week_______

g) Feel too hot

Not during past month _______	Less than once a week_______	Once or twice a week______	Three or more times a week_________

h) Had bad dreams

Not during past month _______	Less than once a week_______	Once or twice a week______	Three or more times a week_________

i) Have pain

Not during past month_______	Less than once a week_______	Once or twice a week______	Three or more times a week_________

j) Other reason(s): ____

How often during the past month have you had trouble sleeping because of this other reason?

Not during past month_______	Less than once a week_______	Once or twice a week______	Three or more times a week_________

6. During the past month, how would you rate your sleep quality overall?

Very good _____________

Fairly good _____________

Fairly bad _____________

Very bad _____________

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during past month_______	Less than once a week_______	Once or twice a week______	Three or more times a week________ ___

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during past month _______	Less than once a week_______	Once or twice a week______	Three or more times a week_______

9. Since you sustained your concussion, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all ___________

Only a very slight problem ___________

Somewhat of a problem ___________

A very big problem ___________

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.

APPENDIX - IIa

EPWORTH SLEEPINESS SCALE: POST-INJURY

Subject ID: ______________________________________ Today's date: ________________
Your age: _______________ Your sex (Male = M, Female = F): ___________

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to how you typically felt since you sustained your concussion.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	___

THANK YOU FOR YOUR COOPERATION
M.W. Johns 1990-97

APPENDIX - IIb

EPWORTH SLEEPINESS SCALE: BASELINE

Subject ID: _______________________________________ Today's date: _________________
Your age: _______________ Your sex (Male = M, Female = F): ___________

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to how you typically feel on a regular basis (>3x/week).

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	___

THANK YOU FOR YOUR COOPERATION
M.W. Johns 1990-97

APPENDIX - IIIa

SPORT CONCUSSION ASSESSMENT TOOL, VERSION 3 (SCAT3)

POST-INJURY

Subject ID: ________________
Date: ______________________

How do you feel? *You should score yourself on the following symptoms based on how you feel now.*

	None	Mild		Moderate		Severe	
Headache	0	1	2	3	4	5	6
"Pressure in Head"	0	1	2	3	4	5	6
Neck Pain	0	1	2	3	4	5	6
Nausea or Vomiting	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Blurred Vision	0	1	2	3	4	5	6
Balance Problems	0	1	2	3	4	5	6
Sensitivity to Light	0	1	2	3	4	5	6
Sensitivity to Noise	0	1	2	3	4	5	6
Feeling Slowed Down	0	1	2	3	4	5	6
Feeling like "in a fog'	0	1	2	3	4	5	6
"Don't feel right"	0	1	2	3	4	5	6
Difficulty Concentrating	0	1	2	3	4	5	6
Difficulty Remembering	0	1	2	3	4	5	6
Fatigue or Low Energy	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
Trouble Falling Asleep	0	1	2	3	4	5	6
More Emotional	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervous or Anxious	0	1	2	3	4	5	6

How many hours did you sleep last night? ________(hrs)
Do the symptoms get worse with physical activity? ☐Yes ☐No ☐N/A
Do the symptoms get worse with mental activity? ☐Yes ☐No

APPENDIX - IIIb

SPORT CONCUSSION ASSESSMENT TOOL, VERSION 3 (SCAT3)

BASELINE

Subject ID: _______________
Date: _____________________

How do you feel? *You should score yourself on the following symptoms based on* *<u>how you typically feel on a regular basis (>3 times per week).</u>*

	None	Mild		Moderate		Severe	
Headache	0	1	2	3	4	5	6
"Pressure in Head"	0	1	2	3	4	5	6
Neck Pain	0	1	2	3	4	5	6
Nausea or Vomiting	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Blurred Vision	0	1	2	3	4	5	6
Balance Problems	0	1	2	3	4	5	6
Sensitivity to Light	0	1	2	3	4	5	6
Sensitivity to Noise	0	1	2	3	4	5	6
Feeling Slowed Down	0	1	2	3	4	5	6
Feeling like "in a fog'	0	1	2	3	4	5	6
"Don't feel right"	0	1	2	3	4	5	6
Difficulty Concentrating	0	1	2	3	4	5	6
Difficulty Remembering	0	1	2	3	4	5	6
Fatigue or Low Energy	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
Trouble Falling Asleep	0	1	2	3	4	5	6
More Emotional	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervous or Anxious	0	1	2	3	4	5	6

How many hours did you sleep last night? ________(hrs)
Do the symptoms get worse with physical activity? ☐Yes ☐No ☐N/A
Do the symptoms get worse with mental activity? ☐Yes ☐No

APPENDIX – IV

ACTIGRAPHY LOG

Start Date: _______________										
Subject Initials: _____________										
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**
Date (month/day)	____/_____	____/_____	____/_____	____/_____	____/_____	____/_____	____/_____	____/_____	____/_____	____/_____
Wake Time		___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM
Bed Time	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM
If the monitor was removed, list the times and reasons for each removal:										
1. Time Took Off:	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM
1. Reason Took Off:										
1. Time Back On:	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM
2. Time Took Off:	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM
2. Reason Took Off:										
2. Time Back On:	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM
TO BE FILLED OUT IN THE MORNING	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**
Last night I fell asleep: (circle one)										
1=easily, 2=after some time, 3=with difficulty		1 2 3	1 2 3	1 2 3	1 2 3	1 2 3	1 2 3	1 2 3	1 2 3	1 2 3
I woke up during the night:										
Number of times										
Total number of minutes		_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes
Last night I slept a total of:	_____ hours	_____ hours	_____ hours	_____ hours	_____ hours	_____ hours	_____ hours	_____ hours	_____ hours	_____ hours
TO BE FILLED OUT IN THE EVENING										
Took a nap?	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
If yes, how many minutes total?	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes
Did you drink caffeine?	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
If yes, how much? *ex. 1 cup coffee*										
Did you drink alcohol?	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
If yes, how much? *ex. 1 drink*	_____ drink(s)	_____ drink(s)	_____ drink(s)	_____ drink(s)	_____ drink(s)	_____ drink(s)	_____ drink(s)	_____ drink(s)	_____ drink(s)	_____ drink(s)
How many total hours did you dedicate to academics? (ex. school work, class, studying)	_____ hours	_____ hours	_____ hours	_____ hours	_____ hours	_____ hours	_____ hours	_____ hours	_____ hours	_____ hours
Did you exercise?	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
If yes, what level of intensity?*	1 2 3	1 2 3	1 2 3	1 2 3	1 2 3	1 2 3	1 2 3	1 2 3	1 2 3	1 2 3
If yes, how many minutes?	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes	_____ minutes
What time did you exercise?	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM	___:___ AM or PM

***Level of Physical Activity Code: 1=light, 2=moderate, 3=vigorous**