Sleep Disturbance, Affective Symptoms, and their Relationship to Post-Concussion Syndrome

A Systematic Review and Research Proposal

By

Robert Palm

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Abstract

In the United States each year, there are an estimated 1.6 to 3.8 million sport-related traumatic brain injuries (TBI), which includes concussions. Due to increasing public awareness of concussion, there has been a significant amount of research and policy effort focused on reducing the overall number of concussion events. However, there has been less focus on the sequelae of concussion, including post-concussion syndrome (PCS). PCS can involve a variety of physical, cognitive, and psychiatric symptoms, and these symptoms persist for months or even years in some patients recovering from concussion. However, PCS has traditionally been diagnosed and treated as a single clinical entity. Many of the studies identified in the included systematic review used PCS diagnosis as the principal outcome, rather than tracking individual symptoms. Only one study examined potential interactions between PCS symptoms, finding that the presence of sleep disturbance was associated with concomitant depressive symptoms. Here, we propose a prospective cohort study that will involve using previously-validated survey instruments to track sleep disturbance and affective symptoms in particular, and quality of life and post-concussion symptoms more generally, to identify and describe relationships between predictor-outcome pairs that show potential for statistical significance, as well as determining direction of causality. The patients included in this study will be recruited from a University-based Post-Concussion Clinic. Each subject will undergo specialized measurements such as posturography and neurocognitive assessment, which may also be examined as potential predictors. The predictor-outcome relationships will be described using either summary measures (for pairs with dichotomous inputs) or an as-yet-undetermined regression model (for pairs with continuous inputs). This study comprises a first step towards the creation of targeted treatments for PCS, a strategy that would lower the public health burden of concussion.
Introduction

“I couldn’t see,” said Richard Sherman, a cornerback for the Seattle Seahawks, in a 2013 column for *Sports Illustrated* [1]. Sherman was describing what he reported was the only concussion he had suffered while playing in the National Football League (NFL). He went on to say that he stayed in that game despite his symptoms, and that this decision “paid off” when he caught his first professional career interception two quarters later.

Sherman’s sentiment on “playing through” pain, including concussions, mirrors that of generations of athletes before him. In recent decades, however, this tradition has been countered by growing concerns about the acute and chronic effects that concussions have upon athletes, particularly at the youth and college sports levels. Two of the potential consequences that have received significant coverage are Chronic Traumatic Encephalopathy (CTE) and Second Impact Syndrome (SIS). CTE is most commonly seen in professional athletes, and is definitively diagnosed via autopsy. It presents similarly to Alzheimer’s disease (e.g. impaired mood, behavior, cognition, motors skills) and develops as a result of repeated head blows during a professional athletic career [2]. SIS is defined as the “catastrophic consequence of repeated head injury in sport,” typically thought to be due to cerebral swelling [3]. It is thought to pose the greatest risk to athletes who suffer repeated concussions within the space of a single athletic game or match without giving the brain sufficient time to heal. After a 13 year-old named Zackery Lystedt suffered debilitating injury thought to be due to SIS in a 2006 junior varsity football game, Washington state passed a law in 2009 mandating automatic removal of athletes from competition if a concussion is suspected [4]. Due to increased public awareness of SIS and other concussion sequelae, all fifty U.S. states had passed similar laws by 2013.
As of 2006, there were an estimated 1.6 to 3.8 million sport-related traumatic brain injuries (TBIs) each year in the United States [5]. Up to 65% of those injuries occur among children aged five to eighteen years [6]. Many of these head injuries are classified as mild TBIs (mTBI), a term which is often used as a synonym of concussion (both terms will be used interchangeably in this paper). A common sequela of these millions of concussions suffered each year is Post-Concussion Syndrome (PCS). As defined in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), the symptoms of this condition include headache, dizziness, fatigue, irritability, insomnia, noise sensitivity, and loss of concentration and/or memory [7]. In order to make the diagnosis, though, the complex of symptoms in a given patient need not involve any specific combination of these. Estimates vary depending on sampling procedures, diagnostic criteria, methodology, and time intervals used, but in general studies have found that around 10% of patients with recent mTBI suffer prolonged recovery or go on to develop persistent PCS [8 – 10].

The economic burden of TBI (including all severity levels) among patients who are treated and released in emergency departments (ED) has most recently been estimated at $17.8 billion (2010 dollars) annually in the United States, which includes costs of medical treatment as well as productivity loss [11]. Among children, the development of PCS is associated with increased risk of chronic conditions including anxiety, depression, and migraine headaches [12]. The daytime confluence of fatigue, emotional symptoms, and mental fogginess in PCS has been shown to negatively affect work and/or school performance for up to a month after concussion in the average patient [13]. Prolonged PCS can also place a significant burden on patients’ family members and disrupt familial dynamics, as parents focus on caring for their affected child, to the detriment of their other children [14, 15].
PCS appears to involve a combination of physiological and psychological etiologies.

Several characteristic manifestations of PCS have been well-established in the peer-reviewed literature, but the natural history and underlying pathophysiology of PCS remains unclear. Some hypothesize that the etiology is largely physiological. Supporting evidence includes studies in animal models, which have shown that concussion can lead to disrupted neuronal cell membranes, poorly-regulated ionic flux, and altered cerebral glucose metabolism [16]. Available clinical evidence in support of this hypothesis includes a 2013 study of 19 patients who demonstrated global brain atrophy on magnetic resonance imaging (MRI) a year after suffering a mTBI when compared to 22 matched healthy controls [17]. Analogous studies using other imaging methods have also documented extensive abnormalities on positron emission tomography (PET) and functional MRI (fMRI) in patients with a history of mTBI, further indicating the possibility of a structural or physiological etiology of PCS [18, 19]. However, many of the imaging findings described in these and related studies were non-specific. Similar findings might also be seen in patients with conditions such as migraines, depression, or neurodegenerative diseases. In addition, the severity of the documented imaging abnormalities was not consistently correlated with symptom severity in these studies.

The contrary (some would say complementary) hypothesis is that PCS has a strong psychological component. This hypothesis appears reasonable on its face; many of the cognitive, mood, and sleep symptoms associated with PCS can also manifest as part of certain somatiform or affective disorders. A 2008 study on American soldiers returning from Iraq, in which a history of mTBI did not significantly affect soldiers’ health after controlling for co-morbid diagnoses of post-traumatic stress disorder (PTSD) and depression, demonstrated the potential for overlap
between PCS and psychiatric conditions [20]. However, this study retrospectively surveyed soldiers concerning “losing consciousness (knocked out),” “being dazed, confused, or ‘seeing stars,’” or “not remembering the injury,” and so the results may have been vulnerable to recall bias and/or confounded by acute stress responses that subjects experienced at the time of injury.

There is some evidence that psychiatric comorbidities are more common in patients who develop PCS relative to the general population [21]. Studies in pediatric patients with recent mTBI have shown that patients may report subjective PCS symptoms even after their cognitive test results have normalized, and that children with pre-morbid behavioral maladjustment are at greater risk of developing PCS [22, 23]. However, few studies have specifically investigated potential interactions between mTBI and psychiatric comorbidities in the development of other PCS symptoms, such as headaches or sleep disturbance.

The study of PCS is made difficult by conflicting diagnostic criteria.

In some ways, research on PCS is made more difficult by the amorphous nature of the PCS symptom complex itself. While there are a number of well-established symptoms and clinical findings associated with PCS, there is no “classic” presentation of the syndrome as a whole. As a result, the clinical diagnosis of PCS is vulnerable to inconsistent application between different providers, or even between different patients of the same provider. The lack of agreement between the definitions of PCS provided by ICD-10 versus that of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) make PCS difficult to diagnose and treat, and thereby presents an obstacle to carrying out robust prospective studies. As an example of this definitional conflict, the ICD-10 definition notes that PCS can include functional impairments such as concentration or memory deficiencies, while the DSM-5 definition (referred
to as “Major or Mild Neurocognitive Disorder due to Traumatic Brain Injury” in the DSM, a revision from earlier editions’ “postconcussion disorder” terminology) requires evidence of affective symptoms or personality changes [7, 22, 24].

In determining the incidence of PCS among patients who have suffered mTBI, the nebulous nature of the syndrome in conjunction with these conflicting definitions can produce contradictory diagnostic results. As illustration of this, PCS incidence in the pediatric population has been estimated at anywhere from 21 to 59%, even if only the ICD-10 definition is used [25]. A 2005 study found that providers’ diagnostic evaluations for PCS tended to produce markedly conflicting results depending on the clinical criteria used (e.g. ICD-10 versus the then-current DSM-IV-TR), even when both sets of criteria were applied to the same slate of patients [26]. Further, some characteristic symptoms of PCS are also prevalent – or at least prevalently self-reported – among populations without head injury [27]. These diagnostic discrepancies have therapeutic implications as well. While the DSM’s criterion that symptoms be present three months following the date of the mTBI may lend that definition greater specificity, the ability to diagnose PCS at earlier intervals via ICD-10 criteria (i.e. within four weeks of injury) allows for earlier and potentially more effective interventions for a given patient.

Given the potential ramifications in the professional and personal lives of patients recovering from concussion, in conjunction with the definitional difficulties inherent to PCS diagnosis, it is important to gain a better understanding of PCS’ etiology and natural history. Which patients are at greatest risk of developing prolonged PCS? Can patients be “categorized” on the basis of risk factors (e.g. male versus female, sport-related versus motor vehicle collision, history of sleep or psychiatric conditions)? Might such categorizations enable early, targeted
In addition to PCS as a whole, there are specific manifestations that especially warrant increased study, such as psychiatric and sleep-related manifestations.

In order to design a study capable of answering some of these questions, a literature review was conducted to assess the status of peer-reviewed literature on this topic, as well as to identify pertinent clinical findings to track. This paper will compare observational studies of incident PCS among patients recovering from recent concussion (i.e. within the prior few months or year). These studies were examined with a focus on comparing outcomes and measures related to sleep disturbance (e.g. quality, quantity, timing, consistency) and affective symptoms (e.g. personal and family historical factors, incident symptoms during recovery), as well as interactions between these two potential manifestations of PCS.
Systematic Review

Literature Search and Article Screening Methods

*Inclusion and exclusion criteria*

No registered review protocol was created or followed in producing this systematic review. The inclusion and exclusion criteria that were used in screening studies are detailed in Appendix #1. Briefly, the search focused on observational studies of patients with recent concussion (typically within twelve months of the concussion). While review articles were not included, the review articles’ citation lists were hand searched to screen for additional publications potentially relevant to this review. The citation lists of included articles were also hand-searched. Clinical trials were not included for the purposes of this review because their research designs seek to eliminate inter-variable relationships inherent to the natural history of PCS; these relationships are our primary interest in planning our new study. Because clinical trials were not included, ClinicalTrials.gov was not consulted as an additional reference source.

Studies that focused on measurement of serum biomarkers in the setting of concussion were excluded. Studies of military or veteran populations were also excluded because the specific injury mechanisms (e.g. blast injuries) and psychosocial stressors experienced by military populations may make these studies’ findings less generalizable to the population from which our new study will draw (e.g. primarily referrals of adolescents and young adults for sports-related concussions). This review specifically included articles that examined risk factors for, or consequences of, sleep and mood symptoms in the setting of concussion recovery. These particular aspects of PCS have not been well-characterized in the literature, and they might lend themselves to early, targeted interventions. Since the acute diagnosis and treatment of concussion has gradually evolved and become increasingly standardized since the early 2000s, particularly
in sports, studies more than ten years old as of June 2016 were excluded. Finally, because our new study will specifically focus on the causes, components, and outcomes of prolonged PCS, only studies with greater than one month of follow-up measurements were included.

Literature search strategy and article screening

The PubMed MEDLINE and Cochrane Library databases were used to conduct the literature search. No article authors were contacted. The literature searches were frozen on June 14, 2016 for final synthesis of results. The full search strategy used with the MEDLINE and Cochrane Library databases is described in Appendix #2. Essentially, there were three groups of search terms that related to our proposed research focus: (1) population of interest (i.e. “adolescents,” “adults,” “humans”), (2) exposure of interest (i.e. “concussion,” “brain injury”), and (3) risk factors/outcomes of interest (i.e. “depression,” “anxiety,” “sleep,” “factors,” and variations thereof). Neither quotation marks nor MeSH term restrictions were used when searching; searches were allowed to automatically map to variations of each search term. The article screening process was performed by one reviewer (RP) as summarized in Appendix #3. To start with, the reviewer discarded duplicate articles from the database searches and applied the criteria shown in Appendix #1 to screen articles based on the information presented in their titles and abstracts. The reviewer retained items that appeared applicable on initial screening, and then performed a full-text screen of the remaining articles, again applying the criteria shown in Appendix #1.
Data extraction and quality assessment

Data extraction was performed by the same reviewer. The reviewer used a piloted form that corresponded to the column headings seen in Appendix #4: Authors (Year), Sample, Study Design, Measurements, Key Findings, Strengths, and Limitations. The “Key Findings” presented in Appendix #4 were narrowed to include only the factors/outcomes of interest (namely, sleep- and mood disorder-related findings), and the “Measurements” column only included those measurements that had a direct bearing upon each article’s key findings. Due to resource constraints, article authors were not contacted regarding methodology or results that were unclear or unstated in the published articles. The reviewer assessed each of the remaining studies for risk of bias, using the approach and risk of bias item bank described by Viswanathan and colleagues [28]. This process included assessments of potential confounding, selection bias, detection bias, and attrition bias for each study.

In the course of the data extraction process, the methods of the included articles were summarized with an eye toward best practices for future research in this field of study. The summarization of results represents an attempt at distilling what is known about sleep disturbance and affective symptom manifestations of PCS thus far. This review of the articles’ results is qualitative. The studies reviewed used a wide variety of survey instruments, scoring methodologies, and outcome reporting formats. Due to this lack of homogeneity, $I^2$ was not computed to determine the consistency of the studies summarized here, nor were any meta-analyses, sub-group analyses, or meta-regressions performed on the extracted data. Finally, the overall risk of bias of the accumulated literature was assessed.
Results

Study selection

The inclusion of post-concussion syndrome (without quotes) as a search criterion restricted the number of search results by a factor of about fifty in both the MEDLINE and Cochrane Library databases. However, we submit that the inclusion of this criterion was justified, as the term “post-concussion syndrome” has been present in the medical lexicon for decades. Experiments with removing this criterion generated ample noise with negligible additional signal in the search results. Hand searches of articles’ citation lists were implemented in part to compensate for the risk that the search strategy may have been overly-narrow.

As shown in the PRISMA flow diagram in Appendix #3, there were 234 total results from the MEDLINE and Cochrane databases. Hand search of review articles and the included articles’ citation lists yielded 17 additional articles. After excluding eight duplicates, 243 items remained. After screening titles and abstracts based on the criteria described in Appendix #1, 159 of these articles were excluded. Following a full-text screen of the remaining 84 articles, 69 of them were excluded. Of these 69 articles, eleven focused on military and veteran populations, eight were review articles (which were subsequently hand-searched for relevant citations), twenty-seven did not specifically examine the risks/outcomes of interest, and twenty-four did not include greater than one month of follow-up measurements. This left fifteen studies meeting all inclusion criteria.

Study characteristics

All fifteen studies included in this review were published in peer-reviewed journals in August 2006 or later. Twelve were prospective cohort studies [27, 29 – 39], five of which
included a control group [27, 35 – 38]. These control groups were composed of healthy controls [27, 37], patients with non-head injuries [35, 36], and patients with orthopedic injuries [37, 38]. Two of these studies’ control subjects were matched on age and sex [37, 38]; the other prospective cohort studies that included controls used either convenience or consecutive sampling. There were two retrospective cohort studies, both of which were conducted via chart review [40, 41]. Neither of these two studies included controls. Finally, there was one case-control study that included two controls for each case, matched on age and sex [42].

Four of the studies only included pediatric patients [30, 31, 38, 41], two of which comprised separate analyses of data from the same cohort [30, 31]. Of note, two studies used pre-existing concussion registries to conduct chart reviews [40, 42]; the remaining thirteen studies recruited subjects (including controls, where applicable) upon their presentation to an emergency department (ED). Study lengths varied widely: the shortest one was six weeks [40], eleven studies were three months long [27, 29 – 32, 35 – 37, 39, 41, 42], one was six months long [33], one was 24 months long [38], and one was three years long [34]. The most common survey instrument used was the Rivermead Post-Concussion Questionnaire (RPQ) [43], which was used as a general inventory to track post-concussion symptoms in eight of the studies [27, 30 – 33, 35, 36, 39, 40]. Beyond the RPQ, however, the survey instruments used varied widely among the articles that were reviewed; no other instrument was used in more than two of the studies.

**Summary of key findings**

Sleep disturbance is one of the symptoms classically associated with PCS, and the studies reviewed here indicated that it is one of the most common symptoms reported by patients with
recent mTBI [31, 33, 35]. More specifically, mTBI patients appear to have increased sleep onset latency [35]. However, the evidence overall paints a mixed picture regarding sleep disturbance in the setting of mTBI recovery. Two studies found greater sleep disturbance in mTBI patients compared to healthy and/or non-head injured controls [37, 38], with a stronger effect size noted in older patients [37]. However, another study with comparable sample size detected a similar prevalence of sleep disturbance (about 21%) both among subjects with mTBI at three months post-injury as well as controls [27]. A separate study indicated that female sex, psychosocial problems, and frequent pain acted as confounding factors in determining the incidence of sleep disturbance among mTBI patients (at least in pediatric populations) [38].

Other evidence sought to characterize the underlying mechanism of PCS-related sleep disturbance. Short sleep duration (e.g. less than 7 hours) and/or self-reported perception of poor sleep was associated with daytime dysfunction [35], poor self-care [38], and greater overall severity of self-reported PCS symptoms [41]. One study found that self-reported reasons for poor sleep evolved over the time course of concussion recovery (e.g. due to “pain from injury” at ten days post-injury, versus “frequent awakenings” at three months post-injury) [40]. Unique among PCS symptoms, self-reported sleep disturbance tended to worsen over time; 21.6% of one study’s subjects developed sleep disturbance after initial treatment and discharge from the ED, suggesting delayed onset of this symptom at three to four weeks post-injury [31]. Another study found that the prevalence of sleep disturbance among mTBI patients increased from 13.3% at ten days post-injury to 33.5% at six weeks [40]. In the latter study, Chaput and colleagues also found that subjects who reported sleep disturbance at ten days and six weeks post-injury were also 9.9 and 6.3 times more likely, respectively, to report concomitant feelings of depression [40].
Finally, for some patients, post-mTBI sleep disturbance symptoms may continue for years – much longer than the typical length of prospective cohort studies in this area of research [34].

Among the studies that measured it, depressed mood was a relatively uncommon PCS symptom, but it was a statistically significant predictor of PCS morbidity. Multiple studies found that patients with pre-mTBI depression (either documented in the patient’s chart or self-reported upon presentation to ED following mTBI) were significantly more likely to suffer from persistent PCS at three months post-injury and required more time to recover before returning to full activity [29, 30, 33, 42]. Morgan and colleagues also found that a positive family history of mood disorders or other psychiatric diagnoses predicted persistent PCS at three months post-injury [42]. Only one study with relatively small sample size (n = 14) found that baseline depression did not correlate with PCS persistence at 3 months post-injury [32]. However, depressed mood was less prevalent among mTBI patients compared to other PCS-related symptoms in these same studies, and it tended to resolve relatively quickly [31].

Some studies also examined the incidence of PTSD and non-specific anxiety symptoms in patients with recent mTBI. Similar to depressed mood, self-reported anxiety at the acute stage of mTBI recovery predicted persistent PCS at three months post-injury [29, 33]. PTSD appears to be more prevalent among mTBI patients versus non-head injured or healthy controls [37]. However, another study that specifically examined interactions between mTBI and PTSD diagnoses found that mTBI was predictive of PTSD diagnosis, but not PCS, at three months post-injury [36].

Some of the reviewed studies evaluated potential predictors of prolonged post-concussion symptom duration. A history of multiple concussions was associated with longer average duration of post-concussion symptoms (about 24 days versus 12 days) [30]. Patients who
expressed belief that post-concussion symptoms would persist chronically tended to have longer duration of symptoms as assessed by the RPQ [39]. Finally, patients who eventually developed PCS were more likely to experience delayed onset of post-concussion symptoms (i.e. onset of symptoms at least three weeks post-injury that were not present at the acute stage following mTBI) [42]. However, Lagarde and colleagues found that PCS diagnosis at three months post-injury (a main outcome used in many of the studies reviewed here) was an imprecise benchmark to use, as the prevalence of PCS among mTBI patients ranged from 21.2% to 53.4% at three months post-injury time point, depending on the PCS definition that was used (i.e. RPQ, ICD-10, DSM-IV, or Laborey) [36].

Risk of bias across studies

Strengths and limitations (including potential sources of bias) for individual studies are documented in Appendix #4. The only study with methodology that was concerning was that of Kostyun and colleagues [41]. Their study did not use universal time points, but instead used one-way analysis of variance (ANOVA) to compare each subject’s first, second, and third Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) results, regardless of timing. The first, second, and third iterations of ImPACT testing for a given patient were (on average) completed 22 ± 18 days, 44 ± 41 days, and 76 ± 74 days post-injury, respectively. More generally, all twelve of the prospective cohort studies reviewed here recruited subjects upon presentation to an ED following a mTBI [27, 29 – 39]. Seven of the twelve prospective trials did not include control groups [29 – 34, 39].

As is common in long-term prospective studies such as those included in this review, several authors had difficulty recruiting a high proportion of eligible patients to avoid sampling
bias, and several suffered large or differential loss to follow-up [29, 30, 35, 36]. Therefore, these studies were vulnerable to confounding via various demographic, socioeconomic, and psychosocial factors. However, inclusion and exclusion criteria were largely sensible and consistent across all studies, except that most studies did not exclude patients taking narcotics or similar medications that affect the brain.

**Discussion**

This systematic review yielded several insights about the predictors, effects, and interactions between sleep disturbance and affective symptoms in the setting of PCS. There was evidence that sleep disturbance was one of the most common features of PCS [33, 35], that the disturbance tended to worsen over the time course of concussion recovery [31, 40], and that for some patients the symptoms took months or even years to resolve [34]. While depressed mood appeared to be a less-common manifestation of PCS overall, it was a significant predictor of PCS morbidity months after a head injury [29, 33, 42], and it tended to appear in conjunction with sleep disturbance [40], at least in a sample of pediatric mTBI patients.

These findings came with some caveats, however. While the statistical analyses appeared to be robust in many cases, the methods used in the article by Kostyun and colleagues were concerning. Subjects’ sequences of ImPACT test results were compared without regard to the time interval since injury for a given test result; for instance, the third ImPACT testing for one subject might conceivably have been completed before (in terms of days since injury) the first or second testing session for another subject. This non-universal timing of assessments likely violates the assumption that responses for each group are independent and identically distributed normal random variables, meaning that it was inappropriate for the authors to use one-way
ANOVA in their analysis. A better approach might have been to use generalized linear mixed model regression [44].

Some of the other studies had methodological concerns. Several articles noted that they conducted follow-up surveys via telephone interviews, but did not note whether these interviewers were masked, rendering the studies vulnerable to interviewer bias [34, 35, 39]. While not always necessary in cohort studies, the lack of a control group in the prospective studies reviewed here does present an issue, due to their outcomes being measured via self-reported responses to subjective questions on symptom inventories [29, 30, 33, 34]. This meant that authors could not adjust for intra-subject variance over time, whether due to changing life circumstances or simply how subjects approach the questions.

The sampling methods used in many of these studies – namely, recruitment from the ED – also presents a methodological problem. A recent descriptive study in a large pediatrics-focused health system found that nearly 82% of patients within their system who suffered a concussion presented first to a primary care provider, not an emergency room [45]. Although this particular study focused on a pediatric population and has not been replicated, it nonetheless raises concerns about the external validity of recruiting from the ED for studies of mTBI.

**Potential limitations**

It is also important to consider the limitations of this review, including the search strategy and the inclusion and exclusion criteria that were used. Although MEDLINE and the Cochrane Library together include a significant portion of the peer-reviewed medical literature, the literature search might have yielded additional articles if additional databases had been included, such as SPORTDiscus or CINAHL. Therefore, there is potential for publication bias that may
influence the validity of this review’s synthesis of evidence. Further, the literature search, article screening, and data extraction procedures were completed by only one reviewer (RP), increasing the risk of errors in article screening or data extraction. As this systematic review was meant to assist the design of a new, longitudinal study based at an outpatient concussion clinic, the inclusion and exclusion criteria were meant to include only articles that focused on populations, exposures, measurements, and outcomes that would be most applicable and useful in designing this new study.

Implications for future research and clinical care

A striking aspect of our literature search results was the relatively young age of the articles that were initially identified: about 76% were published within the past decade. Of the fifteen articles we eventually included, nine of them had been published within the past five years. All this is to say that concussion recovery is a relatively young, growing field of research whose methodological practices continue to evolve.

In particular, methods for measurement of concussion and its effects on the brain and body continue to be a vexing issue. Concussion is a clinical diagnosis; it is often not visible on conventional imaging modalities, and as of yet there is no blood test that can detect it. While there exist objective (albeit costly and relatively invasive) methods for measuring sleep, researchers must rely on patient self-report for most potential manifestations of post-concussion syndrome such as nausea, headache, forgetfulness, fatigue, and depression. Post-concussion symptom inventories such as the RPQ (used by eight of the studies reviewed here) do not autonomously detect these symptoms, but simply ask the patient whether they have noticed them [43]. These questions about symptoms are inherently subjective and may be influenced by social
stigma or similar factors (such as when asking pediatric patients about depression [31]), making it difficult to reliably identify trends in PCS manifestations across a population.

However, based on current evidence, the inherent subjectivity of many post-concussion survey tools such as the RPQ may have a hidden advantage when determining PCS prognosis for a given patient. This advantage lies in the fact that they are measuring patients’ perceived symptoms. One of the most unexpected and compelling themes to arise from this systematic review was the apparent influence of patients’ perceptions upon the course and duration of their post-concussion symptoms. In one of the studies reviewed, patients who expected the duration of their post-concussion symptoms to be similar to that of a chronic disease (rather than, say, a viral illness) were significantly more likely to be diagnosed with PCS at three months post-injury [39]. Separately, perception of poor sleep was associated with greater self-reported PCS symptom severity [41]. In multiple studies, sleep disturbance was one of the few PCS symptoms to exhibit delayed-onset and increased prevalence among mTBI patients in the post-acute period [31, 40].

This phenomenon of evolving PCS symptomatology raises the question of physiological versus psychological contributions to PCS etiology. Future research should further investigate the natural history of sleep disturbance in the setting of PCS. Acute post-mTBI predictors of increased burden or resiliency in regards to post-concussion sleep disturbance should be identified. In particular, the interactions between sleep disturbance and affective symptoms in the setting of PCS should be further elucidated; only one of the included studies examined this potential interaction [40].

From a clinical perspective, the results of this systematic review underscore the importance of concussion education at the initial post-injury evaluation. These findings do not change the current standard of care, which involves a prescription for physical and cognitive rest
initially, and then gradually increasing activity as tolerated. However, this review’s findings regarding the significance of self-perception of symptoms as a predictor for PCS underscore the importance of discussing the typical duration of post-concussion symptoms with the patient and their family at the acute visit. Providers should provide reassurance but follow-up closely if symptoms last longer than expected. Finally, health care providers should specifically counsel mTBI patients about the importance of sleep in concussion recovery, as well as basic techniques for achieving a better night’s rest (i.e. sleep hygiene).

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Proposed Research Design

General Information and Summary

Purpose:
To contribute to improved scientific understanding of the etiology and natural history of post-concussion syndrome (PCS), and to describe clinical measurements, historical risk factors, or other potential predictors associated with shortened duration of symptoms following concussion (or alternatively, factors associated with prolonged duration of post-concussion symptoms).

Participants:
Subjects will be drawn from among patients referred to a weekly post-concussion clinic (PCC) located in a sports medicine and training facility on the campus of a large research university.

Procedures (methods):
1. Standardize the clinical measurements conducted in PCC, such as history-taking (including past medical history, PMH; mechanism of injury; and severity of injury), physical exam, Buffalo Concussion Treadmill Test (BCTT), Sensory Organization Test (SOT), CNS Vital Signs (CNSVS), and self-report survey tools (administered via the Research Electronic Data Capture (REDCap) platform hosted at UNC-Chapel Hill.
2. Use these standardized measurement data in aggregate to identify clinical findings and treatment modalities that are associated with shorter duration of PCS symptoms.
3. Implement these standardized measures prospectively to collect data on symptomatology and typical time required before a given patient can return to full activity (RTA).
**Initial Considerations and Study Rationale**

Sleep disturbance and affective symptoms have long been established as common clinical manifestations of Post-Concussion Syndrome (PCS). As evidenced by the articles reviewed above, the mechanisms of potential interactions between sleep disturbance and affective symptoms, as well as the direction of causality between PCS and these comorbidities, have not been well-characterized. There is also limited data on the usefulness of objective post-concussion measurements, such as posturography and neurocognitive assessment, in predicting PCS prognosis for a given patient. As such, we propose to use our pre-existing outpatient post-concussion clinic (PCC) as a base for a longitudinal study of these potential predictors and comorbidity interactions using detailed medical histories, standardized interviews to evaluate for post-concussion symptoms (including symptoms that are ongoing as well as acute-stage symptoms that may have regressed), objective post-concussion measurements at initial evaluation, and extended follow-up of PCS symptoms using previously-validated surveys.

Although the paradigm is gradually evolving, sleep disturbance and affective symptoms have traditionally been treated as components of the PCS symptom complex using standard protocols such as physical and cognitive rest, rather than as treatable conditions in and of themselves. Ideally, symptom-targeted treatments would allow providers to prescribe pre-emptive (based on risk factors and symptoms at the acute stage) and abortive (in cases where new, unpredicted symptoms develop) therapies to shorten the time course of concussion recovery and mitigate the economic and public health burdens of PCS. Devising effective interventions, though, will require improved understanding of PCS’ etiology and natural history, as well as the interplay between its array of potential manifestations. With our new study, we seek to contribute to this improved understanding.
The articles included in the above systematic review tracked sleep disturbance and affective symptoms using exclusively self-report measurements. This reliance upon self-report measures does present an issue in populations of patients recovering from TBI, as a number of short-duration studies have found significant discrepancies in detection of sleep disturbance via self-report measures (e.g. Pittsburgh Sleep Quality Index, PSQI; Diagnostic Interview for Insomnia, DII; Epworth Sleepiness Scale, ESS) compared to objective measures used in the same slates of patients (e.g. polysomnography, PSG; Multiple Sleep Latency Test, MSLT) [46, 47, 48]. However, beyond their higher costs and relative invasiveness, many of the objective measures used in these studies were cross-sectional and/or vulnerable to measurement bias, as they typically involved only one to three measurements per subject and were generally not measured at universal time points (relative to date of injury) across all subjects.

Self-report measures may yield a less reliable quantitative picture of sleep disturbance in mTBI patients, but they still have some advantages compared to most objective modalities of sleep measurement. Self-report measures can capture night-to-night or week-to-week sleep variability as well as subjects’ self-perception of their sleep quality, the latter of which may be a significant predictor of PCS prognosis [39]. In the future, our research group may explore the use of cost-efficient objective sleep measures for use at home (such as fitness trackers) for potential inclusion in a longitudinal study. This study, however, will use self-report instruments to conduct follow-up measurements of subjects’ sleep disturbance and affective symptoms.

The uniqueness of this research proposal stems from its concurrent measurement of subjects’ sleep, affective symptoms, function (i.e. time required for RTA), and other manifestations of PCS, all tracked in a longitudinal fashion. In addition, subjects will be drawn from an outpatient PCC that receives referrals from variety of providers (including emergency
departments and outpatient primary care physicians) and from a broad geographic area across the Eastern and Piedmont portions of North Carolina. This research design will allow enhanced study of interactions and causal relationships among long-established symptoms and risk factors associated with PCS, while avoiding common issues of external validity (due to recruitment directly from ED) and discrepant application of diagnostic criteria (due to involvement of many different providers) that have been faced by other studies in this area of research.

**Study Aims and Hypotheses**

*Aim #1(a). Describe the relationship between pre-morbid sleep problems and post-concussion sleep disturbance.*

Previous studies have consistently demonstrated an association between PCS and sleep disturbance [49]. Given that sleep disturbance has been shown to sometimes worsen in the month immediately following an mTBI [31, 40], we hypothesize that self-reported pre-morbid sleep problems is associated with greater post-concussion sleep disturbance.

*Aim #1(b). Describe the relationship between pre-morbid personal and/or family history of psychiatric conditions or migraines and post-concussion sleep impairment.*

Prior studies have demonstrated that personal and/or family history of migraines or psychiatric conditions (e.g. affective disorders) are associated with increased risk of prolonged PCS [29, 30, 33, 42]. There is mixed evidence on whether a past medical history of migraines is similarly predictive (both studies focused on pediatric patients) [30, 42]. However, to our knowledge no study has shown whether such historical findings are associated with increased likelihood of post-concussion sleep disturbance. Given this result in conjunction with how
commonly sleep disturbance occurs among post-concussion patients [31, 33, 35, 49], we hypothesize that pre-morbid personal and/or family history of migraines or psychiatric diagnoses is associated with greater PCS-related sleep disturbance, with no differential effect based upon subject age.

Aim #1(c). Describe the effect of at least one previous concussion upon the degree of sleep impairment and affective symptoms in patients recovering from mTBI.

It has been established that the effects of recurrent concussions appear to be additive in some respects, with multiple concussions leading to increased severity of cognitive impairment, longer duration of post-concussion symptoms, and greater risk of additional concussions in the future [8, 30, 50]. However, there is limited data in regard to an additive effect of recurrent concussion in producing specific PCS symptoms. We hypothesize that among patients recovering from recent mTBI, a history of one or more previous concussions is associated with greater sleep disturbance and affective symptoms during recovery.

Aim #2. Describe the relationship between the development of delayed-onset, self-reported, post-concussion sleep disturbance post-concussion affective symptoms.

PCS is often associated with, and can have similar symptomatology as, certain psychiatric conditions such as depression or anxiety disorders [51]. There is evidence that the development of PCS may have a psychological component, including findings that patient perceptions can influence the duration of PCS symptoms that they experience [39]. There is also evidence from studies of pediatric populations that the aggregate burden of PCS-related sleep disturbance tends to increase over the first three to four weeks following concussion. We would
like to investigate whether these findings are connected. The initial symptoms experienced by a patient may result more from a physiological response to the mTBI, before evolving to a combination of symptoms driven more by psychological factors. While this may not hold true for more complex cases such as patients with a history of multiple recent concussions, we hypothesize that subjects with delayed onset of self-reported sleep disturbance (i.e. onset at one-month post-injury or later) is associated with increased likelihood of concomitant affective symptoms.

3. Describe the relationship between the degree of sleep disturbance and/or affective symptoms and the severity of overall PCS symptoms.

Although the underlying mechanisms are not completely understood, sleep is generally thought to benefit neuronal healing as well as overall brain health [52]. One recent study has shown that patients recovering from mTBI who slept more than usual tended to demonstrate greater cognitive deficits on testing; the authors speculated that the increased sleep was needed for healing [41]. As noted above, Chaput and colleagues found that post-concussion sleep disturbance was associated with concomitant depressed mood [40]. Multiple studies have found that pre-injury depression is associated with increased likelihood of PCS at three months post-injury [29, 30, 33, 42].

To our knowledge, none have found that new depression symptoms in the acute stage following concussion is associated with prolonged PCS, although it seems reasonable to expect that anhedonia or similar affective symptoms may lead to decreased motivation or increased apprehension about returning to activity. We hypothesize that sleep disturbance is positively correlated with overall duration of PCS symptoms. While we expect that overall PCS symptom
severity is positively correlated with the presence of pre-injury affective disorder diagnoses, we do not hypothesize a significant correlation with acute-stage affective symptoms following mTBI.

4. Describe the relationship between pre-injury chronotype and the degree of post-concussion sleep disturbance and affective symptoms, as well as its relationship with overall severity of PCS symptoms.

Previous meta-analyses have shown that “morningness” is associated with decreased cognitive ability but increased academic achievement, while “eveningness” is associated with increased cognitive ability but decreased academic achievement [53]. Having an eveningness chronotype also appears to be associated with a greater prevalence of depressive symptoms [54]. However, to our knowledge, the interaction between chronotype, sleep disturbance, and affective symptoms has not been previously evaluated in the setting of PCS. Most previous research on chronotypes has been conducted with shift workers, which may not be generalizable to mTBI patients who have been prescribed physical and cognitive rest. Therefore, we hypothesize that chronotype will not affect the likelihood of sleep disturbance or affective symptoms following concussion. However, since patients recovering from concussion typically require increased sleep, and since circadian rhythms associated with eveningness chronotype are often asynchronous with typical school and work schedules, we hypothesize that eveningness chronotype is associated with increased overall severity of PCS symptoms.
Methods

Participants

The Post-Concussion Clinic (PCC) has been held on a weekly basis for several years now. The patients seen in this clinic tend to be referred due to persistent, refractory post-concussion symptoms, and they may present anywhere from a few weeks to a few years following their concussion(s). It is a unique clinical setting, particularly compared to most primary care offices. A one-hour time slot is allotted for each patient, enough to take a detailed history and collect ample data in-office. Given the PCC’s location within a sports medicine research center and training facility on the campus of a large research university, we are also able to perform specialized clinical measurements. These measures, all of which will be detailed in sections to follow, include posturography, computerized neurocognitive assessments, exercise testing, and functional activity testing.

Of the fifteen articles included in our systematic review, only one directly compared pediatric patients (18 years of age or younger) with young adults (19 to 30 years of age) [37]. Therefore, as part of our longitudinal study, we will recruit patients aged 12 and older in order to investigate age as a factor that may affect the natural history of PCS. We will rely on subjects' verbal confirmations that they are at least the age of majority (which is 18 years old in North Carolina), or alternatively on subjects' parent or guardians' verbal confirmation if the child is younger than the age of majority. Concussion status will be confirmed via medical records and/or communication with the referring provider (e.g. primary care provider or athletic trainer). We will not use any further means of determining each subject's group status.

The majority of the data collected in this study will be derived from history, physical exam, and self-report. Patients will be counseled that they need not disclose sensitive
information (e.g. personal and/or family psychiatric history) if they feel that they would risk psychological trauma by doing so. If a patient has sustained a recent concussion without resolution of most of their concussion-related symptoms (i.e. the patient cannot be described as mildly symptomatic or asymptomatic at time of presentation), then that patient will not be tested in order to avoid physical or mental harm that might result from loss of balance or cognitive exertion. In these cases, the timeline for follow-up testing will be jointly determined by the patient (or their guardian), the providers at the PCC, and the referring provider. We contend that these measures present no greater than minimal risk, as defined in the FDA Code of Federal Regulations (CFR) § 50.3 [55].

Some of the other measures that will be used, including posturography, neurocognitive assessments, and exercise testing, may impart a minor increase over minimal risk to the subject. However, these tests are often clinically indicated for patients that present to the PCC based upon standards of care. In addition, these measurements, when considered in aggregate over the study’s entire sample, will contribute to general knowledge about the natural history and clinical course of PCS. The study subjects, or their guardians if applicable, will always be given the option to halt participation in the study or to decline to complete certain tests. Therefore, we feel that the study includes adequate protection measures for children as a vulnerable population, in accordance with the FDA CFR § 50.53 [56].

Subjects in the proposed study will be recruited through the PCC. Our strategy will be to offer informed consent to participate in this study to all patients seen in PCC who meet the criteria for enrollment. Subjects over the age of majority (18 in North Carolina) will give consent as adults, whereas for subjects who are minors (i.e. less than 18 years old) their parents or guardians will give consent by proxy if they wish for their child to participate. The study will be
fully explained to all potential subjects before consent is requested. Following counseling about the study, potential subjects will be allowed to review the informed consent paperwork in a private room, individually or in conjunction with their parent or guardian if they are younger than 18 years old. They will have a chance to discuss any questions or concerns they have about the study with the investigators after reviewing the informed consent paperwork.

Patients presenting to PCC who do not (or whose parents/guardians do not) wish to participate will undergo normal history and physical, post-concussion testing (if clinically indicated), and treatment. No clinical data generated from this latter group's PCC visits will be included in data analysis; they will still follow-up with in PCC as needed but unlike study participants they will not be sent the batches of follow-up surveys in the months following their appointment.

As of now, the PCC does not see many patients with acute concussion (i.e. less than 21 days since injury). PCC patients are referred from all over the state by a variety of providers and at a wide range of time points in the course of their recovery from concussion. Therefore, a potential difficulty with carrying out this study is the potential variance of time intervals since mTBI event among subjects. In the worst case, the variance of this time interval may interfere with our ability to administer initial testing as well as collect follow-up self-report instruments at universal time points across all study subjects.

*Study Design*

With this study, we are seeking to better understand the natural history of sleep disturbance and affective symptoms in the setting of PCS, investigate possible interactions between these PCS symptoms, and potentially establish direction of causality without testing any
specific interventions other than standard of care. As such, we designed this as a prospective cohort study. We next considered duration of follow-up. Although most uncomplicated concussions resolve within a few weeks (i.e. less than about 21 days), ten of the fifteen studies from our systematic review included three months of follow-up (relative to each subject’s date of head injury). As reported by Spinos and colleagues, between 40% and 80% of mTBI patients report PCS-like symptoms within weeks of suffering mTBI, while about 50% of patients report experiencing these symptoms for up to three months afterward [9]. However, only 10% to 15% of mTBI patients continue to report PCS-like symptoms more than a year after injury. While many of the studies we reviewed included three months of follow-up, they typically used PCS diagnosis (which can present in a variety of ways) as their benchmark outcome. However, since we are examining two specific manifestations of PCS (sleep disturbance and affective symptoms), we opted to include six months of follow-up.

**Participant Inclusion and Exclusion Criteria**

We will define “recent concussion” as any patient who is suspected of having suffered a concussion due to presence of concerning symptoms. This clinical suspicion may be based on the professional impression of a certified athletic trainer, team physician, or the patient's primary care physician. This professional impression should be based at least in part on thorough physical, neurological, and mental status examinations. Inclusion and exclusion criteria were adapted from operational criteria described in a 2014 World Health Organization (WHO) task force report on prognosis after mTBI as well as the 2013 Zurich consensus statement on concussion in sport [57, 58].
Patients will be included if their symptoms stem from an acute injury that involved mechanical energy applied to their head, face, neck, or any other part of the body where the impulsive force may have been transmitted to the head. They must have a Glasgow Coma Scale (GCS) score of 13 to 15 (either immediately post-injury or upon later presentation for treatment), as well as at least one of the following: confusion, loss of consciousness (LOC) for at most 30 minutes, amnesia for at most 24 hours, neurologic abnormalities not requiring surgery (e.g. focal lesions apparent on exam, seizure), or onset of general functional impairment within minutes to hours of the injury.

Patients will be excluded if there is evidence of illicit drug use, there are associated injuries that may limit patient's ability to participate in objective measurements for purposes of the study (e.g. fractures or sprains), there is/was evidence of structural or physiological abnormality via neuroimaging, the patient is currently hospitalized, the patient has a major untreated medical or psychiatric comorbidity (e.g. epilepsy or major depression), the patient or their guardian (if applicable) are unable to complete the surveys administered as part of the study (e.g. due to visual, reading, or language comprehension difficulties), or the patient is already receiving medical treatment (beyond physical and cognitive rest) for post-concussion symptoms. Because the goal of this study is to observe subjects’ symptom progression at universal time points out to six months post-injury, patients whose concussion was more than two months prior to their initial PCC visit will be excluded. At the time of initial presentation to PCC, if a patient was recently started on a new prescription psychoactive medication, then initial evaluation via objective measures will be postponed until the patient returns to baseline (if it is a short course of prescription medication) or until a new baseline is established. No subjects will be excluded due to race, gender, ethnicity, or pregnancy status.
Study Measurements

1. Patient Interview:

The investigator will note the time elapsed since the patient's concussion event, as well as his or her basic demographics (including age, sex, and ethnicity) and insurance status (e.g. Private, Medicaid, None, or Other). History-taking will begin with a review of the patient's current cognitive function and how this has changed over time since their concussion event, including attention, concentration, memory, processing speed, reaction time, and whether or how often the patient feels like they are "in a fog." Other aspects of the patient's concussion event will also be reviewed, including the sport or activity involved, whether the patient was helmeted, whether the patient lost consciousness, medical attention they received, standardized post-concussion assessments that were performed, and whether baseline results for these post-concussion assessments are available. Further, the investigator will review whether any pain medications were prescribed or have been used, and (if the patient initially presents to the PCC more than one month after concussion) whether any new symptoms developed more than two weeks after the initial concussion event.

Physical symptoms reviewed will include sensitivity to environmental stimuli (e.g. light or sound), headache symptoms (including laterality, severity, timing, and aggravating/attenuating factors), other new sources of recurrent pain or discomfort (particularly in the head and neck region), nausea, vomiting, vision changes, uneven gait, seizures, as well as any episodes of dizziness and/or syncope. Sleep will also be quantitatively and qualitatively reviewed, including number of hours of sleep per night, typical bed and awake times, sleep latency, snoring, and frequency of nighttime awakenings. Behavioral changes including irritability, depression,
anxiety, and problems with functioning or succeeding at work or school will be discussed. Finally, for all positive findings during this portion of the interview, it will be important to discuss how that symptom has changed over time, as well as comparing whether the patient also experienced that symptom prior to the concussion.

Next, the investigator will review the patient's past medical history, with particular attention given to historical findings that may be associated with an increased risk of developing PCS. The investigator will start by discussing any concussions that the patient has experienced prior to the most recent one, including timeline, general clinical course, and the associated activity or sport. The investigator will also ask about the patient's sport-playing history and whether the patient has been in any motor vehicle collisions (MVC), as there is a chance that patients may have sustained concussions that they do not know about during sports or in MVCs.

As far as neurological and psychiatric history, the investigator will inquire about any history of migraines or other recurrent headaches, including type of headache, associated symptoms, and typical severity. He or she will also ask whether the patient has had any previous diagnoses of affective, psychotic, or personality disorders. We will review any allergies that the patient has, as well as any medications taken regularly, including prescriptions, over-the-counter (OTC) medications, herbal supplements, recreational drugs, and drugs that were prescribed to someone other than the patient. Finally, the investigator will review the patient's history of tobacco use, alcohol consumption, previous hospitalizations, and surgical operations or other major procedures.

As far as family history, the investigator will specifically inquire whether anyone in the patient’s family has a history of psychiatric disorders, including affective, psychotic, and personality disorders, Attention Deficit Hyperactivity Disorder (ADHD), somatization factitious
disorders, migraines or other recurrent headaches, and any concussions or other head injuries sustained by other members of the patient's family. For social history, the investigator will ascertain pre- and post-morbid work or academic difficulties experienced by the patient, as well as functional difficulties (e.g. attention, whether they complete chores, etc.) and the patient's exercise habits before and after their concussion.

2. Physical Exam:

All physical examinations will be performed by the investigator. After measuring vital signs (including height, weight, blood pressure, pulse rate, and respiratory rate), general inspection will include assessment of mood, appearance, level of cooperation with interview and physical exam, and whether the patient is in acute distress or exhibits increased work of breathing. Psychiatric exam will assess affect, thought process linearity, and orientation to person, place, time, and situation. HEENT (head, eye, ear, nose, throat) exam will include inspection for any head lesions and assessment of eye convergence, accommodation, tracking, and saccades. The investigator will also perform Vestibular-Ocular Motor Screening (VOMS). On skin, musculoskeletal (MSK), and extremity exam, the investigator will inspect for lumps, lesions over the cervical spine, cervical spine tenderness, cyanosis, clubbing, and edema. On neurologic exam, the investigator will assess strength in the upper extremities on the standard scale of 1 to 5 out of 5, reflexes, cranial nerves II through XII, and perform a Romberg test.

3. Buffalo Concussion Treadmill Test (BCTT) [59]:

Disruptions of cerebral autoregulation and consequent blood flow are common physiological sequelae of concussion. While exercise is thought to enhance brain neuroplasticity
and promote healing, many mTBI patients become somewhat deconditioned due to the prescribed period of physical and cognitive rest. This, together with the cerebral autoregulation disruptions, is thought to contribute to exercise intolerance in this population (due to exacerbation of PCS symptoms). The BCTT has proven to be a safe, reliable method of distinguishing concussion from differential diagnoses, determining the severity of concussion, and quantifying the exercise capacity of mTBI patients.

To complete the BCTT, a patient starts by walking at a rate of 3.0 miles per hour (mph) and 0% incline. This incline increased by 1% after two minutes, and then by an additional 1% each minute thereafter without changing the speed. Rating of Perceived Exertion (RPE) and heart rate (HR) are measured every two minutes, and an assessment for exacerbation of post-concussion symptoms is done every minute. The test is stopped when patient reaches RPE of 19 or 20, when symptoms become exacerbated, or when HR reaches 140 beats per minute (bpm). If the treadmill's maximum incline is reached, then speed may be increased 1 mph every two minutes until stopping criteria are reached.

4. **Sensory Organization Test (SOT)** [60]:

This posturography assessment will be measured using the Smart Balance System and will be used as further assessment of postural stability. The device has two force plates that combine to form a platform base. Force sensors under this platform measure vertical and horizontal shear forces exerted by the patient's feet, which are used to estimate vertical reaction forces produced from the body's center of gravity moving around a fixed base of support, and the entire device is enclosed by a movable visual surround. During SOT measurements, the force plate, visual surround, or both can be "sway referenced," and move in accordance with the
subject's anteroposterior (AP) sway. The various permutations of sway referencing that are possible with SOT allows isolation of which afferent sensory modalities of the postural control system are dysfunctional following concussion, if any. Three different visual conditions (eyes open, eyes closed, sway referenced) are tested for each of two different surface conditions (fixed, sway referenced), for a total of eighteen trials of twenty seconds each.

The device then computes a composite score of the patient's overall balance performance, indexed to the patient's height, weight, gender, and age. A higher composite score signifies better balance. The composite is computed based on the average score for condition #1 (eyes open, fixed platform), the average score for condition #2 (eyes closed, fixed platform), and the twelve equilibrium scores from each trial of the other four conditions. The equilibrium score from a given trial represents a non-dimensional percentage that compares the subject's peak amplitude of anterior/posterior sway to the theoretical anterior/posterior limit of stability.

5. **CNS Vital Signs (CNSVS)** [61]:

CNSVS is a computerized neurocognitive test that can administer a battery of well-known neuropsychological tests without requiring a psychologist to be present. It has been shown to have good test-retest reliability and discriminant validity for a number of conditions, including post-concussion syndrome. However, it is only validated as a screening test; it is not meant for use in making a diagnosis. For this study, the neuropsychological function of all subjects will be assessed via CNSVS. Specifically, we will use the Verbal and Visual Memory, Finger Tapping, Symbol Digit Coding, Stroop, Shifting Attention, Continuous Performance, and Non-Verbal Reasoning testing modalities within this instrument.

PROMIS is a toolbox of self-report quality of life survey instruments developed by the National Institutes of Health (NIH). They have three main advantages for this study: (1) PROMIS instruments are domain-specific (e.g. pain, cognitive function, social isolation) rather than disease-specific; (2) the instruments’ scoring was calibrated through trials with a large, diverse population, facilitating the identification of significant disruptions in well-being in concussed individuals; and (3) they are available in computer adaptive test (CAT) formats, which yields highly reliable approximations of results from the full item banks but can be completed in as little as one to two minutes per instrument. This study will utilize four of the PROMIS instruments: Anxiety, Depression, Fatigue, and Sleep. All four of these assessments were developed and validated using large, general population samples. Results for all PROMIS instruments are represented on a transformed scale (T-scale) with a mean score of 50 and a standard deviation of 10 [63].

These four self-report instruments will be administered to subjects via Research Electronic Data Capture (REDCap), a free, web-based, electronic data capture tool for research studies that can also be used to conduct surveys. REDCap is a secure website that increases the ease of survey completion for subjects, and it includes the CAT formats of PROMIS instruments [64]. This will allow us to track multiple domains of each subject’s well-being with less risk of subject fatigue and consequent non-completion of surveys due to high testing burden.

7. **ICD-10 Major Depression Inventory (MDI)** [65]:

The symptomatology of PCS can overlap significantly with certain presentations of major depression. As such, it will be important to delineate whether study subjects meet the diagnostic
criteria for Major Depression Disorder (MDD), as this may impact treatment. Like the PROMIS tools, the ICD-10 MDI is relatively brief (12 questions) and is available for web-based administration free-of-charge via REDCap. Unlike other measures such as the PROMIS Depression tool or the Beck's Depression Inventory, the ICD-10 MDI is available to produce an ICD-10 diagnosis of MDD as well as track the severity of depressive symptoms over time.

8. Pittsburgh Sleep Quality Index (PSQI) [66]:

PSQI is a 19-item self-report that asks the subject to inventory their sleep over the prior month. These 19 items together generate scores for seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. This instrument was “designed to identify good and poor sleepers” as well as “groups that differ in the quality of their sleep,” and a threshold global score of 5 or greater suggests some degree of sleep impairment [66]. Mahmood and colleagues found an average PSQI score of 8.5 in a group of mTBI patients, which was about three points higher than that of the moderate or severe TBI groups in the same study [67]. Although the PSQI is somewhat vulnerable to recall bias given its self-report nature, it has several advantages in that it yields both qualitative and quantitative information about subjects’ sleep habits, and its components can be used to generate a diagnosis of insomnia.

9. Munich Chronotype Questionnaire (MCTQ and MCTQ-Shift) [68, 69]:

The MCTQ assesses individual chronotype on the basis of self-reported sleep- and wake-time habits and preferences. Habits for work days versus free days are assessed separately in the questionnaire, which may prove to be a helpful feature once subjects begin to re-assimilate back
into their normal work and/or school schedules. Based on the subject's responses, the tool can be scored to determine whether the individual's degree of "morningness" (i.e. whether they prefer to go to bed and wake up early) versus "eveningness" (i.e. prefer to go to bed late and wake up late the next morning). These results can then be used in accordance with other measurements such as cognitive performance or daytime sleepiness. The MCTQ had been completed by over 55,000 people as of 2007, and has been validated in concordance with sleeps logs and actimetry, and is correlated with biochemical rhythms such as melatonin and cortisol [70]. The MCTQ Shift is a related questionnaire that is specifically designed for shift workers, which we will use in subjects where this is applicable [69].

10. Post-Concussion Symptom Scale (PCSS) [71]:

The PCSS is a 22-item instrument widely used to evaluate post-concussion symptoms. Subjects are asked to rate the severity of 22 different post-concussion symptoms on a 7-point Likert scale. While many of the symptoms covered by the PCSS may also be experienced by healthy patients, in the setting of concussion the PCSS is able to differentiate PCS patients on basis of affected domains (e.g. cognitive-fatigue-migraine, somatic, affective, sleep). There is evidence that the PCSS demonstrates good test-retest reliability and can also reliably detect changes in symptoms for a given patient. It is important to note that this inventory cannot be used to make any diagnoses other than PCS; it is simply used to document a patient’s self-reported post-concussion symptoms.
**Study protocol and procedures**

This is a prospective cohort study that will track the presence of risk factors and Post-Concussion Syndrome (PCS) symptoms in a population of patients recovering from recent mild traumatic brain injury (mTBI). The study will be based at our Post-Concussion Clinic (PCC) located on the campus of a large research university, to which patients with recent concussion are referred from all over Eastern and Piedmont areas of North Carolina. If a patient who is referred to the PCC consents to participation in the study, then their initial evaluation will include detailed medical history, thorough physical exam, Sensory Organization Test (SOT), and CNS Vital Signs (CNSVS). This evaluation will help us identify the presence of pre- and post-morbid risk factors of PCS faced by the patient, characterize the mechanism of injury as well as neurological and functional deficits present at this initial PCC visit, and establish baseline data for each of these measurements for comparison in case the patient should need to return to the PCC for follow-up of a protracted case of PCS.

The data from this initial visit will be collected in REDCap; a free, secure, web-based electronic data collection and management platform hosted by the university [72]. Our REDCap intake form is shown in Appendix #5, and our physical exam and clinical findings form is shown in Appendix #6. Although the history, physical exam, and treatment planning will need to be completed by the investigator (who is a physician) for purposes of insurance billing, there are otherwise no procedures that require specialized training.

If a subject’s post-concussion symptoms do not improve within a reasonable amount of time, then subjects may need to follow-up in PCC, although this will not be necessary for completion of the study. Regardless of follow-up at the PCC or lack thereof, all subjects will receive notifications to respond to a series of surveys at six universal time intervals relative to the
date of their concussion: 1 month, 2 months, 3 months, 4 months, 5 months, and 6 months. At each of these time points, subjects will complete four PROMIS CAT measures (Anxiety, Depression, Fatigue, Sleep Impairment) as well as the ICD-10 MDI, Pittsburgh Sleep Quality Index (PSQI), and Munich Chronotype Questionnaire (MCTQ). Surveys will be administered via REDCap. Subjects will be contacted via email by default to complete follow-up surveys. If a given subject is non-respondent via email and has not completed a batch of surveys within 1 week of the planned time point, a phone call will be placed to the subject to ascertain whether they wish to continue in the study. Surveys will not be administered over the phone to avoid interviewer bias. As of now, we have not planned a specific duration of this study. It will continue as long as it yields results of value.

_Benefits to subjects and/or society_

This study will benefit society by providing a longitudinal picture of the interactions between psychiatric (mainly affective) symptoms, sleep impairment, and functional deficits in the natural history and clinical course of PCS. This increased understanding could, in conjunction with future research work, lead to better prediction and treatment of PCS, thereby substantively decreasing the overall morbidity associated with concussion. Every patient who presents to Post-Concussion Clinic will receive all clinically-indicated evaluation, testing, and treatment, whether or not they elect to enroll as subjects in the study. Therefore, there is no potential for direct benefit to individual subjects in the study.
Risks, and risk minimization

Tests of postural control and neurocognitive ability may elicit embarrassment as well as some degree of emotional distress, particularly if a subject is worried about doing poorly or if they are a relatively high-functioning individual at baseline. To mitigate this risk, both postural control and neurocognitive testing will be performed behind a closed door, with only the subject and the investigator or a research assistant present in the room. Reassurance will be provided to each subject that only the researchers will see their results, and that these tests are not meant to pass any sort of judgement, but instead provide one part of an overall clinical picture that is needed in order to devise a targeted treatment plan.

Another component of the study that may provoke emotional distress is the historical interview, which will include questions about illicit drug use, personal and family psychiatric history, history of abuse, and other potentially sensitive issues. Similar to the above, the historical interview will take place in a private room with the door closed, where the only people present are the subject, an investigator and/or research assistant, and anyone who the subject wishes to have with them. Further, subjects will be informed at the start of the visit that they may decline to respond to any questions that they do not wish to answer. Subjects will be asked about illicit substance use as a standard part of the historical interview. This information will be kept confidential. Documentation of this information will only be kept on the secure, web-based, password-protected electronic data capture system that will be used for this study. Only the investigators will have access to this data.

It is considered likely (approximate incidence of 10 to 25%) that the SOT and/or exercise testing will elicit nausea, headache, or other post-concussion symptoms that the subject has been experiencing. Exercise testing is specifically designed to test the subject’s limits of exertion, but
testing will be stopped as soon as a subject expresses discomfort. There are also many PCC patients who achieve a high heart rate on exercise testing without experiencing symptoms. However, if the need should arise while working with a subject, researchers will help subjects seek medical or psychological care (billed to the subject's own insurance).

Further information concerning expected typical subject contact and duration of involvement in the study, as well as planned precautions in regard to subject confidentiality and privacy are described in Appendix #7. Data and safety monitoring plans are described in Appendix #8.

Plans for data analysis

This paper proposes an exploratory, prospective cohort study with a primary aim of describing the natural history of PCS. In particular, it will focus on two important manifestations of PCS (namely, sleep disturbance and affective symptoms). The study will involve evaluating whether certain historical factors and clinical findings at the pre-injury and/or acute post-injury stages are statistically significant predictors of an increased burden of sleep disturbance and affective symptoms over the first six months of the post-concussion period. Due to uncertainty over what these relationships will look like, we will complete a pilot study for the predictor-outcome pairs where both are continuous measurements. Afterward, we will graph each subjects' response curves for these continuous predictor-outcome pairs of interest (detailed above in Study Aims) in order to choose an appropriate model to evaluate the statistical significance of our findings from a larger sample. Prior studies in this area of research (such as those covered in our systematic review) have typically used some combination of linear, logistic, or generalized linear mixed model regression analyses to achieve these ends.
For the relationships of interest with dichotomous predictor variables, we will use summary measures to describe our serial measurements, using the method outlined by Matthews and colleagues [73]. A list of predictor-outcome pairs that we will describe for this aspect of our planned data analyses can be found in Appendix #9. Briefly, after stratifying for a potential predictor (e.g. subjects with no prior history of concussion versus those with a history of multiple concussions), we will seek to describe the central tendency and within-subject variability of subjects' recovery trajectories (as judged by outcomes such as PROMIS Sleep survey scores), stratified by exposure group for that potential predictor. Response curves expected to have a peak or trough will be described by their maximum/minimum value and area under the curve (AUC). Response curves expected to show only growth or decline will be described by their rate of change. Data transformations may be applied (e.g. logarithmic) if deemed appropriate. All summary measures will include 95% confidence intervals.

To be clear, this study seeks to explore and describe the predictor-outcome variable pairs of interest (as well as any additional predictors that may present themselves) in order to identify pairs that might be suitable for robust significance testing in a future iteration of the study. We currently have no data on the prevalence or severity of any given PCS symptoms within our clinic population, so any sample size calculation is a rough estimate at best. To ensure that we have a sufficient number of subjects to make substantive observations, though, we calculated a conservative estimate using G*Power 3.1 [74].

To estimate a reasonable effect size, we looked at previous data for PSQI global scores. Our literature search did not yield any longitudinal studies describing the variance and within-subject correlation of PSQI in a population of mTBI patients over time. From our systematic review, though, we have PSQI global estimates of 6.35 (n = 689; 95% CI: 5.93, 6.77) [35], 6.72
± 4.00 (n = 77) [37] among mild TBI patients, as well as a separate finding by Mahmood and colleagues of 8.54 ± 5.87 (n = 24) on average [67]. In addition, the original PSQI validation study found an average global score of 11.09 ± 4.31 in depressed patients (n = 34) and 2.67 ±1.70 in healthy controls (n = 52) [66]. Therefore, it appeared reasonable to expect potential predictors of increased symptom burden to demonstrate at least a moderate effect size of 0.5 (Cohen’s d) to warrant further evaluation in future iterations of this study. Using G*Power’s 2-sample t-test calculator with alpha = 0.05, power = 0.8, and N2/N1 allocation ratio = 1 (since 50% of mTBI patients complain of sleep disturbance [49]), we can see that a sample size of at least 128 subjects would allow detection of an effect size of 0.5 with 80% power. Demographic factors such as age, sex, and certain psychosocial factors (e.g. family income, insurance status) will be evaluated as potential confounding variables for each predictor-outcome pair.

This simplified calculation using the 2-sample t-test provides a conservative of the sample size that will be required, since our study will include six follow-up measurements of PSQI and other survey instruments (rather than just one measurement), and the effect size is likely to be significantly greater than 0.5. Further, this calculated required sample size of at least 128 is in line with similar studies in this area of research [29, 33, 34, 39]. We feel this sample size will be feasible for our subject recruitment method. Over the past nine months (October 2015 to March 2016), the PCC has seen an average of about two new patients per week. If this rate of new patients continues, and if most PCC patients assent to participation (a reasonable assumption given the low risk of doing so), then we expect to meet this sample size requirement within 18 months of beginning the study.
**Conclusions and Public Health Implications**

Concussion has been in the news a lot lately. Over the past few years it has been the subject of many newspaper articles, sports talk show segments, and even a Hollywood movie. The resultant increased public awareness has led to a number of actions in professional, college, and youth sports. These have included primary prevention strategies (e.g. rule changes, sports equipment improvements) and secondary prevention (e.g. mandatory removal if a concussion is suspected, return-to-play protocols). Although it still too early to rigorously assess these interventions, there is a consensus that they have led to improved recognition of concussion events, and should theoretically help prevent some of concussion’s most severe consequences (e.g. CTE and SIS).

However, a significant portion of concussion’s public health burden stems from PCS, which is not as well understood and has not received as much public attention. The above systematic review found that PCS has been shown to last months or even years some patients. However, thus far there have been few studies examining the mechanisms of and interactions between specific, potentially treatable manifestations of PCS.

Here, we have proposed a research design to help close this gap in scientific knowledge by tracking the burden of post-concussion sleep disturbance and affective symptoms in a prospective cohort study of patients with recent mTBI. The goal of this study will be mainly to identify and describe predictor-outcome that could be tested for statistical significance in a future iteration of the study. Traditionally, PCS has been conceptualized as a single entity, despite its wide variety of clinical presentations. Our proposed study is meant as a first step towards identifying targeted interventions for PCS, which would provide an additional secondary prevention strategy to reduce the public health burden of concussions.
Works Cited


[56] Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition, 21 C.F.R. § 50.53.


## Appendix #1: PECOTTSS study inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>PECOTTSS</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
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<tbody>
<tr>
<td><strong>P</strong> (Population)</td>
<td>Adolescents, Adults</td>
<td>Military, Veterans, Children less than 12 years old</td>
</tr>
<tr>
<td><strong>E</strong> (Exposure)</td>
<td>Concussion / Mild TBI</td>
<td>Moderate/Severe TBI, Skull fracture, Blast injury</td>
</tr>
<tr>
<td><strong>C</strong> (Comparator)</td>
<td>Historical factors and acute post-injury clinical findings</td>
<td>Clinical trials of treatment interventions</td>
</tr>
<tr>
<td><strong>O</strong> (Outcomes)</td>
<td>Sleep disturbance, Affective symptoms in the post-concussion setting</td>
<td>Serum biomarkers, imaging, survey outcomes that did not focus on sleep or affective symptoms</td>
</tr>
<tr>
<td><strong>T</strong> (Time of exposure)</td>
<td>Greater than one month of follow-up measurements</td>
<td>1 month or less of follow-up measurements</td>
</tr>
<tr>
<td><strong>T</strong> (Time over which literature will be searched)</td>
<td>Published within the past 10 years</td>
<td>Publication prior to June 2006</td>
</tr>
<tr>
<td><strong>S</strong> (Setting)</td>
<td>Any</td>
<td>None</td>
</tr>
<tr>
<td><strong>S</strong> (Study Design)</td>
<td>Observational studies (e.g. cohort, case-control)</td>
<td>Clinical trials, Review articles will be hand searched for relevant citations</td>
</tr>
</tbody>
</table>

Abbreviations: TBI = Traumatic Brain Injury
Appendix #2: Search strategy for PubMed and Cochrane Library databases

<table>
<thead>
<tr>
<th>Search #</th>
<th>Query</th>
<th>PubMed (# items)</th>
<th>Cochrane (# items)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>Search post-concussion syndrome</td>
<td>901</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>Search adult</td>
<td>6376694</td>
<td>393388</td>
</tr>
<tr>
<td>3</td>
<td>Search adolescent</td>
<td>1756782</td>
<td>103394</td>
</tr>
<tr>
<td>4</td>
<td>Search humans</td>
<td>159545585</td>
<td>550937</td>
</tr>
<tr>
<td>5</td>
<td>Search (#2 or #3 or #4)</td>
<td>16241993</td>
<td>639278</td>
</tr>
<tr>
<td>6</td>
<td>Search concussion</td>
<td>7829</td>
<td>214</td>
</tr>
<tr>
<td>7</td>
<td>Search brain injuries</td>
<td>76396</td>
<td>1908</td>
</tr>
<tr>
<td>8</td>
<td>Search (#6 or #7)</td>
<td>77739</td>
<td>2031</td>
</tr>
<tr>
<td>9</td>
<td>Search depressive disorder</td>
<td>108015</td>
<td>12403</td>
</tr>
<tr>
<td>10</td>
<td>Search mood disorders</td>
<td>120356</td>
<td>4177</td>
</tr>
<tr>
<td>11</td>
<td>Search panic disorder</td>
<td>11133</td>
<td>2176</td>
</tr>
<tr>
<td>12</td>
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<td>53260</td>
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<td>13</td>
<td>Search sleep</td>
<td>158272</td>
<td>19633</td>
</tr>
<tr>
<td>14</td>
<td>Search sleep initiation and maintenance disorders</td>
<td>10210</td>
<td>1599</td>
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<tr>
<td>15</td>
<td>Search sleep wake disorders</td>
<td>70282</td>
<td>1531</td>
</tr>
<tr>
<td>16</td>
<td>Search time factors</td>
<td>1366160</td>
<td>79746</td>
</tr>
<tr>
<td>17</td>
<td>Search Athletic Injuries/complications</td>
<td>2170</td>
<td>30</td>
</tr>
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<td>18</td>
<td>Search (#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17)</td>
<td>2385333</td>
<td>139910</td>
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<td>19</td>
<td>Search (#1 and #5 and #8 and #18)</td>
<td>291</td>
<td>15</td>
</tr>
<tr>
<td>20</td>
<td>Restricted #19 to studies published within last 10 years</td>
<td>222</td>
<td>12</td>
</tr>
</tbody>
</table>
Appendix #3: Results of literature search and screening process (PRISMA diagram)

Records identified through database searching (n = 234)
   MEDLINE: 222
   Cochrane Library: 12

Additional records identified through other sources
   (n = 17)
   Hand searches of reference lists: 17
   ClinicalTrials.gov: n/a

Records after duplicates removed
   (n = 243)

Records screened
   (n = 243)

Records excluded
   (n = 159)

Full-text articles assessed for eligibility
   (n = 84)

Full-text articles excluded, with reasons
   (n = 69)

Studies included in qualitative synthesis
   (n = 15)

Studies included in quantitative synthesis
   (e.g. meta-analysis)
   (n = n/a)
## Appendix #4: Summarized characteristics of studies included in the systematic review

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Sample</th>
<th>Study Design</th>
<th>Measurements</th>
<th>Key Findings</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaput, Giguère, Chauny, et al. (2009) [40]</td>
<td>Chart review of 443 consecutive patients receiving diagnosis of mTBI&lt;br&gt;Majority male (62.8%) with mean age of 46.9 years</td>
<td>Retrospective cohort study with follow-up at 10 days and 6 weeks.</td>
<td>RPQ&lt;br&gt;Self-reported sleep complaints, classified into six categories</td>
<td>Subjects with sleep complaints at 10 days were 6.3 times more likely to express mood complaints at 6 weeks&lt;br&gt;Sleep disturbances affected 13.3% and 33.5% of subjects at 10 days and 6 weeks, respectively&lt;br&gt;Reasons for sleep disturbance evolved over time</td>
<td>Large sample size&lt;br&gt;Able to show evolution of sleep disturbance symptoms</td>
<td>Subjective report of specific sleep complaints&lt;br&gt;Did not examine confounding due to social/economic stressors or subjects' pre-morbid medical issues</td>
</tr>
<tr>
<td>Dischinger, Ryb, Kufera, et al. (2009) [29]</td>
<td>180 mTBI patients presenting to a level I trauma center within 3 days of head injury&lt;br&gt;About half were men, and most subjects had been in MVC.</td>
<td>Prospective cohort study with follow-ups at 10 days and 3 months.</td>
<td>PHQ-2&lt;br&gt;Authors' concussion symptom checklist</td>
<td>Acute complaints of anxiety predicted presence of PCS at 3 months, but acute-stage fatigue was not&lt;br&gt;Subjects with pre-injury depression were 3.56 times more likely to experience PCS at 3 months (univariate OR)</td>
<td>Assessed predictiveness of individual, treatable symptoms (rather than categories of symptoms) for development of persistent PCS.</td>
<td>Non-validated post-concussion symptom survey&lt;br&gt;110 subjects followed up at 3 months (39% dropout)&lt;br&gt;Did not assess sleep disturbance symptoms&lt;br&gt;Did not explain sampling protocol&lt;br&gt;Referral bias (Level I trauma center)</td>
</tr>
<tr>
<td>Authors (Year)</td>
<td>Sample</td>
<td>Study Design</td>
<td>Measurements</td>
<td>Key Findings</td>
<td>Strengths</td>
<td>Limitations</td>
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<tr>
<td>Eisenberg, Andrea, Meehan, et al. (2013) [30]</td>
<td>280 mTBI patients with history of previous mTBI Enrolled upon presentation to ED within 72 hours of head injury 11 to 22 years of age</td>
<td>Prospective cohort study with 12 weeks of follow-up.</td>
<td>RPQ</td>
<td>Multiple previous concussions or concussion with past year associated with persistent PCS symptoms Pre-injury depression associated with increased time to recovery</td>
<td>Able to show that PCS-related effects of multiple concussions can be additive Distinguished between timing and number of previous concussions Increased sensitivity from using broad definition of concussion</td>
<td>207 (74%) subjects completed the study As a group, subjects lost to follow-up were significantly different in terms of demographics and past medical history Referral bias (subjects recruited from ED) Sample size too small too assess PCS predictiveness of many acute and pre-injury medical issues No control group</td>
</tr>
<tr>
<td>Eisenberg, Meehan, and Mannix (2014) [31]</td>
<td>Same cohort as above 280 mTBI patients with history of previous mTBI Enrolled upon presentation to ED within 72 hours of head injury 11 to 22 years of age</td>
<td>Prospective cohort study with 12 weeks of follow-up.</td>
<td>RPQ</td>
<td>21.6% developed sleep disturbance after initial evaluation Sleep disturbance was among the most persistent PCS symptoms Depression symptoms tended to resolve quickly No difference in individual symptoms among subjects with recent or multiple previous concussions</td>
<td>Prospective design allows description of symptom evolution over course of recovery in a pediatric population.</td>
<td>Did not examine interactions between symptoms Did not assess effects of individual symptoms on work or school performance Referral bias (recruited from ED) No control group</td>
</tr>
<tr>
<td>Greenberg, Wood, Spring, et al. (2015) [32]</td>
<td>14 subjects Enrolled within 96 hours of presentation to ED</td>
<td>Prospective cohort pilot study with follow-ups at 1 month and 3 months post-injury.</td>
<td>Authors' battery of NSS maneuvers RPQ BDI-II</td>
<td>Acute-stage BDI-II scores did not significantly correlate with global RPQ scores at follow-up time points On average, BDI-II scores declined at each follow-up time point</td>
<td>Strict inclusion and exclusion criteria</td>
<td>Small sample size Not high-powered enough to detect associations between many of the measures used Referral bias (recruited from ED)</td>
</tr>
<tr>
<td>Authors (Year)</td>
<td>Sample</td>
<td>Study Design</td>
<td>Measurements</td>
<td>Key Findings</td>
<td>Strengths</td>
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</table>
| Hou, Moss-Morris, Peveler, et al. (2011) [33] | • 126 mTBI patients  
• Recruited within 2 weeks of presentation to ED  
• 18 to 60 years of age | Prospective cohort study with follow-ups at 3 months and 6 months post-injury. | • HADS  
• RPQ | • HADS anxiety was a predictor for PCS at 3 months and 6 months  
• HADS depression was a predictor for PCS at 3 months and 6 months  
• Sleep disturbance was among the most common symptoms reported | • Large sample size  
• Used a wide array of assessment tools and examined potential interactions between their results | Assessments used are validated but not commonly used among similar studies. |
| Kempf, Werth, Kaiser, et al. (2010) [34] | • 51 TBI patients recruited consecutively from the ED  
• All subjects had no history of TBI  
• Median age of 40 years | Prospective cohort study with follow-ups at 6 months and 3 years post-injury. | • ESS  
• FSS  
• Sleep Length per 24 hours  
• Standardized interview via telephone  
• BDI | • Daytime sleepiness and overall sleep-wake disturbances fell between 6 months and 3 years post-TBI  
• Prevalence of fatigue, post-traumatic hypersomnia, and insomnia all increased among subjects  
• Depression and fatigue were significantly correlated | • Long-term follow-up | Small sample size  
• Vulnerable to interviewer bias  
• Did not use validated questionnaires for many symptom assessments |
| Kostyun, Milewski, and Hafeez (2014) [41] | • 545 adolescent athletes  
• 11 to 18 years of age  
• Included if they completed first neurocognitive test within 90 days of head injury | Retrospective cohort study with up to three follow-ups at non-universal time points. | • ImPACT  
• PCSS | • Sleeping less than 7 hours and self-perception of sleep disturbance were both correlated with greater self-reported PCS symptom severity  
• Sleeping longer than 9 hours correlated with poorer cognitive performance | • Several months of follow-up for a subset of the patients  
• Larger sample size than many similar studies of concussion | Follow-ups not conducted at universal time points  
• Majority of subjects did not return for second or third follow-ups  
• Sleep quantity and quality measured via self-report |
<table>
<thead>
<tr>
<th>Authors (Year)</th>
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<th>Study Design</th>
<th>Measurements</th>
<th>Key Findings</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kraus, Hsu, Schaffer, et al. (2009) [35]</td>
<td>689 mTBI patients and 1318 patients with non-head injuries&lt;br&gt;Recruited from ED</td>
<td>Prospective cohort study with 3 months of follow-up.</td>
<td>RPQ, PSQI, BSI-18</td>
<td>Increased sleep latency and daytime dysfunction were more common in mTBI group&lt;br&gt;Fatigue and sleep disturbance were most common symptoms reported in mTBI group</td>
<td>38% lost to follow-up&lt;br&gt;Large sample size&lt;br&gt;Control group included</td>
<td>Included confounding variables in statistical model on basis of Table 1 chi-squared calculations&lt;br&gt;Differential loss to follow-up between groups&lt;br&gt;Vulnerable to telephone interviewer bias</td>
</tr>
<tr>
<td>Lagarde, Salmi, Holm, et al. (2014) [36]</td>
<td>534 patients with head injury&lt;br&gt;827 control patients with non-head injuries</td>
<td>Prospective cohort study with 3 months of follow-up.</td>
<td>A symptom survey created for the study, which drew from DSM-IV, ICD-10, and RPQ.</td>
<td>mTBI (vs. non-head injury) was predictive of PTSD but not PCS at 3 months post-injury&lt;br&gt;At three months post-injury, prevalence of PCS in mTBI group varied from 21.2% to 53.4%, depending on definition used</td>
<td>Large sample size&lt;br&gt;Included a control group&lt;br&gt;Accounted for differing definitions of PCS</td>
<td>Considerable amount of missing data&lt;br&gt;Differential loss to follow-up by age of subjects</td>
</tr>
<tr>
<td>Lundin, de Boussard, Edman, et al. (2006) [27]</td>
<td>122 consecutive patients with mTBI recruited from ED&lt;br&gt;35 controls recruited via magazine advertisement</td>
<td>Prospective cohort study with follow-ups at 1, 7, and 14 days, and 3 months post-injury.</td>
<td>RPQ</td>
<td>Principal component analysis included both sleep disturbance and depression in the &quot;affective&quot; category&lt;br&gt;Sleep disturbance was reported by 21% of subjects in both groups</td>
<td>Included a control group that was similar to observation group in terms of baseline characteristics&lt;br&gt;Shows the progression of PCS symptoms from acute to chronic, which could be used to infer causality</td>
<td>High non-participation rate&lt;br&gt;Participating group may be biased towards patients with more severe injuries</td>
</tr>
<tr>
<td>Authors (Year)</td>
<td>Sample</td>
<td>Study Design</td>
<td>Measurements</td>
<td>Key Findings</td>
<td>Strengths</td>
<td>Limitations</td>
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<tr>
<td>Morgan, Zuckerman, Lee, et al. (2015) [42]</td>
<td>40 cases of PCS with 80 controls (matched on age and sex) drawn from concussion clinic database.</td>
<td>Retrospective matched case-control study with 3 months of follow-up</td>
<td>• Cases had documented PCS symptoms for at least 3 months</td>
<td>Subjects more likely to develop PCS if they had delayed-onset of symptoms or a personal or family history of psychiatric diagnoses.</td>
<td>Contributes new data on the risk factors of prolonged PCS in pediatric patients.</td>
<td>Utilized records from a number of different providers (trainers, doctors, etc.) that may have applied varying criteria in making a clinical diagnosis</td>
</tr>
<tr>
<td>Schmidt, Li, Hanten, et al. (2015) [37]</td>
<td>• 71 patients with recent mTBI&lt;br&gt;• 71 patients with recent orthopedic injury&lt;br&gt;• Both of the above recruited consecutively in ED&lt;br&gt;• 43 controls with no recent injury</td>
<td>Prospective matched cohort study with follow-ups at 1 month and 3 months post-injury.</td>
<td>PSQI</td>
<td>Fatigue and PTSD prevalence differed at all three time points&lt;br&gt;Overall, mTBI group had greater sleep disturbance and PTSD prevalence at all three time points&lt;br&gt;Sleep disturbance differential not seen in younger age groups</td>
<td>Able to detect delayed onset of some symptoms&lt;br&gt;Shows evolution of sleep impairment symptoms over time&lt;br&gt;Stratified analysis able to differentiate symptoms based on age group</td>
<td>Did not directly compare PSQI results to PTSD incidence&lt;br&gt;Did not attempt to assess pre-morbid sleep&lt;br&gt;Did not exclude based on medications (e.g. substances that may affect the brain)</td>
</tr>
<tr>
<td>Tham, Palermo, Vavilala, et al. (2012)</td>
<td>• 729 patients with TBI&lt;br&gt;• 197 controls with orthopedic injury&lt;br&gt;• All subjects 2 to 17 years of age</td>
<td>Prospective cohort study with control group (matched for age and sex) with follow-ups at 3, 12, and 24 months.</td>
<td>• PedsQL&lt;br&gt;• PSC-17&lt;br&gt;• ABAS-II</td>
<td>mTBI associated with greater sleep disturbance&lt;br&gt;Female gender, psychosocial problems, and frequent pain were significant risk factors for sleep disturbance&lt;br&gt;Sleep disturbance predicted poor self-care</td>
<td>Large sample of patients suffering from recent TBI, with well-matched control cohort.</td>
<td>First follow-up was not until 3 months post-injury&lt;br&gt;Did not include healthy control</td>
</tr>
<tr>
<td>Whittaker, Kemp, and House (2007)</td>
<td>• 73 patients who presented to ED with mTBI&lt;br&gt;• Mean age was 41 years</td>
<td>Prospective cohort study with follow-up at 3 months.</td>
<td>• RPQ&lt;br&gt;• IPQ-R&lt;br&gt;• IES&lt;br&gt;• HADS</td>
<td>Subjects who believed the duration of PCS symptoms would be closer to that of a chronic disease than a viral illness were more likely to suffer prolonged PCS symptoms, including sleep disturbance.</td>
<td>Operationalizes the hypothesized psychosocial contribution to PCS development in order to examine how strongly these beliefs predict PCS.</td>
<td>Vulnerable to interviewer bias (telephone)&lt;br&gt;Non-participation rate of about 90%&lt;br&gt;Non-participants not compared as a group to subjects</td>
</tr>
</tbody>
</table>

**Appendix #4 Abbreviations:** ABAS-II = Adaptive Behavior Assessment System-II; BDI-II = Beck Depression Inventory; BESS = Balanced Error Scoring System; BSI-18 = Brief Symptom Inventory-18; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders-IV; ED = emergency department; ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; HADS = Hospital Anxiety and Depression Scale; ICD-10 = International Statistical Classification of Diseases and Related Health Problems; IES = Impact of Event
Scale; ImPACT = Immediate Post-Concussion Assessment and Cognition Testing; IPQ-R = Illness Perception Questionnaire-Revised; mTBI = mild traumatic brain injury; MVC = motor vehicle collision; NSS = Neurological Soft Signs; PCS = Post-Concussion Syndrome; PCSS = Post-Concussion Symptom Scale; PedsQL = Pediatrics Quality of Life Inventory; PHQ-2 = Personal Health Questionnaire - 2; PSC-17 = Pediatric Symptom Checklist-17; PSQI = Pittsburgh Sleep Quality Index; PTSD = Post-Traumatic Stress Disorder; RPQ = Rivermead Post-Concussion Questionnaire
Appendix #5: Preview of new patient intake form (for use in REDCap)

Medical History Intake Form

Please complete the survey below regarding your medical history and recent concussion-related symptoms.

Thank you!

### Information about Patient

<table>
<thead>
<tr>
<th>Field</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Name</td>
<td></td>
</tr>
<tr>
<td>Last Name</td>
<td></td>
</tr>
<tr>
<td>UNC Health Care Medical Record Number</td>
<td></td>
</tr>
<tr>
<td>Date of Birth</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Are you pregnant, trying to get pregnant, or breastfeeding?</td>
<td>Yes</td>
</tr>
<tr>
<td>Who referred you to us?</td>
<td></td>
</tr>
<tr>
<td>How did you hear about the Gfeller Center Concussion Clinic?</td>
<td>Physician or other health care provider, Family Member, Friend, or Acquaintance, Website, Other</td>
</tr>
<tr>
<td>If you selected “Other” as the way you heard about us, please describe:</td>
<td></td>
</tr>
</tbody>
</table>

### Previous Care for this Issue & Goals for the Visit

What are your goals for your upcoming visit at the Gfeller Center Concussion Clinic?
- Diagnosis
- Discuss treatment options
- Obtain medication prescription
- Review test/lab results
- Referral for X-ray
- Referral for MRI
- Obtain prescription for steroid injection

What other diagnostic tests or procedures have you had for this problem?
- None
- X-ray
- MRI
- CT Scan
- Consultation with Primary Care Provider
- Consultation with other medical specialist (e.g., Neurologist or Orthopedist)
- Electromyography
- Other

If you selected “Other” when describing previous diagnostic tests for this health issue, please describe:

Is this a Worker’s Compensation Claim, or is there litigation pending?
- Yes
- No

07/02/2016 7:25pm
# Appendix #6: Preview of initial clinic visit form (for use in REDCap)

**First Visit: Phys Exam, Assessment, Plan**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>________________________________</th>
</tr>
</thead>
</table>

## Vital Signs

- **Height (inches):**  ________________________________
- **Weight (pounds):**  ________________________________
- **Systolic Blood Pressure:**  ________________________________
- **Diastolic Blood Pressure:**  ________________________________
- **Pulse Rate (bpm):**  ________________________________
- **Respiratory Rate:**  ________________________________

## Physical Exam

- **General:**  ________________________________
- **Psychiatric:**  ________________________________

### HEENT Findings

- Visible lesions on head
- Eye convergence insufficiency
- Eye accommodation insufficiency
- Nystagmus noted
- Poor tracking ability
- Difficulty with saccades
- VOMS positive
- None of the above

### HEENT (additional notes):  ________________________________

### Respiratory Findings

- Increased Work of Breathing
- Dyspneic
- None of the above

### Respiratory (additional notes):  ________________________________

### Cardiac (check all that apply)

- Irregular rate
- Irregular rhythm
- Abnormal S1 or S2
- Murmur
- Rub
- Gallop
- None of the above

### Cardiac (additional notes):  ________________________________
Appendix #7: Subject Contact, Duration, Privacy, and Confidentiality

Number of Subject Contacts: At least five contacts (subject's initial visit to PCC plus four batches of follow-up surveys sent via email). Subjects are welcome to schedule additional follow-up visits at the PCC as clinically indicated, but this is not required for participation.

Duration of Subject Participation in Study: 1.5 hours for initial clinical visit to PCC, including history, physical exam, and standardized post-concussion tests. Follow-up batches of survey instruments will be emailed to subjects at pre-defined universal time points (at 1, 2, 3, 4, 5, and 6 months post-injury), and on average these should require no more than 60 minutes to complete, at each follow-up time point. Therefore, this study will involve at most a 7.5-hour time commitment (1.5 hours for initial PCC visit plus 6 x 60 minutes per batch of follow-up survey instruments), providing that no follow-up visits to PCC are required. Of note, this estimated time commitment does not include travel time to and from PCC. While travel time is relatively brief for many PCC patients, in the past referrals have come from as far away as Wilmington (about 3 hours' one-way drive from Chapel Hill).

Participant Privacy: Each subject's initial evaluation will be conducted entirely at the sports medicine and training facility on the campus of a large research university. Physical copies of identifiable information generated from these encounters will be kept in a locked filing cabinet at the PCC. No testing results, and no identifiable information on computer screens or on paper will be visible to anyone other than the subject, their parent or guardian (if subject is a minor), and the co-investigator(s) conducting the evaluation. When working on the computer to provide demographic information or to complete CNSVS neuropsychological test battery, the door to the computer lab will be closed, or if need be, a physical divider will be placed between subjects working on adjacent computers. Patients will not receive any stipends, reimbursements, or otherwise tangible incentives for participation. They will bear no cost for participation beyond the cost of the clinic visit itself.

Subjects’ responses to follow-up surveys administered via REDCap will similarly be neither visible nor accessible to anyone not on the immediate research team for this study. Although we
cannot guarantee subjects' privacy when completing follow-up surveys off-site, subjects will be counseled to position themselves and their computer in such a way that their screen is not visible to others while they are responding to the surveys, in order to maintain their privacy.

**Participant Confidentiality:** All potential study subjects will be informed of their rights via counseling and an informed consent form. Potential subjects will be advised in person and via the informed consent form that they have the right not to participate in the study, and that a decision not to participate will affect neither their status as a patient at the PCC nor eventual decisions to clear the patient for return to activity. Data will only be seen or accessed by members of the study's research team, and will be kept locked in a file cabinet within the Matthew Gfeller Sport-Related Traumatic Brain Injury Center on the UNC-Chapel Hill campus. The data will be password-protected, and the computers and servers used to store the data will also be stored in securely-locked rooms. Personal names and email addresses will not be stored on the electronic data files. Subjects who are longitudinally followed will be assigned a unique master identification number that will be used to link the multiple data records on that patient.

As part of the study, we will be evaluating the effects of past and present factors upon the natural history and clinical course of PCS in a longitudinal manner among patients who have recently suffered TBI. As such, we will need to assess any historical factors that may affect subjects' neurological function and mental status, as these factors may also have a bearing upon the incidence and persistence of PCS. The factors to be assessed are personal and family history of psychiatric conditions (including affective, psychotic, and personality disorders) as well as corresponding treatments for those conditions, HIV status, and past or present recreational drug use. We will also collect information on social factors that may include a history of physical abuse, difficult family environment, or socioeconomic disadvantage.
Appendix #8: Data and Safety Monitoring

Data will be stored within REDCap, a cloud-based data capture application that uses secure web authentication, data logging, and Secure Sockets Layer (SSL) encryption. Only members of the research team will have password-protected access to this data. Data will not be shared with anyone outside the immediate research team. Following completion of the study, all physical materials with identifying information will be shredded to the extent that no information can be obtained from the shredded documents.

Data will be monitored for poor patient outcomes, adverse effects from testing, and other indications of possible safety concerns by a co-investigator at least once annually. If safety concerns should arise, the co-investigator will report the concern to the primary investigator as well as the IRB. There will be no specific criteria used for withdrawing individual subjects from the study, provided that they meet the inclusion and exclusion criteria and are willing to continue participation. As we are not testing any novel interventions, we have not defined criteria for halting the entire study due to safety concerns, and this study will not involve a data and safety monitoring board or committee.
### Appendix #9: Predictor-Outcome pairs of interest

<table>
<thead>
<tr>
<th>Aim</th>
<th>Predictor(s)</th>
<th>Predictor Data Type</th>
<th>Outcome(s)</th>
<th>Outcome Data Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(a)</td>
<td>Pre-injury sleep impairment (based on history-taking)</td>
<td>Dichotomous</td>
<td>PSQI global score, PROMIS Sleep</td>
<td>Continuous</td>
</tr>
<tr>
<td>1(b)</td>
<td>Pre-injury personal or family history of psychiatric diagnoses (based on history-taking)</td>
<td>Dichotomous</td>
<td>PSQI global score, PROMIS Sleep</td>
<td>Continuous</td>
</tr>
<tr>
<td>1(c)</td>
<td>History positive for multiple concussions (based on history-taking)</td>
<td>Dichotomous</td>
<td>PSQI global score, PROMIS Sleep, MDI-10, PROMIS Depression, PROMIS Anxiety</td>
<td>Continuous</td>
</tr>
<tr>
<td>2</td>
<td>PSQI global score at 1-month follow-up</td>
<td>Continuous</td>
<td>PSQI global score (full six months of follow-up), PROMIS Sleep, MDI-10, PROMIS Depression, PROMIS Anxiety</td>
<td>Continuous</td>
</tr>
<tr>
<td>3</td>
<td>PSQI global score, PROMIS Sleep, MDI-10, PROMIS Depression, PROMIS Anxiety</td>
<td>Continuous</td>
<td>PCSS global score</td>
<td>Continuous</td>
</tr>
<tr>
<td>4</td>
<td>MCTQ at time of clinic visit</td>
<td>Categorical</td>
<td>PSQI global score, PROMIS Sleep, MDI-10, PROMIS Depression, PROMIS Anxiety, PCSS global score</td>
<td>Continuous</td>
</tr>
</tbody>
</table>