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Sex-Based Differences in Concussion Outcomes Among Adolescents and Young Adults

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DEDICATION

To my wife, Keelyn Abigail Rogers, you have been a constant source of support, encouragement, love and happiness during the challenges of graduate school and in life. I am incredibly fortunate to have you by my side. I cherish every adventure we've shared together, and look forward to many more. With all my heart, thank you.

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ABSTRACT

Concussive injuries among youth are a serious public health concern in the United States, with increasing incidence leading the Centers for Disease Control and Prevention to classify these injuries a "silent epidemic." Though most concussions in youth resolve within a few weeks, a significant proportion (~15-20%) of individuals will experience persisting symptoms that can negatively affect important aspects of social life, as well as academic and vocational performance. Furthermore, guidelines from the most recent *Consensus Statement on Concussion in Sport* highlight the importance of considering individual characteristics that may modify the nature and outcomes of concussion. Biological sex is one such factor gaining interest among researchers and health care professionals. Present scientific literature indicates adolescent and young adult females may experience higher rates of concussion and may be more likely to experience longer recoveries when compared to male counterparts. However, current evidence regarding the influence of biological sex on symptoms, cognitive function, and psychological health following concussive injury remains tentative and incomplete. Additionally, important biological factors, such as sex hormones, may moderate recovery outcomes in females; though current evidence is limited. Therefore, the purpose of this study was to further examine the influence of biological sex and sex-based hormones on concussion outcomes among adolescents and young adults. The series of investigations that comprise this study span clinical, population-based, and college athletic settings to thoroughly examine potential sex-based differences across symptom, cognitive, and psychological outcomes

of concussion. Overall, results from the present study suggest that females may exhibit increased symptom burden and greater cognitive dysfunction following concussion when compared to males. In general, results from the present study do not indicate concussed females and males experience differing levels of depression which cannot be explained by potential baseline differences. However, when factoring for other key moderators of injury (i.e., frequency prior concussion), our results indicate females and males may exhibit differing mental health risk behaviors. Specifically, results indicate females with single or multiple concussions exhibit greater odds of reporting increased suicidal behaviors; whereas males with history of concussion may only exhibit increased odds of reporting increased suicidal behaviors in the context of multiple concussions. Lastly, our results do not indicate that hormonal factors (i.e., hormonal contraceptives) influence post-concussive recovery outcomes. Altogether, findings from the studies described herein address important gaps in current literature, and illuminate the influence of biological sex on symptom, cognitive, and psychological outcomes of concussion.

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Overall Introduction

Concussion is a form of traumatic brain injury induced by rapid acceleration and deceleration forces to the head.[1] These forces are transmitted to neural tissues, resulting in a complex neurometabolic cascade of events leading to disruption of cerebral homeostasis and microstructural alterations.[2] Individuals that incur a concussion often experience transient, but debilitating symptoms (e.g., headache, dizziness, nausea, etc.), cognitive dysfunction, and declines in psychological health.[3] Though most concussive injuries resolve within a few weeks, a significant proportion (~15-20%) of individuals will experience persisting symptoms that can negatively affect important aspects of social life, as well as academic and vocational performance.[4] Emerging research has also shown increased frequency of concussion (particularly during short period of time) can amplify negative outcomes following subsequent concussive injury.[5]

Incidence rates of concussion have grown steadily over the last decade, highlighting an important public health concern in the United States and worldwide.[6] As such, researchers and clinicians have called for examination of specific factors that may moderate injury risk and recovery from concussive injury. Biological sex is one such factor gaining interest among researchers and health care professionals. While there appears to be a substantive knowledge base on sex-based differences in concussion incidence and risk, less is known regarding the influence of biological sex on symptoms, cognitive function, and psychological health following concussive injury.[7] Prior research in the greater TBI

literature appears to demonstrate poorer outcomes and longer recovery time among females;[8] however, relatively few studies have sought to examine the relation between sex and outcomes following less severe brain injuries, such as concussion. Though gaining attention in recent years, fewer studies have sought to examine the relation between biological sex and symptoms, cognitive function, and psychological health following concussive injury among adolescents.[9]

Research has shown adolescent and young adult females may endorse greater concussion symptoms than males; though findings appear dependent upon age.[10,11] While trends in symptom reporting appear consistent among young adults, the available evidence is less clear among adolescents.[12] Current evidence suggests older female youths (13-22 years) may endorse greater symptom burden than their male counterparts;[10-15] whereas the inverse relation may be true among younger adolescents (10-12 years).[10,12] Further, current findings regarding sex-based differences in specific symptom clusters are also variable, with the exception of potentially greater endorsement of affective symptoms among females, irrespective of age.[10,12-15] However, many studies examining the relation between biological sex and reporting of concussion symptoms have utilized cross-sectional design and have failed to control for other potential covariates, such as baseline measures and concussion history, which may also influence post-concussive outcomes.[12,16,17] Although researchers and health care professionals should be aware of the potentially different symptom profiles between males and females, given the critical limitations of available evidence, our current understanding of sex-based differences in post-concussive symptom reporting among adolescents and young adults remains incomplete.

Research examining sex-based differences in cognitive functioning following concussion commonly include samples that span high school and collegiate athletes. Overall, studies suggest females may exhibit greater cognitive dysfunction following concussion than do males.[18] However, current research on sex-based differences in post-concussive cognitive functioning has largely failed to find consistent patterns of impairment across specific cognitive measures (attention, learning, memory) between the sexes. While some studies have shown that females may exhibit slower reaction times[19,20] and greater memory impairment[14,21] following concussion when compared to males, others have observed no such differences.[22-24] Although, similar to observations with clinical symptom reports, current findings may be dependent upon age. For example, researchers have observed poorer visual memory ~3 days post-injury among adolescent females ≥14 years when compared to age-matched males, but no sex differences among adolescents ≤13 years.[25] In addition to age, researchers have identified a number of other potential moderators; such as, pre-existing conditions (neurodevelopmental, neuropsychiatric, or other neurological disorders), genetic factors, concussion history, injury characteristics (loss of consciousness, post-traumatic amnesia), post-concussive physical rest/activity, and time to specialty care.[26-28] Thus, evaluating sex-based differences in cognitive functioning (and any other outcome measure) following concussion can be very difficult. Nonetheless, given the gaps in current literature, continued effort to examine potential differences in post-concussive outcomes between females and males is imperative.

Though gaining attention in recent years, psychological outcomes are perhaps the most overlooked areas in concussion research, and evidence for sex-based differences is relatively sparse, especially among adolescents.[12,18] Overall, existing research on sex-based

differences in post-concussive psychological health has been inconsistent. While some studies indicate females may experience more severe psychological symptoms following concussion,[29-32] other studies have failed to replicate these findings.[21,33,34] Interestingly, research has shown increased frequency of prior concussion is strongly correlated with increased depressive symptoms in females, but not males.[30] Though fascinating, it remains unclear to what degree concussion exacerbates emotional-behavioral problems, as these patterns of behavior are also evident between females and males without history of brain injury.[32] However, additional research using advanced psychophysiological techniques to evaluate autonomic nervous system function as well as neural substrates of emotional processing may provide additional insight.[35-37] Researchers have shown decreased parasympathetic activity during the first week of injury predicts elevated depressive symptoms several months following concussion in females, but not in males.[35] Furthermore, studies using EEG have shown females with history of multiple concussions exhibit similar neural processing of emotion to uninjured females, whereas males with history of multiple concussions exhibit blunted neural processing of emotion when compared to uninjured males.[36,37] Altogether, current evidence (though limited and tentative) indicates that concussion may differentially affect post-concussive psychological health and emotional-behavioral functioning between females and males, and these effects may be partially moderated by frequency of prior injury. Further investigation of sex-based differences in post-concussive psychological health is needed, particularly given the growing body of evidence linking concussion with chronic psychological health problems and potentially fatal risk behaviors among youth.[5,33,38-40]

Given the divergent trends in sex-based differences across age, researchers have speculated that underlying biological factors, such as sex-based steroid hormones (e.g., progesterone, estrogen, testosterone), may play a significant role in post-concussive outcomes.[10] Indeed, studies have demonstrated females who experience a significant reduction of progesterone following moderate-to-severe brain injury exhibit poorer outcomes than females with more stable (natural or artificial) hormone levels.[41,42] These findings have led researchers to formulate the *hormonal withdrawal hypothesis,* which asserts that the stability of hormones following brain injury may influence recovery in females.[43] Interestingly, results from recent randomized-controlled trials (RCTs) have demonstrated little-to-no treatment effect with early administration of progesterone following moderate-to-severe brain injury.[44-46] Though considered "gold standard" research design, current RCT evidence is limited by inclusion of predominantly male samples (70%+), failure to examine differences in treatment response between females and males, variance in treatment and evaluation schedules, and poor stratification by severity of injury.[47,48] Despite these shortcomings, there is some evidence to suggest progesterone may exhibit greater neuroprotective effects in less severe brain trauma, such as concussion.[44] Importantly, researchers have observed females concussed during the luteal phase of their menstrual cycle (when progesterone concentration is highest and potential reduction is greatest) reported poorer quality of life and greater symptoms compared to females concussed during the follicular phase (when progesterone concentration is low and potential reduction is lowest), and concussed females using hormonal contraceptives (stable progesterone level through each phase).[43] Additional research has shown females using hormonal contraceptives reported significantly lower peak symptom severity,

relative to females that did not use hormonal contraceptives.[49] Though informative, prior studies examining the relation between sex hormones/contraceptives and concussion outcomes have been limited cross-sectional designs, small group sizes, and subjective outcome measures (e.g., clinical symptoms and self-reported quality of life). Thus, additional longitudinal investigation utilizing more objective measures of brain function is needed to better understand the influence of hormonal contraceptives on clinical recovery following concussion, if any.

In sum, present scientific literature indicates adolescent and young adult females may experience higher rates of concussion, and may be more likely to experience protracted recovery when compared to male counterparts.[50] However, less is known regarding the influence of biological sex on symptoms, cognitive function, and psychological health following concussive injury.[12] Additionally, there is some evidence that important biological factors, such as sex hormones, may moderate recovery outcomes in females.[43,49] Altogether, the majority of existing evidence has been drawn from cross-sectional investigations and lack appropriate consideration of other important moderating variables that may also influence concussion outcomes. To this end, the purpose of the studies described herein was to address important knowledge gaps in current literature, and specifically sought to examine the influence of biological sex and sex-based hormones on concussion outcomes among adolescents and young adults.

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CHAPTER 2

SEX-BASED DIFFERENCES IN CONCUSSION SYMPTOMS, PSYCHOLOGICAL HEALTH, AND COGNITIVE FUNCTION FOLLOWING ADOLESCENT CONCUSSION[1]

[1]Jacob J. M. Kay; Jeffrey P. Holloway; Toni M. Torres-McGehee; Steven P. Broglio; & Robert D. Moore. To be submitted to *J Clin Med* (in preparation).

ABSTRACT

Current literature highlights important sex-based differences between females and males following adolescent concussion; with females generally exhibiting greater symptom burden than males. Less is known regarding the moderating effect of biological sex on post-injury psychological health and cognitive functioning. This study expanded upon current knowledge by prospectively examining the relation between biological sex and clinical symptoms, psychological health, and cognitive function following adolescent concussion. Twenty-five females (Age: 14.32±1.70years) and twenty-five males (Age: 14.12±1.51years) who sustained concussions were examined at a local pediatric sports medicine clinic. Initial evaluations were completed on average within three weeks of injury, with follow-up evaluations on average six weeks post-injury. Clinical symptoms were measured using the Rivermead Post-Concussion Symptoms Questionnaire; psychological health with the depression subscale of the Beck Youth Inventories – Second Edition; and cognitive functioning with a computerized brain injury test battery and the Behavioral Rating Inventory of Executive Function – Parent Form. Concussion outcome variables were examined via 2 (group) X 2 (time) repeated-measures ANOVAs. Post-hoc comparisons were performed to identify the source of the interactions by means of independent samples t-tests with Bonferroni correction for multiple comparisons. On average, females reported a greater number of somatic, affective, and cognitive symptoms across recovery timepoints (p's ≤ 0.01). Females and males did not differ in terms of post-concussive levels of depression ($p > 0.05$). Computerized testing revealed slower response times among females across several measures of cognitive function when compared to males (p's ≤ 0.05). Further, concussed female participants were rated significantly worse

by parent/guardian(s) on behavioral self-regulation when compared to male participants (p's ≤ 0.05). Our results corroborate evidence that concussed adolescent females report greater symptom burden than concussed adolescent males. Moreover, findings from the present study illuminate potential sex-based differences in cognitive functioning following adolescent concussion.

INTRODUCTION

Guidelines from the most recent *Consensus Statement on Concussion in Sport* highlight the importance of considering individual characteristics that may modify the nature and outcomes of concussion.[1] Biological sex is one such factor gaining interest among researchers and health care professionals. There is a substantive knowledge base regarding sex-based differences in incidence of concussive injury, with females generally demonstrating higher rates than males.[2] However, less is known regarding the influence of biological sex on concussion recovery outcomes. Although prior works in greater TBI literature demonstrate poorer outcomes among females, fewer studies have sought to examine the relation between biological sex and outcomes following less severe brain injuries, such as concussion.[3] Further, the majority of existing research in this area has focused on adults, with less attention paid to potential sex-based differences in concussion recovery outcomes among younger individuals.[3] Therefore, developing a better understanding of the influence of biological sex on post-concussive outcomes, particularly among developing adolescents, is of critical importance.

Prior studies have observed significant differences between females and males on post-concussion symptom inventories.[4-13] Among young adults, research has consistently shown females report a higher total number and greater severity of acute post-concussion

symptoms than males.[4-10] However, findings have been less consistent among adolescents. Some studies have shown females endorse higher number and greater severity of symptoms when compared to males,[11-13] while other studies have observed no such differences.[14-15] Additional research aiming to determine if particular symptom clusters (somatic, psychological, cognitive) differ between adolescent males and females has also been largely inconclusive, though trends in current literature may suggest greater endorsement of affective symptoms among females.[16-19]

Measures of psychological health are perhaps the most overlooked areas of clinical research regarding the effects of concussion on neurobehavioral health.[20] Yet, existing studies have demonstrated higher rates of mood disorders and psychological distress among individuals (irrespective of age) with history of one or more concussions, relative to uninjured counterparts.[20-22] Overall, current evidence suggests females may experience more severe psychological symptoms and may be more likely to carry psychological diagnoses long-term following concussion.[10,21-23] However, research in this area is relatively sparse among adolescents, and have largely failed to control for potential baseline differences.[19,24-26] Kontos and colleagues (2012a)[19] found females endorsed greater affective symptoms 1—7 days post-concussion when compared to males, but no differences in other symptom clusters (cognitive, somatic). In a follow-up study,[25] the authors found no differences in Beck Depression Inventory scores between females and males at 2, 7, or 14 days following concussive injury. In contrast, Covassin, Schatz, & Swanik (2007)[26] found males reported more post-concussive sadness when compared to females at ~3 and 10 days following injury. Altogether, limited evidence and inconsistent

findings hinder any strong conclusions for potential sex-based differences in psychological health following concussion. Thus, additional investigation is warranted.

Research aiming to examine sex-based differences in post-concussive cognitive outcomes has also been inconsistent. Some studies have shown no differences between males and females in acute post-concussive cognitive performance,[27-30] whereas others have observed differences within specific cognitive measures. While existing studies have examined broad age ranges spanning adolescence and young adulthood, researchers have observed slower reaction times[5,6] and lower memory scores[4,26] in females when compared to males. Majerske and colleagues (2008)[31] found a greater proportion of adolescent females (53.3%) demonstrated impaired memory and visuomotor reaction time at 1-month following injury when compared to adolescent males (26.3%). In contrast, Henry and colleagues (2016)[32] prospectively examined sex-based differences in cognitive function in athletes age 14-23 years and reported no differences in performance on any cognitive tests between females and males. Though current literature indicates there may be sex-based differences in post-concussive cognitive performance, existing studies have largely failed to find consistent patterns of impairment between females and males.[4-6,26-32]

In sum, current research on adolescent sex-based differences indicates that females may experience greater symptom burden when compared to males following concussion. While there is some evidence that females may be at greater risk of post-concussive decline in psychological health relative to males, investigations have largely failed to confirm sex-based differences in psychological health following injury that cannot be explained by potential differences at baseline. Additionally, while several studies have aimed to examine sex-based differences in cognitive function following concussion, existing research

remains inconclusive.[4-6,26-32] Thus, the purpose of this investigation was to prospectively examine sex-based differences across clinical symptoms, psychological health, and cognitive function following concussion among adolescents. We hypothesized females would exhibit higher symptom scores, decreased psychological health, and greater post-injury deficits in cognitive functioning when compared to males.

METHODS

Sampling Procedures and Participants

Between August 2017 and August 2020, ~500 children and youths suspected of having sustained a concussion were evaluated at a local specialty clinic. During initial evaluation, concussion diagnoses were confirmed by the attending physician in accordance with guidelines established by the most recent *Consensus Statement on Concussion in Sport*.[1] To monitor recovery, patients were instructed to return for follow-up examination between 2-3 weeks following their initial evaluation. Patients and their parents/legal guardians were verbally informed by the attending physician of all clinical research activities, and were provided the opportunity to decline participation. Protected health information was removed from all clinical records prior to data analyses. All study procedures were approved by the Institutional Review Board, including waivers of Health Insurance Portability and Accountability Act authorization and informed consent.

Adolescents between 10 and 17 years of age that sought care at the local concussion clinic and returned for follow-up evaluation were screened for inclusion (Figure 2.1). Participants with a history of a neurodevelopmental disorder, history of a psychiatric or mood disorder, and/or use of psychotropic medication were excluded from the present study. Participants with history of moderate-severe brain injury, or other neurological

disorder (including migraines) were also excluded. Additionally, only those participants that completed the full battery of tests at initial and follow-up examinations were included in the statistical analyses. Participant medical records were utilized to determine "biological sex" and subsequent group assignment. The final sample of twenty-five females and twenty-five males were matched on key demographics and injury information, including age, body mass index, race/ethnicity, concussion history, and current injury characteristics (e.g., mode of injury, loss of consciousness, post-traumatic amnesia).

Assessment Procedures and Measures

Surveys of clinical symptoms (Rivermead Post-Concussion Symptom Questionnaire), psychological health (Beck Youth Inventories – Second Edition), and parent-reported neurobehavioral function (Behavioral Rating Inventory of Executive Function) were collected via HIPPA-compliant, Research Electronic Data Capture (REDCap; Vanderbilt University, 2019) roughly 24 hours prior to each clinic visit. Computerized cognitive tests (CogState) were completed during in-clinic visits. Assessment measures are briefly described below:

The *Rivermead Post-Concussion Symptoms Questionnaire* (RPQ)[33] is a 16-item self-report survey that assesses the presence and severity of somatic (headache; dizziness; nausea), affective (irritable/easily angered; depressed/tearful; frustrated/impatient), and cognitive symptoms (forgetful/poor memory; poor concentration; taking longer to think) commonly experienced following concussion. The RPQ is designed to compare post-concussive symptom burden with pre-injury status on a 5-point Likert scale, (0 = Not experienced) to (4 = A severe problem), and demonstrates good/high reliability in evaluating individual/total symptoms following concussion among youth.[33]

The depression subscale of the *Beck Youth Inventories—Second Edition* (BYI-2)[34] is a 20-item self-report inventory designed to measure symptoms of depression in children and adolescents aged 7 to 18 years. The survey includes items related to negative thoughts about self, life, and the future, as well as feelings of sadness, guilt, and sleep disturbance. Participants are asked to choose between 4 statements, rated from (0 = Never) to (3 = Always), which best describes how they have been feeling during the last two weeks. The BYI-2 demonstrates adequate-good reliability in evaluating psychological symptoms in clinical traumatic brain injury populations.[34] Higher raw and standardized scores indicate greater depressive symptoms.

The *CogState Brain Injury Test Battery* (CogState)[35] is a validated computerized assessment for rapid and reliable measure of cognitive function following traumatic brain injury. A modified version including one-back and two-back tests (working memory), a Groton maze learning test (executive function), and a Groton maze delayed recall test (visual memory recall) were administered to assess post-concussive cognitive functioning.

The *Behavior Rating Index of Executive Function* (BRIEF)[36] is an 86-item questionnaire aimed at assessing multiple sub-domains of executive function, including: inhibitory control (*Inhibit*), attention shifting (*Shift*), emotional control, task initiation (*Initiate*), working memory (*Working Mem.*), planning and organization (*Plan / Organize; Org. of Materials*), as well as self- and task-monitoring behaviors (*Monitor*). The parent-report version of the BRIEF requires either a parent/guardian to respond (N = Never, S = Sometimes, or O = Often) on items that best characterize their child, based on their daily observations, and demonstrates good reliability adolescent concussion cohorts.[36] Higher raw and standardized scores indicate greater executive dysfunction.

Statistical Analyses

A priori power analysis (G*Power 3.1)[37] estimated a participant sample of 24 to detect large effect sizes (Cohen's $f = 0.40$; $\eta p^2 = 0.14$), which is comparable to prior research.[5] All hypothesis testing was conducted using the Statistical Package for the Social Sciences Version 27 (SPSS; IBM, Armonk, NY). Independent samples t-tests were used for continuous data, and χ^2 tests were used for categorical data to compare male and female demographics (age, body mass index, race/ethnicity) and injury characteristics (concussion history, mode of injury, loss of consciousness, post-traumatic amnesia). Concussion outcome variables (RPQ, BYI-2, CogState, BRIEF) were examined via 2 (group: female, male) x 2 (time: initial exam, follow-up exam) repeated measures ANOVAs. Post-hoc comparisons were performed to identify the source of the interactions by means of independent samples t-tests with Bonferroni correction for multiple comparisons. Levene's tests were employed to evaluate violations in the assumption of equal variances and corrected accordingly in the event of a violation. To address concerns for potential baseline differences, T-scores were included in ANOVA models. For all significant effects, partial eta squared (ηp^2) was calculated to estimate magnitude of effect on significant differences between male and female participants (.01 = small; .06 = medium; 0.14 = large). An *a priori* alpha level of 0.05 was set for all analyses.

Results

Demographics and injury characteristics are presented in Table 2.1. Demographic characteristics did not differ between females and males (p's ≥ 0.39). In terms of injury characteristics, there were no differences between females and males across concussion history, time from injury to initial and follow-up examinations, loss of consciousness, or

post-traumatic amnesia (p's ≥ 0.41). Chi-square analyses revealed a greater proportion of males were injured during contact/collision sport when compared to females (84% males vs. 32% females; Adjusted Residual = ±3.7; $p < 0.01$); whereas a greater proportion of females were injured during limited-contact sport when compared to males (32% females vs. 4% males; Adjusted Residual = ±2.6; $p < 0.01$). Importantly, females and males did not significantly differ across MVA or non-contact sport categories.

Descriptive statistics for RPQ can be found in Table 2.2. No group X time interaction was observed for RPQ total symptom severity score ($F[1,48] = 0.37$, $p = 0.55$). However, a significant main effect of group was observed for RPQ total symptom severity scores ($F[1,48] = 10.33$, $p = 0.01$, $\eta p^2 = 0.18$), with females (19.08 ± 2.13) exhibiting higher scores than males (9.40 ± 2.13) across timepoints. Analyses of specific RPQ symptom domains revealed no interaction among somatic and cognitive symptoms (F's$[1,48] \leq 0.14$, p's ≥ 0.71). However, group main effects were observed (F's$[1,48] \geq 6.72$, p's ≤ 0.02), with females reporting higher somatic (4.14 ± 0.44) and cognitive (4.02 ± 0.50) symptom severity scores when compared to males (2.52 ± 0.44 and 2.02 ± 0.50, respectively) across timepoints. With respect to affective symptoms, a significant interaction was observed ($F[1,48] = 5.87$, $p = 0.02$, $\eta p^2 = 0.11$). Post-hoc analyses revealed significantly higher affective symptom severity scores among females at both timepoints; though a significantly larger group difference was observed at initial examination (4.48 vs. 1.60; $t[48] = 3.73$; $p = 0.01$) than follow-up examination (2.20 vs. 0.64; $t[48] = 2.39$; $p = 0.02$), when compared to males.

Descriptive statistics for BDI can be found in Table 2.2. No group X time interaction was observed for BDI raw scores ($F[1,48] = 0.98$, $p = 0.33$). However, a

significant main effect of group was observed (F[1,48] = 5.06, p = 0.03, ηp^2 = 0.10), with females (6.78 ± 1.16) exhibiting higher scores than males (3.10 ± 1.16) across timepoints. Neither group X time interaction effects, nor group main effects were observed on BDI T-Scores (F's[1,48] ≤ 2.14, p's ≥ 0.15).

Descriptive statistics for CogState can be found in Table 2.3. No group X time interaction was observed on One Back Reaction Time scores (F[1,48] = 0.39, p = 0.54). However, a significant main effect of group was observed (F[1,48] = 4.06, $p < 0.05$, ηp^2 = 0.08), with females (1023 ± 1.05ms) exhibiting slower reaction times (RTs) when compared to males (912 ± 1.05ms) across timepoints. Neither group X time interaction, nor group main effects were observed on One Back Accuracy scores (F's[1,48] ≤ 0.05, p's ≥ 0.83). No group X time interaction was observed on Two Back Reaction Time scores (F[1,48] = 0.01, p = 0.93). However, a significant main effect of group was observed (F[1,48] = 6.50, p = 0.01, ηp^2 = 0.12), with females (1259 ± 1.05ms) exhibiting slower RTs when compared to males (1096 ± 1.05ms) across timepoints. Neither group X time interaction, nor group main effects were observed on Two Back Accuracy scores (F's[1,48] ≤ 1.43, p's ≥ 0.23). Neither group X time interaction effects, nor group main effects were observed on correct moves per second, nor total errors on the Groton Maze Learning task (F's[1,48] ≤ 2.41, p's ≥ 0.13). With respect to T-scores, a significant main effect of group was observed on One Back Reaction Time (F[1,48] = 4.81, p = 0.03, ηp^2 = 0.09), with females (65.67 ± 1.88) exhibiting higher scores (slower RT) when compared to males (59.85 ± 1.88) across timepoints. No interaction effects, nor any other group main effects were observed on N-back T-scores (F's[1,48] ≤ 2.28, p's ≥ 0.14).

A significant main effect of group was observed on the Groton Maze Recall task ($F[1,48] = 5.57$, $p = 0.02$, $\eta p^2 = 0.10$), with females (0.90 ± 0.05) exhibiting fewer correct moves per second than males (1.10 ± 0.05) across timepoints. No interaction effects, nor any other group main effects were observed on raw performance indices of the Groton Maze Recall task (F's$[1,48] \leq 1.39$, p's ≥ 0.25). With respect to Groton Maze T-scores, no interaction effects, nor group main effects were observed (F's$[1,48] \leq 2.64$, p's ≥ 0.11).

Descriptive statistics for BRIEF can be found in Table 2.4. With respect to raw scores, a significant interaction was observed for *Initiate* sub-score ($F[1,48] = 5.61$, $p = 0.02$, $\eta p^2 = 0.11$). However, post-hoc comparisons failed to reveal significant differences between females and males at either timepoint (p's ≥ 0.19). No other significant interaction effects were observed for BRIEF raw scores (F's$[1,48] \leq 1.85$, p's ≥ 0.18). A significant main effect of group was observed on *Shift* sub-score ($F[1,48] = 5.65$, $p = 0.22$, $\eta p^2 = 0.11$), with females (11.02 ± 0.48) exhibiting higher scores than males (9.42 ± 0.48) across timepoints. A significant main effect of group was observed on *Emotional Control* sub-score ($F[1,48] = 12.10$, $p \leq 0.01$, $\eta p^2 = 0.20$), with females (14.14 ± 0.54) exhibiting higher scores than males (11.48 ± 0.54) across timepoints. A significant main effect of group was observed on *Behavioral Regulation Index* ($F[1,48] = 9.48$, $p \leq 0.01$, $\eta p^2 = 0.17$), with females (36.90 ± 1.19) exhibiting higher scores than males (31.74 ± 1.19) across timepoints. No other significant group main effects were observed for BRIEF raw scores (F's$[1,48] \leq 3.19$, p's ≥ 0.80). With respect to BRIEF T-scores, a significant interaction was again observed for *Initiate* ($F[1,48] = 4.82$, $p = 0.03$, $\eta p^2 = 0.09$). However, post-hoc comparisons failed to reveal significant differences between females and males at either timepoint (p's ≥ 0.12). No other interaction effects were observed for BRIEF T-scores

(*F*'s[1,48] ≤ 1.71, *p*'s ≥ 0.29). However, a significant main effect of group was again observed on *Behavioral Regulation Index* (F[1,48] = 4.39, p = 0.04, $\eta p^2 = 0.08$), with females (46.38 ± 1.28) exhibiting higher scores than males (42.58 ± 1.28) across timepoints. No other group main effects were observed on BRIEF T-scores (*F*'s[1,48] ≤ 2.81, *p*'s ≥ 0.10).

DISCUSSION

The present study sought to examine the influence of biological sex on clinical symptoms, psychological health, and cognitive function following adolescent concussion. We found adolescent females reported significantly higher symptom severity across somatic, affective, and cognitive domains. Regarding specific measures of depressive symptoms (i.e., BYI-2), findings from the present study did not support our hypothesis that adolescent females would exhibit greater decreases in psychological health than males following concussion when incorporating age- and sex-adjusted normative data. However, we consistently observed slower reaction times and processing speed among adolescent females when compared to male adolescents across several cognitive measures. Furthermore, we found parents of females reported greater problems with behavioral regulation when compared to parents of males. Thus, while biological sex does not appear to influence psychological health post-concussion (beyond standard concussion symptom reports), the present study illuminates potential sex-based differences in cognitive and neurobehavioral functioning, with females exhibiting slower cognitive processing speed that may underly greater difficulties regulating everyday behaviors of executive function.

With respect to concussion symptoms, we found adolescent females consistently reported higher overall symptom severity across initial and follow-up examinations. These

results agree with prior works that have observed greater symptom burden among adolescent females, when compared to adolescent males.[11-13] Though, current research on sex-based differences in symptom reporting across specific domains among adolescents remains somewhat mixed.[38,39] We observed greater symptom burden among females across all subdomains analyzed. These results do not fully agree with prior findings of Kontos and colleagues (2012a)[19] that reported no differences in somatic or cognitive symptoms between females and males. However, similar to Kontos and colleagues (2012a),[19] our study corroborates other prior works that demonstrate heightened affective symptoms following concussion among adolescent females, relative to adolescent males.[16-18] Importantly, results from the present study suggest larger differences in reporting of affective symptoms may be observed during earlier (acute/subacute) phases of recovery. Thus, adolescent females may be more prone to heightened post-concussive affective symptoms when compared to adolescent males, particularly within the first few weeks following injury.

Despite observing greater affective symptoms among adolescent females in this study, our results largely demonstrate no differences between the sexes on measures of depressive symptoms. While analysis of raw BYI-2 depression scores indicated higher depressive symptoms among females, secondary analysis of BYI-2 depression T-scores failed to reveal any significant differences between females and males. Importantly, these findings also corroborate those of Kontos and colleagues (2012b)[25] that found no differences in BDI scores between females and males at 2, 7, and 14 days following concussion. Together, these findings suggest females and males share similar depression levels following concussive injury. Further, analysis of BYI-2 T-scores revealed relatively

low levels of depression at both initial and follow-up examinations. While this is a bit perplexing, given greater severity scores in the affective symptom cluster, it is plausible that differences may be observed in other domains of psychological health. Indeed, sub-analyses of the RPQ items revealed no differences in reporting of depressive symptoms between females and males (Table 2.2), suggesting that observed differences in affective symptoms between females and males were driven by "irritable/angry" and "frustration/impatient" symptoms. Further, it is important to note that the RPQ instructs patients to rate present symptoms relative to their perceived baseline, and a robust normative database for evaluating post-injury change in symptom burden has yet to be developed. Though ratings of depressive symptoms appear to agree between the RPQ and BYI-2, it is difficult to determine if the results from other affective items are due to potential differences at baseline. Thus, while standard concussion symptom scales may be useful in screening for alterations in psychological health, clinicians and other health care professionals should consider additional, validated instruments to evaluate specific domains of psychological health (e.g., BYI-2: anger, disruptive behavior, anxiety and self-concept subscales).

With respect to cognitive function, we found adolescent females exhibited greater impairment across several CogState tasks when compared to adolescent males (Table 2.3). More specifically, females demonstrated significantly slower RTs on both one- and two-back working memory tasks. Similarly, females completed significantly fewer correct moves per second during the delayed recall condition of the Groton Maze task, indicating slower processing speed when compared to males. This finding is consistent with greater self-reporting of "*taking longer to think*" on RPQ among females. Moreover, these results

corroborate findings from Colvin and colleagues (2009)[6] that also observed slower reaction time scores on the ImPACT battery among adolescent females when compared to males at ~2 weeks post-concussion. In a more recent study, Sicard and colleagues (2019)[40] also demonstrated slower reaction times on the 2-back condition of the CogState test battery among females with history of concussion, when compared to males with history of concussion. Though participants in their study were of college age, the most recent concussion reported was ~2 years prior to the investigation, suggesting that sex differences observed in the first few weeks following concussion may persist well into the chronic phase of injury. No differences were observed in terms of performance accuracy across tasks. However, prior investigations of cognitive function among healthy adolescents suggest females and males process information differently. More specifically, research using various tests of executive function has shown females tend to sacrifice speed for greater accuracy on tests of executive function, whereas males tend to sacrifice accuracy for faster responses.[41,42] Thus, our results demonstrating slower RTs and processing speed among females when compared to males, but no differences in performance accuracy, suggest that observed differences in the present study cannot be fully explained by baseline characteristics in cognitive functioning between sexes. While it should be acknowledged that other studies have shown no differences in post-concussive cognitive performance between adolescent females and males,[6,11] authors have suggested that discrepancies in current research may be due to lack of control for baseline measures.[18] Importantly, our analyses of CogState T-scores strengthen our findings that females may be slower to react to test stimuli when compared to males, irrespective of potential baseline differences. Together, findings from CogState suggest that adolescent females may exhibit greater

detriments in cognitive performance following concussion than adolescent males, particularly on objective tests of executive function.

Findings from the BRIEF substantiate results from CogState measures suggesting that adolescent females may experience greater alterations in executive functioning than do adolescent males following concussion. Evaluation of BRIEF raw scores indicate that females were rated (by parent or guardian) significantly higher on *Shift* and *Emotional Control* subscales of the *Behavioral Regulation Index* (BRI), indicating poorer behavioral regulation among females when compared to males. Analysis of BRIEF T-scores revealed consistent deficits in behavioral regulation among females, though results failed to reach statistical significance on any specific subscale of the BRI. To date, few studies have employed the BRIEF to examine the influence of concussion on executive functioning in adolescents,[43-46] and only one study describes potential differences between females and males.[47] Interestingly, our findings contradict those of Rieger and colleagues (2013)[47] who observed parents of adolescent males reported greater disruption of executive functions when compared to parents of adolescent females at ~3 days post-injury and again at ~3 month follow-up. However, the authors report only on total score for the *Global Executive Index*; thus, limiting evidence for differences on specific domains of executive function. Despite contrasting findings, incorporating parent-reported inventories, such as the BRIEF, may provide clinicians and caregivers with valuable information regarding the impact of concussion on adolescent executive functioning in daily life. Future investigations are necessary for developing a better understanding of potential sex-based differences in adolescent neurobehavioral health following concussion.

Limitations

The present study is not without limitations. Though a strength of our study includes analyses of T-score values, true baseline measures could not be evaluated. Normative data was available for the BYI-2, CogState, and BRIEF, but not the RPQ. Thus, it is possible that differences in baseline characteristics contributed to observed sex differences, particularly on post-concussion symptoms. To address this, female and male participants were carefully matched on key demographics (age, BMI, race/ethnicity) and injury characteristics (loss of consciousness, post-traumatic amnesia, time between injury and examinations, concussion history). We also excluded pre-existing medical conditions that may have influenced recovery outcomes, such as neurodevelopmental, neuropsychiatric, or other neurological disorders (including migraines). Another important limitation of the present study was the small sample size, which restricted our ability to control other factors known to influence concussion outcomes. For example, given the wide age range of participants included in the study (10 – 17 years), it would have been advantageous to factor age as a covariate in our statistical models. Additionally, our evaluation of psychological health was limited to depressive symptoms, and findings from the present investigation suggest that other components of emotional and psychological well-being, such as anxiety, may differ between females and males following concussion. Lastly, we emphasize caution when interpreting results from CogState measures, as research demonstrates reliability lower than desired for clinical decision-making, particularly in test-retest settings.[48]

CONCLUSION

Findings from the current study corroborate evidence that concussed adolescent females report greater symptom burden than concussed adolescent males. Further, our results suggest that depression levels following concussion may not differ between females and males. Findings from the present study also illuminate potential sex-based differences in cognitive and neurobehavioral functioning following adolescent concussion. Future investigations should go beyond subjective symptom scales to capture a more comprehensive understanding of post-concussive psychological and neurobehavioral health among female and male adolescents. Additionally, future longitudinal research should incorporate baseline evaluations to gain a more accurate understanding of sex-based differences before-and-after concussion.

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Table 2.1. Participant Demographics

	FEMALES	MALES
Age (years)	14.32 ± 1.70	14.12 ± 1.51
Body Mass Index (kg/m^2)	25.19 ± 6.99	23.64 ± 5.46
Race / Ethnicity		
Caucasian	12 (48%)	15 (60%)
African American	10 (40%)	9 (36%)
Hispanic/Latino	1 (4%)	1 (4%)
Multiple Races / Unknown	2 (8%)	0 (0%)
Contact Category		
MVA	6 (24%)	2 (8%)
Contact	**8 (32%)***	**21 (84%)***
Limited Contact	**8 (32%)***	**1 (4%)***
Non-Contact	3 (12%)	1 (4%)
Injury Characteristics		
Loss of Consciousness	4 (16%)	6 (24%)
Post-traumatic Amnesia	8 (32%)	7 (28%)
Assessment Timeline		
DOI to Exam 1 (days)	17.80 ± 8.19	15.72 ± 9.30
DOI to Exam 2 (days)	39.76 ± 15.20	39.52 ± 14.96
Prior Concussions		
None	20 (80%)	18 (72%)
One	4 (16%)	4 (16%)
Two	1 (4%)	3 (12%)

Note: Values are presented in M±SD or sample size (percent). Boldface indicates group difference; *Indicates significant difference ≤ 0.01.

Table 2.2. Descriptive Statistics: RPQ & BYI-2 (Depression)

	FEMALES			MALES		
Outcome Measures	**Exam 1**	**Exam 2**	**Average**	**Exam 1**	**Exam 2**	**Average**
RPQ						
Symptom Severity Scores						
Total	23.96 ± 2.36	14.20 ± 2.45	**19.08 ± 2.13****	13.32 ± 2.36	5.48 ± 2.45	**9.40 ± 2.13****
Somatic	5.24 ± 0.50	3.04 ± 0.54	**4.14 ± 0.44***	3.48 ± 0.50	1.56 ± 0.54	**2.52 ± 0.44***
Headache	2.92 ± 0.21	1.60 ± 0.23	**2.26 ± 0.17****	2.12 ± 0.21	0.72 ± 0.23	**1.42 ± 0.17****
Dizziness	1.44 ± 0.22	0.88 ± 0.20	1.16 ± 0.18	1.00 ± 0.22	0.56 ± 0.20	0.78 ± 0.18
Nausea/Vomiting	0.88 ± 0.19	0.56 ± 0.18	0.72 ± 0.16	0.36 ± 0.19	0.28 ± 0.18	0.32 ± 0.16
Affective^{X}	**4.48 ± 0.55****	**2.20 ± 0.46***	3.34 ± 0.47	**1.60 ± 0.55****	**0.64 ± 0.46***	1.12 ± 0.47
Irritable/Angry	1.80 ± 0.23	0.92 ± 0.18	**1.36 ± 0.18****	0.64 ± 0.23	0.20 ± 0.18	**0.42 ± 0.18****
Depression/Tearful	0.80 ± 0.20	0.48 ± 0.16	0.64 ± 0.17	0.24 ± 0.20	0.16 ± 0.16	0.20 ± 0.17
Frustrated/Impatient^{X}	**1.88 ± 0.22****	0.80 ± 0.17	1.34 ± 0.18	**0.72 ± 0.22****	0.28 ± 0.17	0.50 ± 0.18
Cognitive	4.92 ± 0.60	3.12 ± 0.54	**4.02 ± 0.50****	2.96 ±0.60	1.08 ± 0.54	**2.02 ± 0.50****
Poor Memory	1.00 ± 0.23	0.88 ± 0.19	0.94 ± 0.19	0.56 ± 0.23	0.36 ± 0.19	0.46 ± 0.19
Poor Concentration	1.88 ± 0.25	1.08 ± 0.19	**1.48 ± 0.19***	1.24 ± 0.25	0.36 ± 0.19	**0.80 ± 0.19***
Taking Longer to Think	2.04 ± 0.23	1.16 ± 0.21	**1.60 ± 0.19****	1.16 ± 0.23	0.36 ± 0.21	**0.76 ± 0.19****
BYI-2 (Depression)						
Raw Score	8.48 ± 1.49	5.08 ± 1.09	**6.78 ± 1.16***	3.96 ± 1.47	2.24 ± 1.09	**3.10 ± 1.16***
T-Score	45.28 ± 1.62	41.52 ± 1.30	43.40 ± 1.30	41.76 ± 1.62	39.68 ± 1.30	40.72 ± 1.30

Note: Mean ± SEM for RPQ and BYI-2 (Depression) are provided. Boldface indicates group difference; ^{X}Indicates significant interaction effect; **Indicates significance difference $p \leq 0.01$; *Indicates significant difference $p \leq 0.05$.

Table 2.3. Descriptive Statistics: CogState

	FEMALES			MALES		
Outcome Measures	**Exam 1**	**Exam 2**	**Average**	**Exam 1**	**Exam 2**	**Average**
CogState (Raw Scores)						
One Back (ONB)						
RT (ms)	1096 ± 1.05	933 ± 1.05	**1023 ± 1.05***	977 ± 1.05	851 ± 1.05	**912 ± 1.05***
Accuracy (%)	87.54 ± 0.01	91.78 ± 0.01	89.45 ± 0.01	87.54 ± 0.01	92.32 ± 0.01	90.06 ± 0.01
Two Back (TWOB)						
RT (ms)	1349 ± 1.05	1175 ± 1.05	**1259 ± 1.05***	1175 ± 1.05	1000 ± 1.05	**1096 ± 1.05***
Accuracy (%)	76.95 ± 0.01	81.02 ± 0.01	78.61 ± 0.01	76.10 ± 0.01	85.49 ± 0.01	81.02 ± 0.01
Groton Maze Learn (GML)						
Correct Moves/Second	0.61 ± 0.03	0.74 ± 0.03	0.68 ± 0.03	0.68 ± 0.03	0.81 ± 0.03	0.74 ± 0.03
Total Errors	57.88 ± 2.94	51.48 ± 2.29	54.68 ± 2.31	56.48 ± 2.94	48.12 ± 2.29	52.30 ± 2.31
Groton Maze Recall (GMR)						
Correct Moves/Second	0.83 ± 0.05	0.97 ± 0.60	**0.90 ± 0.05***	1.00 ± 0.05	1.13 ± 0.60	**1.06 ± 0.05***
Total Errors	7.08 ± 0.61	6.68 ± 0.76	6.88 ± 0.55	6.16 ± 0.61	5.76 ± 0.76	5.96 ± 0.55
CogState (T-scores)						
ONB: RT Score	69.74 ± 2.35	61.60 ± 2.00	**65.67 ± 1.88***	62.98 ± 2.35	56.71 ± 2.00	**59.85 ± 1.88***
ONB: Accuracy Score	40.81 ± 3.32	45.59 ± 2.48	43.20 ± 2.47	41.06 ± 3.13	46.77 ± 2.48	43.90 ± 2.47
TWOB: Accuracy Score	48.36 ± 2.46	51.04 ± 2.05	49.70 ± 1.91	48.61 ± 2.46	56.51 ± 2.05	52.56 ± 1.91
GML: Total Errors	54.65 ± 1.87	50.95 ± 1.38	52.80 ± 1.43	54.68 ± 1.87	49.38 ± 1.38	52.03 ± 1.43
GMR: Total Errors	47.21 ± 1.05	46.38 ± 1.22	46.80 ± 0.88	45.22 ± 1.05	44.32 ± 1.22	44.77 ± 0.88

Note: Mean ± SEM values for CogState tasks are provided. Boldface indicates group difference; [x]Indicates significant interaction effect; **Indicates significance difference p ≤ 0.01; *Indicates significant difference ≤ 0.05.

Table 2.4. Descriptive Statistics: BRIEF

	FEMALES			MALES		
Outcome Measures	**Exam 1**	**Exam 2**	**Average**	**Exam 1**	**Exam 2**	**Average**
BRIEF (Raw Scores)						
Behav. Reg. Index	38.08 ± 1.46	35.72 ± 1.20	**36.90 ± 1.19****	32.08 ± 1.46	31.40 ± 1.20	**31.74 ± 1.19****
Inhibition	12.04 ± 0.44	11.44 ± 0.35	11.74 ± 0.36	11.04 ± 0.44	10.60 ± 0.35	10.82 ± 0.36
Attention Shifting	11.36 ± 0.60	10.68 ± 0.52	**11.02 ± 0.48***	9.52 ± 0.60	9.32 ± 0.52	**9.42 ± 0.48***
Emotional Control	14.68 ± 0.66	13.60 ± 0.53	**14.14 ± 0.54****	11.52 ± 0.66	11.44 ± 0.53	**11.48 ± 0.54****
Metacognition Index	65.56 ± 2.96	61.52 ± 2.79	63.54 ± 2.73	61.28 ± 2.96	59.32 ± 2.79	60.30 ± 2.73
Initiate[X]	12.00 ± 0.58	10.80 ± 0.54	11.40 ± 0.53	10.92 ± 0.58	10.92 ± 0.54	10.92 ± 0.53
Working Mem.	15.60 ± 0.82	14.52 ± 0.85	15.06 ± 0.76	13.92 ± 0.82	13.32 ± 0.85	13.62 ± 0.76
Plan/Organize	16.64 ± 0.88	15.76 ± 0.74	16.20 ± 0.77	16.56 ± 0.88	15.16 ± 0.74	15.86 ± 0.76
Org. of Materials	10.72 ± 0.67	10.28 ± 0.61	10.50 ± 0.60	9.32 ± 0.67	9.40 ± 0.61	9.36 ± 0.60
Self-Monitor	10.60 ± 0.52	10.16 ± 0.47	10.38 ± 0.45	10.56 ± 0.52	10.52 ± 0.47	10.54 ± 0.45
Global Executive Index	103.64 ± 4.09	97.24 ± 3.76	100.44 ± 3.68	93.36 ± 4.09	90.68 ± 3.76	92.02 ± 3.68
BRIEF (T-scores)						
Behav. Reg. Index	47.64 ± 1.60	45.12 ± 1.26	**46.38 ± 1.28***	43.12 ± 1.60	42.04 ± 1.26	**42.58 ± 1.28***
Inhibition	46.76 ± 1.39	45.12 ± 1.02	45.94 ± 1.08	45.12 ± 1.39	42.96 ± 1.02	44.04 ± 1.08
Attention Shifting	49.20 ± 2.03	46.92 ± 1.80	48.06 ± 1.64	44.76 ± 2.03	43.80 ± 1.80	44.28 ± 1.64
Emotional Control	46.84 ± 2.08	45.64 ± 1.25	46.24 ± 1.49	43.44 ± 2.08	43.00 ± 1.25	43.22 ± 1.49
Metacognition Index	49.71 ± 1.75	46.88 ± 1.71	48.29 ± 1.61	45.95 ± 1.75	45.14 ± 1.71	45.54 ± 1.61
Initiate[X]	49.48 ± 1.91	45.60 ± 1.74	47.54 ± 1.72	45.24 ± 1.91	45.08 ± 1.74	45.16 ± 1.72
Working Mem.	54.12 ± 2.07	51.64 ± 2.13	52.88 ± 1.92	49.16 ± 2.07	47.48 ± 2.13	48.32 ± 1.92
Plan/Organize	48.44 ± 1.74	46.80 ± 1.49	47.62 ± 1.52	45.76 ± 1.74	43.28 ± 1.49	44.52 ± 1.52

Table 2.4. Descriptive Statistics: BRIEF *continued…*

	FEMALES			MALES		
Outcome Measures	**Exam 1**	**Exam 2**	**Average**	**Exam 1**	**Exam 2**	**Average**
BRIEF (T Scores)						
Org. of Materials	48.48 ± 2.04	47.24 ± 1.86	47.86 ± 1.82	46.16 ± 2.04	46.20 ± 1.86	46.18 ± 1.82
Self-Monitor	44.56 ± 1.65	43.44 ± 1.51	44.00 ± 1.43	43.12 ± 1.66	42.84 ± 1.51	42.98 ± 1.43
Global Executive Index	48.40 ± 1.76	45.80 ± 1.61	47.10 ± 1.58	44.12 ± 1.76	42.76 ± 1.61	43.44 ± 1.58

Note: Mean ± SEM for BRIEF are provided. Boldface indicates group difference; ^{x}Indicates significant interaction effect; **Indicates significance difference $p \leq 0.01$; *Indicates significant difference $p \leq 0.05$.

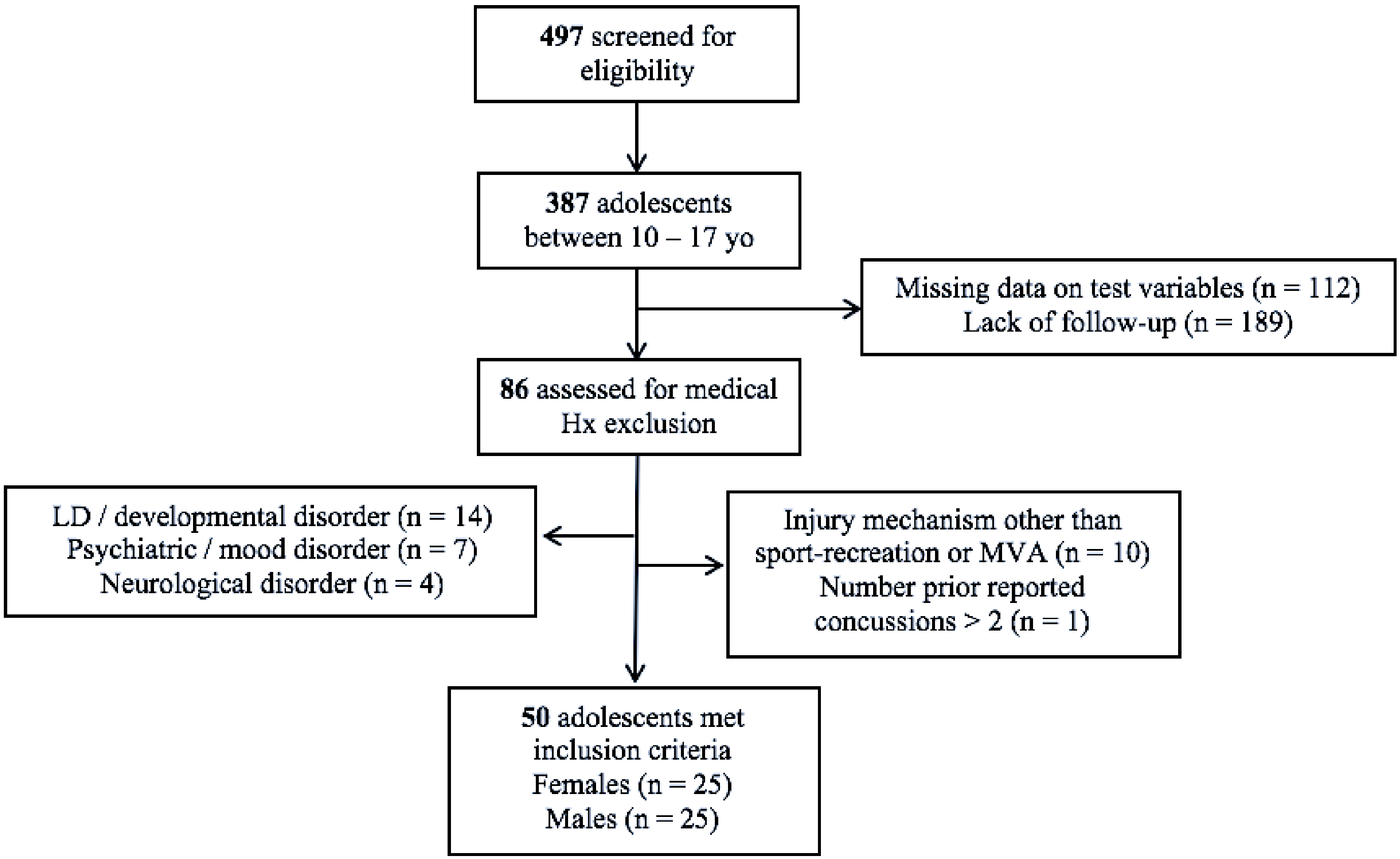

Figure 2.1. Flow Diagram of Sampled Participants

CHAPTER 3

ASSOCIATION BETWEEN CONCUSSION FREQUENCY AND NONFATAL SUICIDAL BEHAVIORS AMONG U.S. HIGH SCHOOL STUDENTS[1]

[1]Jacob J. M. Kay; Colt A. Coffman; Abbas S. Tavakoli; Toni M. Torres-McGehee; Steven P. Broglio; Robert D. Moore. To be submitted to *Med Sci Sports Exerc.* (in preparation).

ABSTRACT

Purpose: To examine potential cumulative effects of concussion on adolescent suicidal behaviors. **Methods:** Data from the 2017 National Youth Risk Behavior Survey (N = 14,765 respondents) were analyzed. Exposure variables included frequency of sport/recreation-related concussion in the previous 12 months (0, 1, 2+). Outcome variables included suicidal ideation, planning, and attempts. Weighted multivariate logistic regressions were run, controlling for age, sex, race/ethnicity, and alcohol use. **Results:** Students that reported ≥1 concussion during the past 12 months were at significantly higher odds of reporting feeling sad or hopeless (AOR = 1.38 [95% CI = 1.22, 1.56]) and engaging suicidal behaviors (AORs 1.34 – 2.40 [95% CIs = 1.14, 1.57 – 1.77, 3.26]) when compared to students that did not report concussion. Students that reported ≥2 concussions were at significantly greater odds of reporting suicidal attempts (AOR = 1.70 [95% CI = 1.19, 2.43]) when compared to students reporting a single concussive event during the past 12 months. Females with single or multiple concussions were at greater odds of reporting increased suicidal behaviors (AORs = 1.68 – 2.64 [95% CIs = 1.37, 2.06 – 1.55, 4.51]); whereas males with history of concussion were only at increased odds of reporting increased suicidal behaviors in the context of multiple concussions (AORs = 1.42 – 4.23 [95% CIs = 1.01, 2.00 – 2.13, 8.41]). **Conclusion:** Findings from the present study suggest adolescents who reported concussion were at increased odds of reporting poor mental health and suicidal behaviors. Moreover, increased number of concussive events was associated with significantly greater odds of reporting suicidal attempts. Healthcare professionals should also be cognizant of potentially different risk behavior profiles between adolescent females and males, particularly in the context of multiple concussions.

INTRODUCTION

Concussion is a form of mild traumatic brain injury induced by biomechanical forces applied directly to the head or transmitted peripherally from the neck or body. Recent epidemiological investigations estimate a rise in concussion incidence from 569.4 per 100,000 in 2006 to 807.9 per 100,000 in 2012.[1] This growing epidemic has been largely attributed to increases in sport- and recreation-related concussion (SRRC) in adolescents. An estimated 1.1 to 1.9 million SRRCs occur each year in the United States (US) among youth.[2] The increase in SRRC incidence between 2001 and 2012 was greatest among adolescents aged 10-19 years (>140%).[3] Adolescence marks a time period of robust neurodevelopment, and sustaining a brain injury during this stage of life may increase the risk of complicated recovery.[4] Thus, understanding the behavioral consequences following concussion in adolescents is of great importance.

Although most adolescents are symptom-free within the first few weeks following injury,[5] accumulating evidence indicates that 20%-30% of individuals experience persistent symptoms that may become a chronic condition lasting several months.[6] Important domains of cognitive function, such as behavioral regulation and emotional control, are often affected following adolescent SRRC.[7] Many theories of mental health agree on the important role played by cognition, but less attention has been paid to psycho-affective outcomes following concussion among adolescents. Research consistently demonstrates higher rates of mood disorders and socio-emotional distress in adolescents with a history of concussion, relative to uninjured counterparts.[8,9] However, additional investigations are needed, particularly given the growing body of evidence linking SRRCs with chronic alterations in mental health and suicidality.[10]

The term *suicidality* refers to suicidal ideation (serious thoughts about taking one's own life), suicide planning, and nonfatal suicide attempts (intentional self-harm). Adolescents who experience suicidal thoughts and behaviors are at significant risk of completing suicide.[11] Suicide is the second leading cause of death among adolescents in the US.[12] Between 2001 and 2017, youth suicide rates increased from 10.7 per 100,000 to 14.0 per 100,000, respectively.[12] In the US, suicides and nonfatal suicide behaviors are estimated through Web-based Injury Statistics Query and Reporting System (WISQARS) maintained by the Centers for Disease Control and Prevention (CDC). According to WISQARS, over 50,000 adolescents aged 10 to 19 years were hospitalized for intentional self-harm, which accounted for nearly $500 million in direct medical costs in 2010 (latest available data).[13] Thus, it is critical to understand the factors that influence suicidality in adolescents.

Researchers have identified a number of moderating factors that may influence risk of suicide, including age, sex, and alcohol use.[14] In addition, an increasing number of studies indicate that concussion history is associated with poor mental health, and may be a significant predictor of suicidal behaviors.[15] To date, few investigations have been conducted in adolescents. This is problematic, given the increased rates of sport participation[16] and suicidal behaviors[12] among this age group. Although sport participation in youth has been shown to protect against suicidality,[17] adolescents that incur SRRC may be at greater risk of experiencing suicidal thoughts, planning, and attempts.[18-20] However, to date, no study has examined the potential influence of multiple concussions on suicidal behaviors in adolescents. Thus, our current understanding of the influence of concussion on adolescent suicidality remains incomplete and tentative.

Accordingly, the purpose of our investigation was to examine the association between concussion frequency and nonfatal suicidal behaviors in a nationally representative sample of adolescents using data from the 2017 National Youth Risk Behavior Survey (YRBS). We hypothesized adolescents reporting SRRC in the last 12 months would exhibit an increased risk of reporting sadness/hopelessness, suicidal ideation, planning, and attempts when compared to adolescents with no history of concussion. When factoring for number of SRRCs in the previous 12 months, we further hypothesized greatest risk among adolescents reporting two or more injuries.

METHODS

Study Design

Data from the 2017 YRBS were analyzed using a retrospective cross-sectional design. The YRBS is biennial a school-based survey, approved by an institutional review board at the Centers of Disease Control and Prevention (CDC) and implemented by the CDC to monitor the prevalence of priority health risk behaviors among youth. In 2017, a three-stage cluster sampling design was used to produce a nationally representative sample of public and private school students in grades 9-12. Following local procedures to obtain parental permission, student respondents voluntarily and anonymously provided their information on computer-scannable answer sheets. Respondent records are weighted to adjust for nonresponse and oversampling of certain demographics (grades, sex, racial/ethnicity). Additional details regarding YRBS sampling methodology can be found elsewhere.[21]

Study Sample

The response rate for the 2017 YRBSS was 75% for schools and 81% for students, resulting in a 60% overall response rate. A total sample of 14,765 respondent questionnaires were available for analysis. As a result of missing data (n = 5889) for variables in our analysis, including missing data for concussion history (n = 628), sadness/hopelessness (n = 198), suicidal ideation (n = 62), suicidal planning (n = 37), suicide attempts (n = 3539), injurious suicide attempts (n = 70) , and other variables of interest (i.e., covariates; n = 1355), a final sample of 8876 students were included in the study, which comprised 60.1% of the total sample.

Measures

The YRBS monitors several major categories of health-related behaviors that contribute to leading causes of disability and death among youth, and provides valid and reliable measures of these important health-related behaviors among this cohort.[22,23] For the purposes of the present study, survey measures of sport/recreation-related concussive injuries, mental health, suicidal risk behaviors, and other variables known to influence health-related behaviors among youth[24] were examined. A detailed description of included measures is provided below:

Exposure variable: concussion frequency. Concussion exposure was a new variable included in the 2017 national YRBS. The question included in the survey was specific to the respondent's participation in sport or recreational activities. Students were prompted on the following definition of SRRC: *A concussion is when a blow or jolt to the head causes problems such as headaches, dizziness, being dazed or confused, difficulty remembering or concentrating, vomiting, blurred vision, or being knocked out.* In the

following question, students were asked: *During the past 12 months, how many times did you have a concussion from playing a sport or being physically active?* In addition, students were instructed to report their number of concussions (e.g., *0 times*, *1 time*, *2 times*, *3 times*, or *4 or more times*).

Outcome variables: mental health and suicidality. The outcome variables selected for this study included five questions from the 2017 national YRBSS regarding mental health and suicidal behaviors. Students were prompted with the following description of suicidality: *Sometimes people feel so depressed about the future that they may consider suicide that is, taking action to end their own life.* Self-reported indicators of mental health and suicidality included: 1) Sadness / hopelessness (i.e., *During the past 12 months, did you ever feel so sad or hopeless almost every day for two weeks or more in a row that you stopped doing some usual activities?* Response options: *Yes* or *No*); 2) Suicidal ideation (i.e., D*uring the past 12 months, did you ever seriously consider attempting suicide?* Response options: *Yes* or *No*); 3) Suicidal planning (i.e., *During the past 12 months, did you make a plan about how you would attempt suicide?* Response options: *Yes* or *No*); 4) Suicidal attempt (i.e., *During the past 12 months, how many times did you actually attempt suicide?* Response options: *0 times*, *1 time*, *2 or 3 times*, *4 or 5 times*, or *6 or more times*); 5) Injurious suicidal attempt (i.e., *If you attempted suicide during the past 12 months, did any attempt result in an injury, poisoning, or overdose that had to be treated by a doctor or nurse?* Response options*: I did not attempt suicide during the past 12 months*, *Yes*, or *No*). Responses to all suicidality questions were bifurcated as “Yes” or “No”. Categorization of response variables can be found in Table 3.1.

Covariate measures: The covariates selected for this study included questions to identify respondents' 1) biological sex (i.e., *What is your sex?* Response options: *Female or Male*); 2) age (i.e., *How old are you?* Response options: *12 years old or younger, 13 years old, 14 years old, 15 years old, 16 years old, 17 years old, 18 years old or older*); 3) race/ethnicity (i.e., *What is your race?* Response options: *American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White*; i.e., *Are you Hispanic or Latino?* Response options: *Yes or No*); and current alcohol use (i.e., *During the past 30 days, on how many days did you have at least one drink of alcohol?* Response options: *0 days, 1 or 2 days, 3 to 5 days, 6 to 9 days, 10 to 19 days, 20 to 29 days, All 30 days*). Responses to age, race/ethnicity, and alcohol use were recategorized to ensure adequate statistical power and approach, see Table 3.1.

Data Analysis

All hypothesis testing was performed on weighted data using Statistical Analysis System Version 9.4 (SAS Institute; Cary, NC). Descriptive statistics were conducted to examine frequency of specific demographic characteristics (i.e., age, sex, and race/ethnicity) known to be associated with suicidal behaviors among youth.[24] Alcohol use has also shown to be associated with suicidal behaviors in adolescents.[24] Therefore, predictive demographic factors and current alcohol use were included as covariates in our analyses. Inferential statistics included chi-square statistics to examine bivariate association categorical outcome and predictors. GENMOD procedure in SAS was used to examine the association between concussion history and 1) sadness / hopelessness; 2) suicidal ideation; 3) suicidal planning; 4) suicidal attempt; and 5) injurious suicidal attempt. In addition, adjusted odds ratios (AOR) with 95 % Confidence Intervals (CI) were

calculated. Weighted Generalized Linear Models, including logistic and probit models, were used to examine binary response data (e.g., *yes* versus *no*) for each of the five associations of concussion history and suicidality. Additional Generalized Linear Models, including log-linear and Poisson regression models, were used to examine the association between concussion frequency – including three levels: no SRRC history (*0 times*; reference), one SRRC (*1 time*), and multiple SRRCs (*2 or more times*) – and suicidality. All statistical models were conducted to adjust for the covariates of age, sex, race/ethnicity, and alcohol use. For each model, an interaction term for sex was included to examine potential differences between females and males. An *a priori* alpha level of 0.05 was set for all analyses.

RESULTS

Overall, 52.5% (n = 4,712) of U.S. high school students identified as female and 47.5% (n = 4,164) identified as male. Approximately 58.0% were white, non-Hispanic, 10.1% were black, non-Hispanic, 21.5% were Hispanic/Latino, and 10.4% were other race/ethnicity; 12.0% were 14 years old or younger, 24.8% were 15 years old, 25.3% were 16 years old, 24.6% were 17 years old, and 13.3% were 18 years old or older. Roughly 30% of U.S. high school students reported alcohol use within the past 30 days (Table 3.2).

Among respondents, 13.4% (n = 1156) reported ≥1 SRRC during the past 12 months. A greater proportion of male students reported ≥1 SRRC during the past 12 months than female students (15.1% vs 11.8%; Cramer's *V* = 0.048) (Table 3.2). A greater proportion of female students reported feeling sad or hopeless (40.1% vs 20.9%; Cramer's *V* = 0.207), suicidal ideation (21.7% vs 11.7%; Cramer's *V* = 0.134), suicidal planning (16.8% vs 8.9%; Cramer's *V* = 0.118), attempting suicide (8.9% vs 4.1%; Cramer's *V* =

0.096), and being injured from an attempted suicide (3.1% vs 1.1%; Cramer's $V = 0.068$) in the past 12 months (Table 3.3).

Among U.S. high school students, those that reported ≥1 SRRC during the past 12 months were at significantly greater odds than those that did not report SRRC to report feeling sad or hopeless (AOR = 1.38 [95% CI = 1.22, 1.56]), suicidal ideation (AOR = 1.40 [95% CI = 1.21, 1.61]), suicidal planning (AOR = 1.34 [95% CI = 1.14, 1.57]), attempting suicide (AOR = 1.69 [95% CI = 1.39, 2.06]), and being injured from an attempted suicide (AOR = 2.40 [95% CI = 1.77, 3.26]) in the past 12 months. Students that reported ≥2 SRRCs did not significantly differ in odds of reporting suicidal behaviors than those who reported a single SRRC event during the past 12 months, with the exception of suicidal attempts (AOR = 1.70 [95% CI = 1.19, 2.43]).

The association between frequency of SRRC and suicidal behavior in the past 12 months differed significantly by sex. Among female students, those that reported a single SRRC during the past 12 months were at significantly higher odds to report suicidal behaviors; felt sad or hopeless (AOR = 1.68 [95% CI = 1.37, 2.06]), suicidal ideation (AOR = 1.70 [95% CI = 1.37, 2.12]), suicidal planning (AOR = 1.72 [95% CI = 1.36, 2.18]), attempting suicide (AOR = 1.64 [95% CI = 1.21, 2.22]) and being injured from an attempted suicide (AOR = 2.45 [95% CI = 1.60, 3.76]) than those that did not report SRRC, but the strength of this association did not significantly increase with multiple (≥2) SRRCs (Table 3.4, Table 3.5). Among male students, odds of reporting suicidal behaviors did not significantly increase with a single concussion; however, significantly greater odds of reporting suicidal behaviors were seen in males that reported multiple SRRCs in the past 12 months (Table 3.4, Table 3.5). Males that reported ≥2 SRRCs during the past 12 months

were at significantly greater odds of reporting feeling sad or hopeless (AOR = 1.58 [95% CI = 1.21, 2.08]), suicidal ideation (AOR = 1.42 [95% CI = 1.01-2.00]), suicidal attempt (AOR = 2.78 [95% CI = 1.82, 4.26]), and being injured from an attempted suicide (AOR = 4.23 [95% CI = 2.13, 8.41]) than males that did not report SRRC during the past 12 months (Table 3.4, Table 3.5).

Discussion

The present study contributes to a growing body of literature on the association between concussion and suicidal behaviors among adolescents. To our knowledge, this study is the first to examine the cumulative effects of concussion on suicidal behaviors in a nationally representative sample of U.S. high school students. Results from this study not only corroborate literature suggesting that high school students who experienced recent SRRC are at greater odds of reporting suicidal behaviors (ideation, planning, attempts) when compared to students that did not experience SRRC,[18-20] but suggest that odds of reporting such risk behaviors (specifically, suicide attempts) may be compounded by increased SRRC exposure. Additionally, the association between concussion history and reporting of suicidal behaviors may differ between male and female adolescents.

Our results demonstrate similar estimates to Yang et al.[18] that also utilized YRBS data to examine the association between concussion and suicidal behaviors in a smaller, regional sample of adolescent high school students. Compared to our study, Yang and colleagues[18] observed similar odds of reporting feeling sad/hopeless (AOR=1.48), suicidal ideation (AOR=1.26), planning (AOR=1.27), and attempts (AOR=3.10) among adolescents with concussion history. Our findings also corroborate those of Wangnoo et al.[19] whom observed significantly greater odds of reporting feeling sadness/hopeless

(AOR=1.87), suicidal ideation (AOR=1.95), planning (AOR=1.97), and attempts (AOR=2.31) among adolescents with concussion history.

Importantly, our study builds upon prior literature by examining the association between adolescent concussion and suicidal behaviors, stratified by number of self-reported SRRCs during the preceding 12 months of the survey. Results indicate that odds of reporting suicidal behavior may increase along with number of injuries in the same survey year, suggesting a potentially cumulative effect of concussion on adolescent suicidal behavior. More specifically, high school students that reported two or more concussive injuries were at significantly greater odds (AOR = 1.70) of reporting suicidal attempt, when compared to adolescents that reported a single concussive event within the preceding 12 months of the survey. Though this is the first study to demonstrate the cumulative effect of concussion on suicidal behavior among adolescents, our findings corroborate research that has shown history of multiple concussions and shorter duration of recovery prior to subsequent injury is associated with potentially longer and more complicated (decreased mental health) recovery profiles among adolescents.[25,26]

Findings from the present study also illuminate potential differences between male and female adolescents. During the 12 months preceding the survey, a greater proportion of males experienced concussion (15.1%) when compared to females (11.8%). While these findings corroborate prior YRBS-based research,[18-20] it is vital to note these findings contrast other important literature which demonstrates greater incidence of concussion among females.[27-29] This inconsistency is likely due to asynchrony in study design; in which the YRBS more broadly examines concussion across sport and recreational activities, whereas latter aforementioned studies have been better able to control for

specific sport and recreational activity. However, findings from the present study are more consistent with current literature regarding sex differences in reporting mental health and suicidal behaviors, with adolescent females reporting lower subjective well-being and greater concerns about mental health issues when compared to adolescent males.[30-34] In the present study, a greater proportion of females reported feeling sad or hopeless (40.1% vs 20.9%), as well as suicidal ideation (21.7% vs 11.7%), planning (16.8% vs 8.9%), and attempts (8.9% vs 4.1%), when compared to males during the preceding 12 months of the survey.

To date, only one prior study has specifically aimed to examine sex differences in the association between concussion history and suicidal behaviors.[20] In contrast to the present study, no differences between females and males were observed when factoring concussion history (irrespective of SRRC frequency). Furthermore, our findings suggest adolescent females and males may exhibit differing risk behavior profiles in the context of multiple concussion. More specifically, increased odds of reporting suicidal behaviors were similar across females that reported a single or multiple concussion, when compared to females that reported no concussion history during the preceding 12 months of the survey. In contrast, odds of reporting suicidal behaviors did not increase significantly among males that reported a single concussive event but increased significantly among males that reported multiple concussions during the preceding 12 months of the survey. Though these findings may reflect trends in broader adolescent risk behavior literature (females more likely to report suicidal behaviors),[35] this evidence does not fully explain sex differences observed in the current study. Current research on concussion and adolescent mental health indicates that females may be more prone to disturbances in

psychological well-being following concussion when compared to males.[36,37] In addition, other investigations that have used more objective psychophysiological measures (e.g., electroencephalography) have demonstrated blunted emotional-processing in males, particularly in the context of multiple concussions.[38,39] While mechanisms for observed sex-based differences remain largely unknown, this study provides the first evidence toward potential sex differences across effects of multiple concussion on adolescent suicidal behavior.

Limitations

Though the present study strengthens extant knowledge regarding the association between concussion and adolescent suicidality, several limitations should be considered. Foremost, due to YRBSS cross-sectional nature, we were unable to establish the temporal sequence of concussive events and adolescent risk behaviors during the 12 months of the survey. This limitation prevents us from inferring causal relation between concussion and adolescent suicidality. Second, despite emphasis of anonymity toward respondents, YRBSS data is self-reported and unable to account for under- nor over-reporting of concussive events and risk behaviors. For example, students may exhibit tendency to answer in a socially desirable manner (i.e., they may report fewer concussive events or suicidal behaviors than actually experienced). Third, the YRBSS sampling methodology only accounts for youth who attend school, therefore the present study does not represent all youth in this age group (sample bias). Additionally, though a strength of our study includes the evaluation of several mental health measures, our investigation lacks clinical diagnoses and validated psychological inventories – increasing the potential for response

bias. Lastly, it remains unknown whether sex-based differences observed in this study are due to sociocultural or other biomechanical factors.

CONCLUSION

In conclusion, we found adolescents who reported concussion were at increased odds of reporting poor mental health and suicidal behaviors; including feelings of sadness/hopelessness, as well as suicidal ideation, planning, and attempts during the preceding 12 months of the survey. More importantly, increasing number of concussions incurred in the previous 12 months may be associated with greater risk of suicidal attempts. In addition, healthcare professionals should be aware of potentially different risk behavior profiles between adolescent females and males, particularly in the context of multiple concussions. Future investigations are necessary to better understand cumulative effects of concussion on adolescent mental health, and toward development of earlier prevention strategies aimed to mitigate the link between concussive injury and potentially fatal risk behaviors.

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Table 3.1. Categorization of Variables- National Youth Risk Behavior Surveillance System, 2017

Variable	Questionnaire Item / Response Options		Statistical Coding
Sport- or recreation-related concussion	*The next question asks about concussions. A concussion is when a blow or jolt to the head causes problems such as headaches, dizziness, being dazed or confused, difficulty remembering or concentrating, vomiting, blurred vision, or being knocked out.* *During the past 12 months, how many times did you have a concussion from playing a sport or being physically active?*		Yes (≥1) vs. No (0) times Frequency of concussion: 2 or more times 1 time 0 times
Suicide Attempt(s)	*During the past 12 months, how many times did you actually attempt suicide?*		Yes (≥1) vs. No (0) times
Age	*How old are you?*	*12 years old or younger* *13 years old* *14 years old* *15 years old* *16 years old* *17 years old* *18 years old or older*	14 years old or younger 15 years old 16 years old 17 years old 18 years old or older
Race/ Ethnicity	*Are you Hispanic or Latino?* *What is your race?*	*Yes* *No* *American Indian or Alaska Native* *Asian* *Black or African American* *Native Hawaiian or Other Pacific Islander* *White*	White (non-Hispanic) Black (non-Hispanic) Hispanic/Latino Other Race/Ethnicity
Alcohol Use	*During the past 30 days, on how many days did you have at least one drink of alcohol?*		Yes (≥1) vs. No (0) days

Table 3.2. Weighted Prevalence of Demographic Characteristics Among U.S. High School Students by Frequency of SRRC

Variable	*n* (wt%)	Frequency of SRRC[a] 0	1	≥2	χ^2
Total	8,876 (100)	7,720 (86.6)	726 (8.6)	430 (4.8)	
Sex					
Male	4,164 (47.5)	3,566 (84.9)	373 (9.7)	225 (5.4)	**24.9****
Female	4,712 (52.5)	4,154 (88.2)	353 (7.5)	205 (4.3)	
Age, years					
≤14	1,076 (12.0)	936 (86.7)	96 (9.3)	44 (4.0)	**25.3***
15	2,108 (24.8)	1,820 (85.9)	192 (9.7)	96 (4.4)	
16	2,247 (25.3)	1,950 (87.1)	178 (7.9)	119 (5.0)	
17	2,258 (24.6)	1,953 (85.6)	191 (9.1)	114 (5.3)	
≥18	1,187 (13.3)	1,061 (89.0)	69 (5.8)	57 (5.2)	
Race/Ethnicity					
White	4,184 (58.0)	3,618 (86.4)	396 (9.4)	170 (4.2)	**29.9****
Black	1,261 (10.1)	1,103 (86.9)	78 (6.2)	80 (6.9)	
Hispanic or Latino	2,303 (21.5)	2,019 (86.8)	166 (8.1)	118 (5.1)	
All Other	1,128 (10.4)	980 (87.4)	86 (7.1)	62 (5.5)	
Alcohol Use[b]					
Yes	2,631 (30.5)	2,154 (81.1)	297 (11.6)	180 (7.3)	**126.6****
No	6,245 (69.5)	5,566 (89.1)	429 (7.2)	250 (3.7)	

Note: Data are reported as n (weighted %). Boldface indicates statistical significance (*p<0.01, **p<0.001). [a]During the 12 months prior to the survey; [b]During the 30 days prior to the survey.

Table 3.3. Weighted Prevalence of Demographic Characteristics Among U.S. High School Students by Suicidal Behaviors

Variable	Sadness/ Hopelessness[b]	Suicidal Ideation[c]	Suicidal Planning[d]	Suicide Attempt(s)[e]	Injurious Suicide Attempt(s)[f]
Total	2,804 (31.0)	1,532 (17.0)	1,187 (13.0)	615 (6.6)	204 (2.1)
Sex					
Male	883 (20.9)	490 (11.7)	382 (8.9)	117 (4.1)	46 (1.1)
Female	**1921 (40.1)****	**1042 (21.7)****	**805 (16.8)****	**438 (8.9)****	**158 (3.1)****
Age, years					
≤14	326 (31.9)	191 (17.0)	152 (12.8)	**96 (9.7)****	36 (3.2)
15	636 (29.5)	349 (16.2)	264 (12.4)	146 (7.0)	49 (2.0)
16	714 (31.5)	384 (16.6)	296 (13.0)	155 (6.8)	41 (2.2)
17	737 (31.0)	406 (17.2)	314 (13.3)	143 (5.0)	49 (1.7)
≥18	391 (32.2)	202 (18.5)	161 (14.0)	75 (5.5)	29 (2.0)
Race/Ethnicity					
White non-Hispanic	**1244 (29.4)****	**730 (16.7)***	**535 (12.2)****	**251 (5.8)***	**75 (1.8)****
Black non-Hispanic	376 (29.7)	192 (15.2)	155 (12.0)	104 (7.7)	37 (3.1)
Hispanic or Latino	799 (34.1)	387 (16.6)	309 (13.8)	171 (7.8)	61 (2.4)
All Other	385 (34.9)	223 (20.8)	188 (17.3)	89 (7.6)	31 (2.7)
Current Alcohol Use[a]					
Yes	**1133 (42.0)****	**636 (23.3)****	**519 (19.4)****	**299 (10.2)****	**118 (4.1)****
No	1671 (26.1)	896 (14.2)	668 (10.2)	316 (5.0)	86 (1.3)

Note: Data are reported as n (weighted %). Boldface indicates statistical significance (*p<0.01, **p<0.001). [a]During the 30 days prior to the survey; [b]Answered yes to *During the past 12 months, did you ever feel so sad or hopeless almost every day for two weeks…?*; [c]Answered yes to *During the past 12 months, did you ever seriously consider attempting suicide?*; [d]Answered yes to *During the past 12 months, did you make a plan about how you would attempt suicide?*; [e]Attempted suicide 1 or more times during the past 12 months; [f]Answered yes to *If you attempted suicide during the past 12 months, did any attempt result in an injury…that had to be treated by a doctor or nurse?*

Table 3.4. Adjusted Odds of Suicidal Behaviors by SRRC Exposure Among U.S. High School Students by Sex

	Males		Females	
SRRC[a]	%	AOR (95% CI)	%	AOR (95% CI)
Sadness/Hopelessness[b]				
One or more times				
No	20.1	1.00 (ref)	38.7	1.00 (ref)
Yes	25.5	**1.22[e] (1.02, 1.47)***	51.0	**1.51[e] (1.28, 1.79)*****
Interaction	Likelihood ratio test (χ^2 = 2.71, df = 1, p = 0.1000)			
Frequency of SRRC				
0	20.1	1.00 (ref)	38.7	1.00 (ref)
1	22.0	1.04 (0.82, 1.31)	53.6	**1.68[e] (1.37, 2.06)*****
≥2	31.9	**1.58[e,f] (1.21, 2.08)*****	46.3	1.26 (0.97, 1.65)
Interaction	Likelihood ratio test (χ^2 = 10.72, df = 2, p = 0.0047)			
Suicidal Ideation[c]				
One or more times				
No	11.3	1.00 (ref)	20.5	1.00 (ref)
Yes	13.5	1.14 (0.90, 1.44)	30.1	**1.61[e] (1.35, 1.94)*****
Interaction	Likelihood ratio test (χ^2 = 6.30, df = 1, p = 0.0121)			
Frequency of SRRC				
0	11.3	1.00 (ref)	20.5	1.00 (ref)
1	11.8	0.98 (0.73, 1.32)	32.2	**1.70[e] (1.37, 2.12)*****
≥2	16.7	**1.42[e] (1.01, 2.00)***	28.8	**1.47[e] (1.10, 1.97)***
Interaction	Likelihood ratio test (χ^2 = 9.03, df = 2, p = 0.0110)			
Suicidal Planning[d]				
One or more time				
No	8.8	1.00 (ref)	15.6	1.00 (ref)
Yes	9.0	0.93 (0.70, 1.22)	25.4	**1.67[e] (1.38, 2.04)*****
Interaction	Likelihood ratio test (χ^2 = 13.97, df = 1, p = 0.0002)			
Frequency of SRRC				
0	8.8	1.00 (ref)	15.6	1.00 (ref)
1	7.0	0.73 (0.51, 1.06)	26.0	**1.72[e] (1.36, 2.18)*****
≥2	12.4	1.28 (0.87, 1.88)	24.5	**1.60[e] (1.17, 2.19)****
Interaction	Likelihood ratio test (χ^2 = 17.31, df = 2, p = 0.0002)			

Note: AORs adjusted for age, race/ethnicity, and alcohol use. Boldface indicates statistical significance (*p<0.05, **p<0.01, ***p<0.001). [a]During the past 12 months; Answered 'yes' to *During the past 12 months,…*[b]*did you ever feel so sad or hopeless almost every day for two weeks or more in a row?*; [c]*did you ever seriously consider attempting suicide?*; [d]*did you make a plan about how you would attempt suicide?*; [e]Significantly different than students who did not report SRRC during previous 12 months.; [f]Significantly different than students who had one SRRC during the 12 months prior to the survey.

Table 3.5. Adjusted Odds of Suicide Attempt(s) by SRRC Exposure Among U.S. High School Students by Sex

Suicide Attempt(s)[b]				
	Males		**Females**	
SRRC[a]	**%**	**AOR (95% CI)**	**%**	**AOR (95% CI)**
One or more times				
No	3.7	1.00 (ref)	8.0	1.00 (ref)
Yes	6.2	**1.56[d] (1.11, 2.19)***	14.9	**1.79[d] (1.40, 2.28)*****
Interaction	Likelihood ratio test ($\chi^2 = 0.68$, df = 1, p = 0.4105)			
Frequency of SRRC				
0	3.7	1.00 (ref)	8.0	1.00 (ref)
1	3.5	0.89 (0.54, 1.49)	13.9	**1.64[d] (1.21, 2.22)****
≥2	10.8	**2.78[d,e] (1.82, 4.26)*****	16.6	**2.06[d] (1.43, 2.98)*****
Interaction	Likelihood ratio test ($\chi^2 = 5.75$, df = 2, p = 0.0564)			
Injurious Suicide Attempt(s)[c]				
One or more times				
No	0.9	1.00 (ref)	2.5	1.00 (ref)
Yes	2.2	**2.33[d] (1.29, 4.22)****	7.1	**2.52[d] (1.76, 3.60)*****
Interaction	Likelihood ratio test ($\chi^2 = 0.34$, df = 1, p = 0.5610)			
Frequency of SRRC				
0	0.9	1.00 (ref)	2.5	1.00 (ref)
1	1.0	1.13 (0.43, 2.94)	6.9	**2.45[d] (1.60, 3.76)*****
≥2	4.4	**4.23[d,e] (2.13, 8.41)*****	7.4	**2.65[d] (1.55, 4.51)*****
Interaction	Likelihood ratio test ($\chi^2 = 4.47$, df = 2, p = 0.1608)			

Note: AORs adjusted for age, race/ethnicity, and alcohol use. Boldface indicates statistical significance (*$p<0.05$, **$p<0.01$, ***$p<0.001$). [a]During the past 12 months; [b]Attempted suicide one or more times during the past 12 months; [c]Answered yes to *If you attempted suicide during the past 12 months, did any attempt result in an injury, poisoning, or overdose that had to be treated by a doctor or nurse?*; [d]Significantly different than students who did have an SRRC during the 12 months prior to the survey; [e]Significantly different than students who had one SRRC during the 12 months prior to the survey.

CHAPTER 4

THE INFLUENCE OF HORMONAL CONTRACEPTIVES ON CONCUSSION OUTCOMES IN COLLEGIATE ATHLETES[1]

[1]Jacob J. M. Kay; Andrew Lapointe; Christopher Giza; Dorothy Harris; Thomas McAllister; Michael McCrea; Steven Broglio; Robert D. Moore; & CARE Consortium Investigators. Submitted to *J Neurotrauma* (under review).

ABSTRACT

The *hormonal withdrawal hypothesis* suggests that reduction of progesterone in women following concussion may lead to worse outcomes. Thus, female athletes using hormonal contraceptives (HCs) may exhibit better recovery profiles as their hormone levels are artificially stabilized. The purpose of our investigation was to longitudinally examine the relation between HC use and concussion outcomes in female student-athletes. Females participating in the CARE Consortium were assessed at preseason baseline, 24-48 hours post-concussion, and when cleared for return-to-play (RTP). To provide an index of recovery trajectory, days between injury and return-to-play were calculated. Symptoms (SCAT) and cognitive functioning (SAC, ImPACT) were measured at each timepoint. Females who sustained a concussion were separated into those who were (n = 50) and were not (n = 50) using HCs. The average number of days between injury and RTP did not differ between groups. Decomposition of group X time interactions revealed no significant differences in symptoms or cognitive functioning at baseline or any post-injury timepoint. However, across all timepoints, females using HCs demonstrated higher average SAC concentration (p = .04), ImPACT verbal memory (p = .03) and ImPACT cognitive efficiency (p = .01) scores than females not using HCs. No differences in change scores (post-injury relative to baseline) were observed between groups on any measure. The current results indicate that HCs do not influence recovery trajectory, symptoms, nor cognitive functioning following concussion. However, our findings suggest HCs may be associated with a general cognitive benefit, irrespective of injury status.

INTRODUCTION

Concussive injuries are a serious public health concern, with increasing incidence leading the Centers for Disease Control and Prevention to call these injuries a silent epidemic.[1-3] Although most individuals are symptom-free within a few weeks of injury,[4] a significant portion of individuals will experience persistent physical, cognitive, and emotional symptoms[5] – which can negatively affect academic and vocational performance, as well as overall effective functioning.[4] Therefore, understanding the factors which moderate concussion outcomes is of critical importance.

Research indicates several factors are associated with poorer injury outcomes, including: age,[6,7] concussion history,[8,9] pre-existing mental health conditions,[10-12] and neurodevelopmental disorders.[12,13] In addition, an increasing number of studies indicate that biological sex is associated with a higher risk of concussion[14-16] and may be a significant moderator of post-concussive symptoms and recovery trajectory.[17-26] Researchers and clinicians have posited many reasons for potential differences in concussion sequelae between males and females. These include cultural factors that lead to differences in symptom reporting, differing cognitive strategies, sex-related comorbidities (e.g., migraine, depression) as well as biomechanical differences in the neck and head.[23-26] However, one factor gaining attention is the role of sex-based steroid hormones.[27]

Sex-based steroid hormones refer to the principal glandular secretions of males and females such as progesterone, estrogen, and testosterone.[28] In addition to regulating sexual functions, these hormones modulate neuronal structure, function, and plasticity in males and females differently.[28] With respect to brain injury, multiple studies indicate that

females who experience a significant reduction of progesterone following moderate-to-severe brain injury exhibit poorer outcomes than females with more stable (natural or artificial) hormone levels.[29,30] Translational research also demonstrates a strong link between progesterone and brain injury outcomes.[31-35] These findings have led researchers to formulate the *hormonal withdrawal hypothesis*, which suggests that the stability of hormones following brain injury may influence recovery in females.[36]

Interestingly, results from recent randomized-controlled trials (RCTs) have demonstrated little-to-no treatment effect with early administration of progesterone following moderate-to-severe brain injury.[37-39] Although current RCTs have stratified by sex, samples were predominantly male (70%+), and differences between sexes were not statistically analyzed.[40] Other shortcomings include variance in treatment and evaluation schedules and limited stratification by severity of injury – perhaps due to less than optimal psychometric properties of primary outcome measures.[41] Despite these shortcomings, there is some evidence to suggest progesterone may exhibit greater neuroprotective effects in less severe brain trauma.[37]

Specific to concussion, Wunderle and colleagues[36] sought to evaluate the *hormonal withdrawal hypothesis* by cross-sectionally examining the influence of menstrual phase on functional outcomes following concussion. These researchers observed that females injured in the luteal phase of their menstrual cycle (when progesterone concentration is highest and potential reduction is greatest) reported poorer quality of life and greater symptoms compared to females injured in the follicular phase (when progesterone concentration is low and potential reduction is lowest), and females using hormonal contraceptives (stable progesterone level through each phase). In addition, the only study

to examine the influence of hormonal contraceptives on sport-related concussion recovery observed that females using hormonal contraceptives reported significantly lower peak symptom severity, relative to females that did not use hormonal contraceptives.[42] Thus, hormonal stability may be neuroprotective for concussive brain injuries.

Although informative, prior studies examining the relation between sex hormones/contraceptives and concussion outcomes used cross-sectional designs, small group sizes, and subjective outcome measures (e.g., clinical symptoms and self-reported quality of life). As such, our understanding of the relationship between sex hormones and concussion outcomes is both incomplete and tentative. Accordingly, the purpose of the current investigation was to longitudinally examine the relation between self-reported hormonal contraceptive use and concussion outcomes by evaluating recovery trajectory, self-reported symptoms, and objective measures of cognitive function. By evaluating female athletes on and off of hormonal contraceptives at baseline and multiple timepoints following concussion, we aimed to examine the influence of hormonal contraceptives on clinical recovery following concussion. We hypothesized that female athletes using hormonal contraceptives would exhibit shorter time between injury and when medically cleared for unrestricted return to play, fewer and less severe symptoms, and smaller post-injury deficits in cognitive functioning when compared to females not using hormonal contraceptives.

METHODS

Sampling Procedures and Participants

Between 2014 and 2017, the Concussion Assessment, Research, and Education (CARE) Consortium conducted a 30-site investigation on the 6-month natural history of

concussive injuries. All female National Collegiate Athletic Association (NCAA) student-athletes at participating academic institutions were eligible for the study following the provision of written informed consent. The Institutional Review Board at each participating site and the Human Protection Research Office (HRPO) approved all research activities. A detailed description of CARE methods can be found elsewhere.[43]

Females who completed baseline, 24-48 hours post-concussion, and return-to-play (RTP) assessments were screened for inclusion (Figure 4.1). Exclusion criteria included having a self-reported history of learning disability or developmental disorder, psychiatric or mood disorder, and neurological disorder other than concussion (including migraines). Additionally, females reporting the use of intrauterine devices were excluded from this study, due to localized hormonal effects. Groups were determined by self-reported medication use recorded at baseline. In total, 50 females using hormonal contraceptives (HC) were included in the current study. HC users (HC+) were matched to 50 non-HC users (HC-) on key demographic and injury information, including: age, body mass index, race/ethnicity, sport contact level, concussion history, and current injury characteristics (e.g., loss of consciousness, amnesia).

Assessment Procedures and Measures

Baseline assessments were completed prior to the beginning of the sport season. Athletes were re-assessed 24-48 hours post-concussion, and again when cleared for RTP. Clinical assessments included measures of concussion symptoms (Sport Concussion Assessment Tool – 3rd Edition) and tests of cognitive functioning (Standardized Assessment of Concussion; Immediate Post-Concussion Assessment and Cognitive Testing). Assessment measures are briefly described below:

The *Sport Concussion Assessment Tool – 3rd Edition (SCAT3)* includes a 22-item self-report inventory designed to evaluate the total number and severity of common concussion symptoms (headache, nausea, dizziness) on a 7-point Likert scale, (0 = none) to (6 = severe).[44]

The *Standardized Assessment of Concussion (SAC)* is an observer-rated inventory designed to evaluate cognitive function by assessing orientation, immediate memory, concentration, and delayed recall performance.[45,46]

The *Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)* is a 25-minute computerized cognitive test battery that evaluates working memory, attention, speed of information processing, and multi-tasking performance.[47]

Statistical Analyses

Data were analyzed using the Statistical Package for the Social Sciences Version 26 (SPSS; IBM, Armonk, NY). Independent samples t-tests were used for continuous data, and χ^2 tests were used for categorical data to examine group demographics (age, race, body mass index, sport contact level) and injury characteristics (concussion history, post-traumatic amnesia). To examine recovery trajectories, independent samples t-tests were used to evaluate group differences in the average number of days between injury and when medically cleared for RTP. Concussion outcome variables from the SAC, SCAT-3, and ImPACT test were examined via 2 (group: HC+, HC-) x 3 (time: baseline, 24-48 hours, RTP) repeated measures ANCOVAs. Due to heterogenous nature of concussive injuries and known moderating effects of concussion history on subsequent injury outcome,[48] number of prior concussions was imputed as covariate in our analyses. Each continuous outcome variable was assessed for normality via the Kolmogorov-Smirnov test,

and Mauchly's sphericity tests were employed to evaluate violations in the assumption of homogeneity of variance. In the event a violation occurred, a Greenhouse–Geisser correction for sphericity was applied. Post-hoc comparisons were performed to identify the source of the interactions by means of independent samples t-tests with Bonferroni corrections. To evaluate the potential influence of baseline group differences on recovery profiles, change scores were calculated for each outcome measure and analyzed via 2 (group: HC+, HC-) x 2 (change score: baseline-to-24-48 hours, baseline-to-RTP) repeated measures ANCOVAs, again with number of prior concussions used as the covariate. For all significant effects, partial eta squared (ηp^2) was calculated to estimate effect size (.01 = small; .06 = medium; 0.14 = large). An *a priori* alpha level of 0.05 was set for all analyses.

RESULTS

Neither demographics nor acute injury characteristics differed between HC+ and HC- groups (p's ≥ 0.29), see Table 4.1. The racial and ethnic composition of the current sample was similar to that of all NCAA Division I-III athletes across sports for academic years between 2014-2017.[41] Among all HC+ females, forty-six reported combined progesterone/estrogen oral contraceptive pill (OCP), three reported NuvaRing (releases similar estrogen/progesterone levels into the bloodstream as OCP),[49] and one reported progestin implant. Regarding OCP type, forty (~87%) were monophasic and six (~13%) were triphasic. The average time between baseline assessment and injury was less than four months and did not differ between groups (HC+ = 119.18 days, HC- = 118.76 days; p > .05).

Descriptive statistics for outcome measures can be found in Table 4.2. The average number of days between injury and when medically cleared for RTP did not differ between

HC+ and HC- females ($t[98] = .54$, $p = .59$). Analyses did not reveal any significant differences between HC+ and HC- females on total number or severity of SCAT3 symptoms at baseline, 24-48 hours post-injury, or when medically cleared for RTP (Fs$[1,98] \leq 1.75$, p's ≥ 0.18).

With respect to cognitive function, analyses revealed no significant differences between HC+ and HC- females on SAC or ImPACT measures at baseline, 24-48 hours post-injury, and when medically cleared for RTP (Fs$[1,98] \leq 3.71$, p's ≥ 0.06). However, analyses did reveal group main effects, with HC+ females exhibiting significantly higher scores for SAC concentration ($F[1,98] = 4.18$, $p = 0.04$, $\eta p^2 = 0.04$) (Figure 4.2), ImPACT verbal memory ($F[1,98] = 4.61$, $p = 0.03$, $\eta p^2 = 0.05$) (Figure 4.3), and ImPACT cognitive efficiency ($F[1,98] = 8.03$, $p = 0.01$, $\eta p^2 = 0.08$) (Figure 4.4) than HC- females. With respect to change scores, no significant differences were observed on any outcome measure (Fs$[1,97] \leq 3.94$, p's ≥ 0.05). Both HC+ and HC- females consistently performed worse at 24-48 hours post-injury relative to baseline, but tended to do slightly better at RTP relative to baseline.

Discussion

The aim of the current study was to examine the influence of HC on recovery trajectory, clinical symptoms, and cognition following concussion. We found no group difference in average number of days between injury and RTP. Furthermore, our hypotheses that HC would attenuate post-concussive alterations in symptom severity and cognition were not supported. However, HC did seem to confer a general cognitive benefit across all three timepoints in terms of concentration, verbal memory, and cognitive efficiency.

Prior studies indicate that sex hormones, namely progesterone, may be neuroprotective following traumatic brain injury.[50] However, animal models comprise the vast majority of research observing better TBI outcomes following treatment of progesterone;[31-35] and although there is some evidence of positive treatment effects in human studies (decreased mortality, better neurological status),[37,38] large-scale (Phase III) clinical trials have failed to demonstrate favorable outcomes with treatment of progesterone.[39] Further, no existing human research studies demonstrate a relation between sex hormones and shorter duration of symptoms following concussion. Therefore, our findings agree with those of Gallagher and colleagues[42] which also indicated that HC does not influence trajectory of recovery following concussion.

In contrast to Gallagher and colleagues,[42] however, we failed to observe any differences in symptom severity between HC+ and HC- groups. Although perplexing (given they used a sub-set of the same data set), prior literature examining the influence of HC on symptom severity is equivocal. That is, some studies have observed lower symptom severity and better test-retest reliability among females using HC,[42,51] while others have not.[52] The same is observed for studies examining menstrual phase and concussion symptomology, with some studies reporting varied symptom reports through different phases of the menstrual cycle,[36,53] and others reporting no change in symptom severity across menstrual phase.[54]

The present study also sought to evaluate the influence of HC on concussion outcomes by using more objective measures of functioning (i.e., SAC and ImPACT). However, similar to our symptom severity data, we observed no differences in change scores between groups for any measure on the SAC or ImPACT test, suggesting that HC

has little-to-no effect on concussion outcomes. However, even performance on objective evaluations of cognition such as the SAC and ImPACT test are influenced by factors such as effort and motivation.[55] Indeed, irrespective of group, all athletes consistently exhibited the lowest symptoms, and best cognitive performance at the return-to-play assessment. Thus, effort and motivation likely influenced the current results. That being said, effort and motivation cannot explain the fact that HC+ athletes exhibited greater concentration on the SAC and greater verbal memory and cognitive efficiency on the ImPACT test across all timepoints. This finding suggests that, irrespective of injury status (as well as other factors), HC may confer a general benefit for certain aspects of cognition.

Several studies have observed enhanced cognition among females using hormonal contraceptives.[56] For example, females using HC often demonstrate greater working memory and ability to concetrate.[57-59] Researchers have also observed that HC+ females exhibit greater verbal memory[59,60] and visuospatial performance compared to HC- females.[59,61-63] Concordantly, we also observed increased concentration, verbal memory, and cognitive efficiency (derived from the speed-accuracy tradeoff during visuospatial performance). Thus, our findings corroborate prior research.

Limitations

Although this was the first study to longitudinally measure the influence of HC on concussion outcomes by using both subjective and objective measures, there are several limitations to consider. Foremost, HC status was recorded at baseline, and it is possible that some females altered their mode of contraceptive prior to injury. Second, we did not directly measure hormone levels or self-reported menstrual cycle information (e.g., status, phase, regularity), nor were we able to conduct sub-analyses with respect to the influence

of specific hormone type (i.e., estrogen or progestin) or dosage. There is evidence that chemical makeup of HC differentially influences cognition.[64] Thus, it is possible that varying levels of hormones due to heterogeneous dosages and medications prevented neuroprotective effects from being observed. In addition, missing data prohibited us from evaluating other key covariates (i.e., sociodemographic) that may also moderate concussion outcomes.[65,66] We were also unable, given the size and scope of the study, to examine objective measures of neuropathology and neurophysiological functioning. Accumulating evidence suggests that even when symptom reports, clinical exams, and cognitive test batteries fail to detect concussion-related alterations in neuro-behavioral functioning, many athletes still exhibit alterations in white-matter integrity,[67] cerebral hemodynamics,[68] and electrophysiological functioning.[69] Therefore, it is possible that HC may influence concussion outcomes on the neurophysiological level, but go undetected with measures such as the SAC and ImPACT test.[55,70] Therefore, future research should aim to more closely evaluate hormone levels and employ one or more neurophysiological measures in order to gain a more accurate understanding of the influence of HC on concussion outcomes.

CONCLUSION

Findings from the current study indicate that HC may not influence concussion outcomes. That being said, additional research is necessary in order to more accurately determine the influence of HC on concussion recovery. Prospective dose-response designs, including unbiased endocrinologic measurements to confirm menstrual cycle phase, as well as including measures neurophysiological functioning will help to form more substantive knowledge on this topic. Although the influence of HC on concussion

outcomes remains tentative, researchers and clinicians should be aware of the potentially different cognitive profiles of HC+ and HC- females, as post-concussive cognitive testing often occurs without a baseline comparison.

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Table 4.1. Participant Demographics

	HC+	HC-
Age (years)	19.16 ± 1.22	18.90 ± 1.23
Body Mass Index (kg/m^2)	22.67 ± 2.31	23.12 ± 3.29
Race / Ethnicity		
White	38 (76%)	38 (76%)
African American	3 (6%)	3 (6%)
Asian / Pacific Islander	5 (10%)	5 (10%)
Multiple Races / Unknown	4 (8%)	4 (8%)
Hispanic	4 (8%)	4 (8%)
Sport Contact Level		
Contact	29 (58%)	30 (60%)
Limited Contact	13 (26%)	13 (26%)
Non-Contact	8 (16%)	7 (14%)
Prior Concussions		
None	32 (64%)	32 (64%)
One	15 (30%)	14 (28%)
Two	3 (6%)	4 (8%)
Amnesia	6 (12%)	7 (14%)

Note: Values are presented as mean ± standard deviation or sample size (percent). Neither demographics nor injury characteristics differed between HC+ and HC- groups (p's ≥ 0.29). No participants in either group reported loss of consciousness at the time of injury.

Table 4.2. Descriptive Statistics

Time to RTP		HC+			HC-	
Days		20.14 ± 14.86			18.60 ± 13.84	
Outcome Measures	**Baseline**	**24-48 Hours**	**RTP**	**Baseline**	**24-48 Hours**	**RTP**
SCAT3						
Number of Symptoms	3.98 ± 4.18	10.30 ± 5.23	0.12 ± 0.39	3.02 ± 3.37	11.46 ± 6.62	0.20 ± 0.64
Symptom Severity	6.06 ± 7.13	24.60 ± 19.45	0.14 ± 0.50	4.77 ± 6.50	26.66 ± 22.72	0.26 ± 0.85
SAC						
Orientation	4.96 ± 0.20	4.82 ± 0.52	4.94 ± 0.24	4.94 ± 0.24	4.94 ± 0.24	4.92 ± 0.27
Immediate Memory	14.84 ± 0.42	14.76 ± 0.55	14.62 ± 0.83	14.64 ± 0.69	14.73 ± 0.53	14.86 ± 0.35
Concentration	3.90 ± 0.99	4.04 ± 0.88	4.54 ± 0.68	3.64 ± 1.12	3.84 ± 1.04	4.18 ± 0.98
Delayed Memory	4.14 ± 1.13	3.66 ± 1.14	4.42 ± 0.78	3.86 ± 1.01	3.56 ± 0.95	4.26 ± 0.92
ImPACT						
Verbal Memory	91.46 ± 8.61	87.84 ± 12.77	94.32 ± 5.65	88.20 ± 8.81	83.30 ± 13.49	93.64 ± 5.84
Visual Memory	79.44 ± 12.50	73.40 ± 15.50	80.48 ± 9.69	76.90 ± 12.41	73.32 ± 14.04	78.42 ± 13.63
Visual Motor Speed	43.27 ± 4.87	40.10 ± 7.26	45.71 ± 5.05	41.07 ± 5.84	39.45 ± 8.06	44.42 ± 6.19
Reaction Time	0.57 ± 0.08	0.64 ± 0.12	0.54 ± 0.06	0.60 ± 0.08	0.63 ± 0.11	0.58 ± 0.08
Impulse Control	5.94 ± 4.53	6.52 ± 5.50	6.29 ± 4.94	5.69 ± 3.99	6.96 ± 4.87	5.88 ± 4.16
Cognitive Efficiency	0.41 ± 0.15	0.40 ± 0.14	0.48 ± 0.10	0.35 ± 0.15	0.34 ± 0.14	0.44 ± 0.13

Note: Values are presented as mean ± standard deviation for LOR (days), SCAT3, SAC, and ImPACT scores at baseline, 24-48 hours, and RTP assessments for HC+ and HC- females.

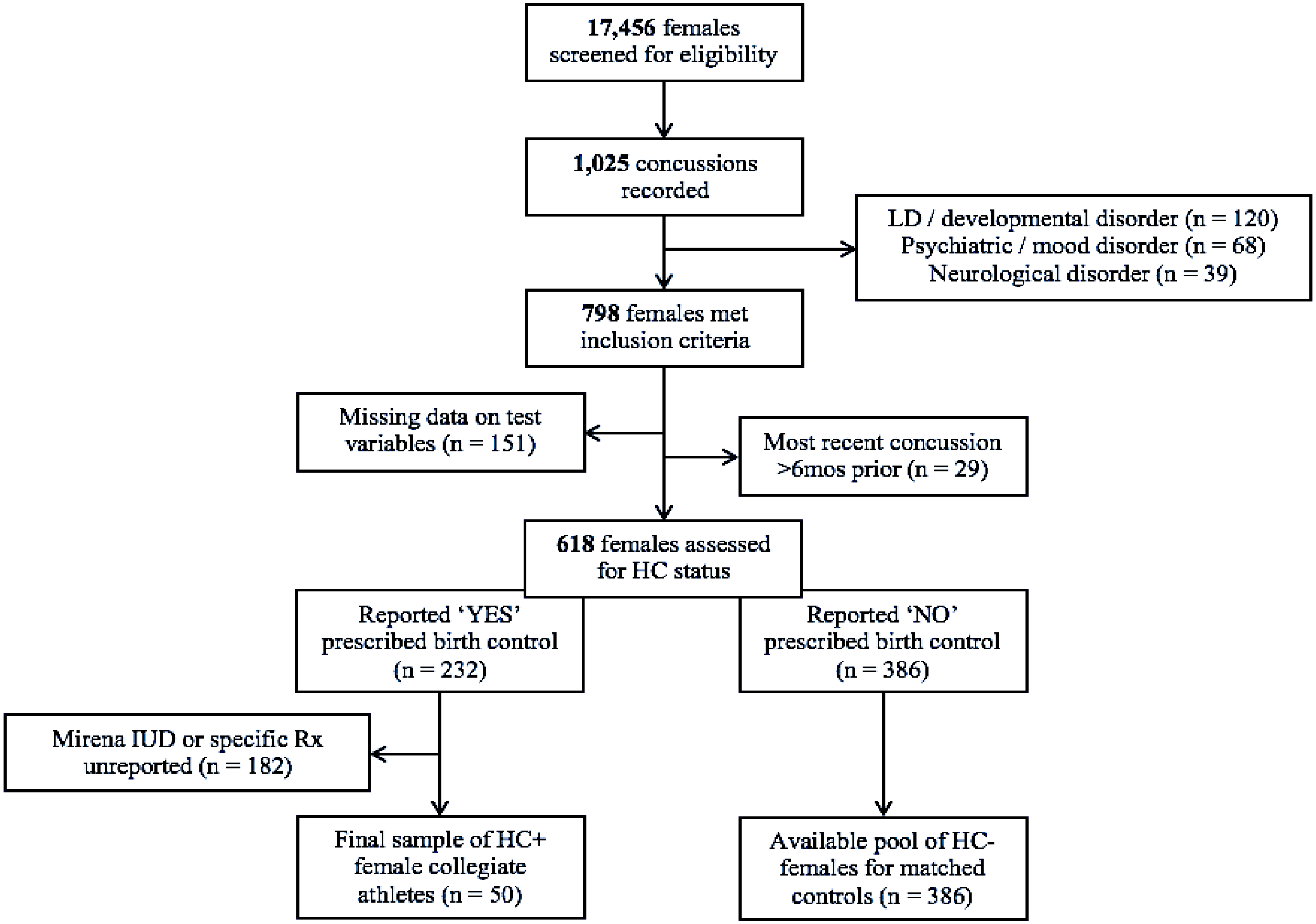

Figure 4.1. Flow Diagram of Sampled Participants

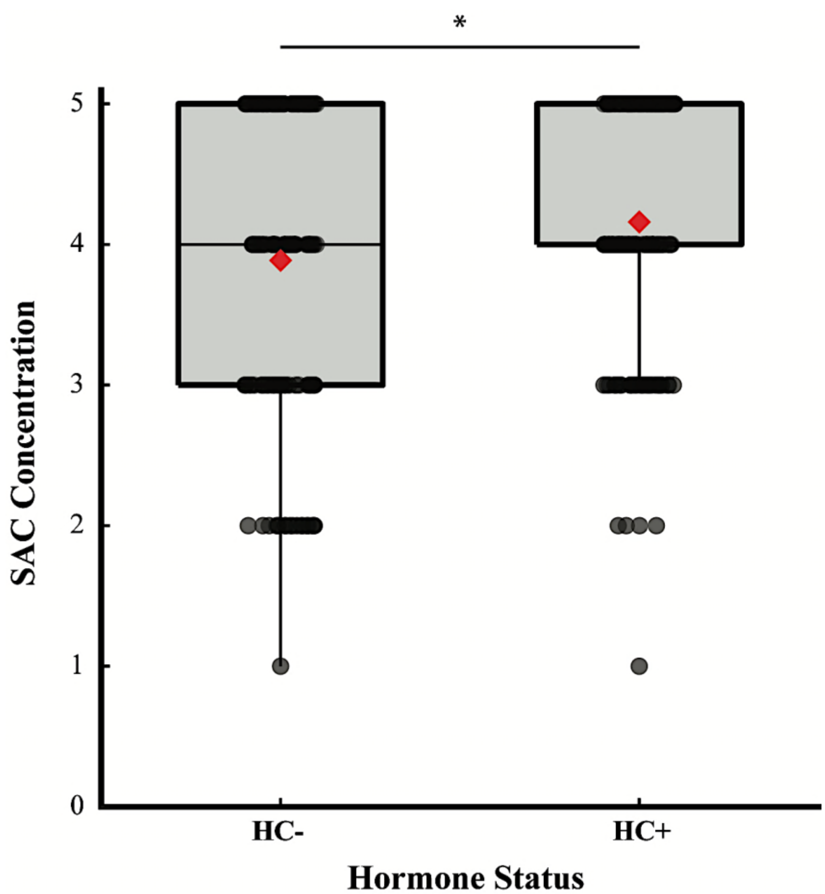

Figure 4.2. Group Main Effect for SAC: *Concentration*
Significance * (p = 0.04; ηp^2 = 0.04)

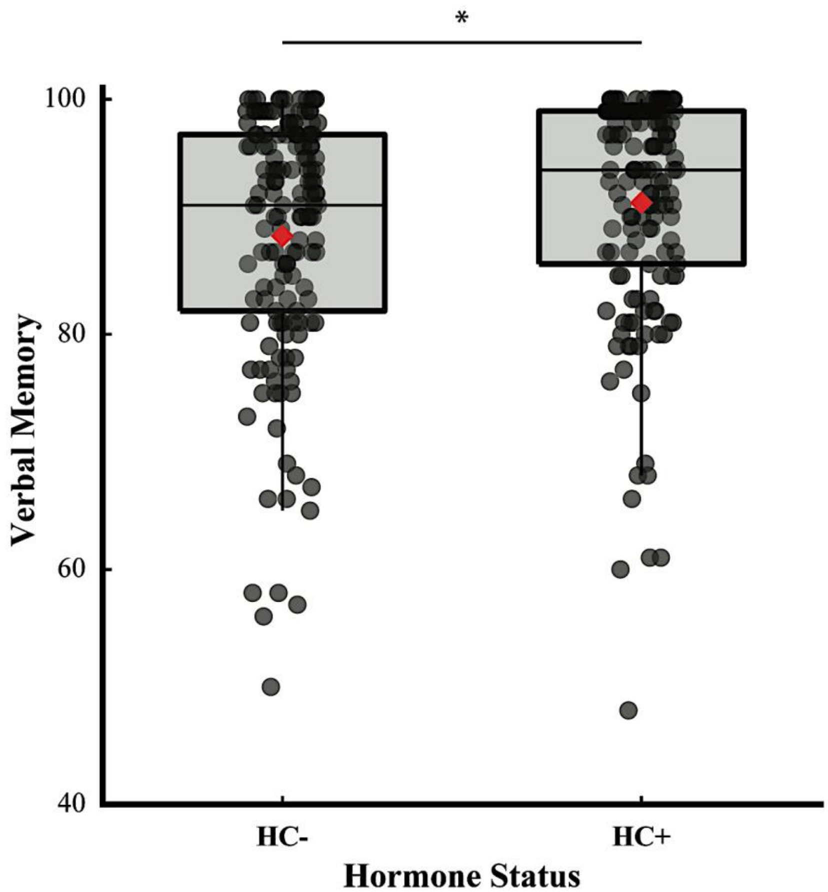

Figure 4.3. Group Main Effect for ImPACT: *Verbal Memory*
Significance * (p = 0.03; ηp^2 = 0.05)

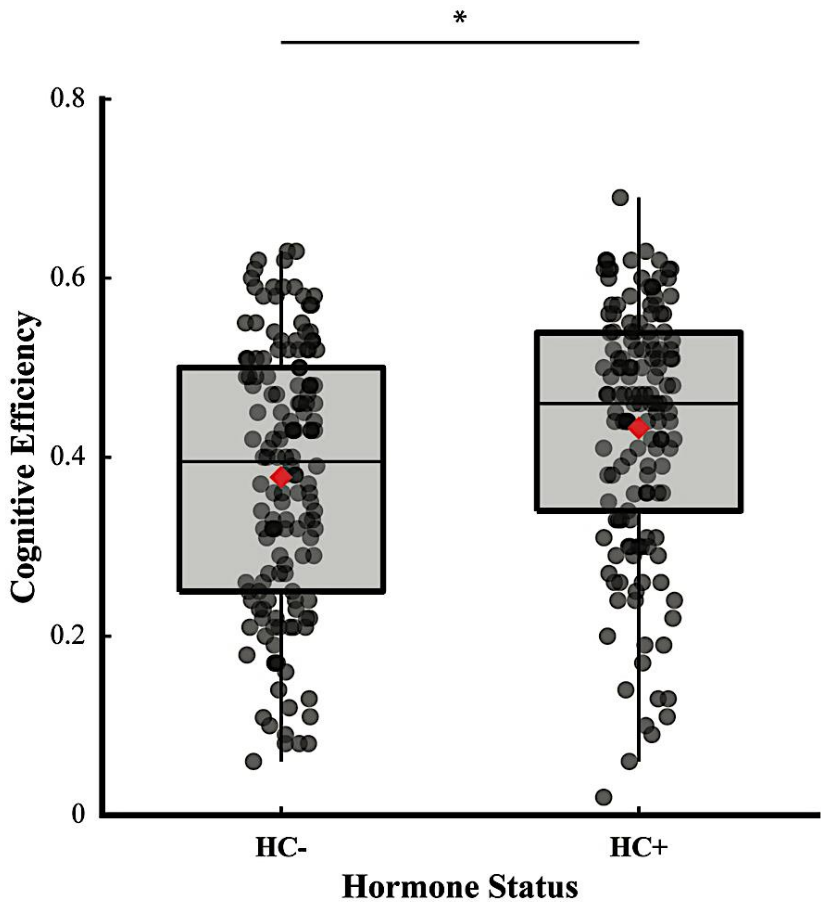

Figure 4.4. Group Main Effect for ImPACT: *Cognitive Efficiency*
Significance * (p = 0.01; ηp^2 = 0.08)

CHAPTER 5

PROPOSAL

INTRODUCTION

Concussion is a traumatic brain injury induced by rapid acceleration and deceleration forces to the head.[1] These forces are transmitted to neural tissues, resulting in a complex neurometabolic cascade of events leading to disruption of cerebral homeostasis and microstructural alterations.[2] Individuals that incur a concussion often experience transient, but debilitating symptoms (headache, dizziness, nausea), cognitive dysfunction, and declines in psychological health.[3] Though most concussive injuries resolve within a few weeks, a significant proportion (~15-20%) of individuals will experience persisting symptoms that can negatively affect important aspects of social life, as well as academic and vocational performance.[4]

Incidence rates of concussion have grown steadily over the last decade, highlighting an important public health concern in the US and worldwide.[5] As such, researchers and clinicians have called for examination of specific factors that may moderate injury risk and recovery from concussive injury. Biological sex is one such factor gaining interest among researchers and health care professionals. While there appears to be a substantive knowledge base on sex-based differences in concussion incidence and risk, less is known regarding the influence of biological sex on symptoms, cognitive function, and psychological health following concussive injury.[6] Prior research in the greater TBI literature appears to demonstrate poorer outcomes and longer recovery time among females;[7] however, relatively few studies have sought to examine the relation between sex and outcomes following less severe brain injuries, such as concussion. Moreover, relatively few studies have sought to examine the relation between sex and physical, cognitive, and psychological outcomes following concussive injury among youth.[8]

STATEMENT OF THE PROBLEM

Present scientific literature indicates adolescent and young adult females may experience greater symptom burden and longer recoveries following concussion when compared to male counterparts.[9] Additionally, there is some evidence that important biological factors, such as sex hormones, may moderate recovery outcomes in females.[10] However, the majority of existing evidence has been drawn from cross-sectional investigations and lack appropriate consideration of other important moderating variables that may also explain potential sex-based differences. Thus, our current understanding of the influence of biological sex on concussion outcomes remains incomplete and tentative.

SPECIFIC AIMS AND HYPOTHESES

Overall Hypothesis. Females will exhibit greater symptoms, as well as attenuated cognitive functioning and psychological health outcomes of concussion when compared to males. Further, females using hormonal contraceptives will exhibit faster recovery profiles in terms of concussion symptoms, cognitive performance, and psychological health when compared to females not using hormonal contraceptives.

Specific Aim 1. Prospectively examine sex-based differences in concussion symptoms, cognitive function, and psychological health between concussed female and male adolescents.

Hypothesis 1.1. Concussed adolescent females will exhibit greater symptom burden in terms of total number of symptoms and symptom severity when compared to concussed adolescent males.

Hypothesis 1.2. Concussed adolescent females will exhibit greater cognitive dysfunction, as indicated by objective measures of cognitive performance and

parent-reported executive functioning, when compared to concussed adolescent males.

Hypothesis 1.3. Concussed adolescent females will exhibit greater detriments in psychological health, as indicated by self-reported depressive symptoms, when compared to concussed adolescent males.

Specific Aim 2. Cross-sectionally examine sex-based differences in psychological outcomes and the cumulative effects of concussion on suicidality using data from the 2017 National Youth Risk Behavior Survey (YRBSS).

Hypothesis 2.1. Adolescents males will exhibit significantly greater odds of reporting having incurred a concussive injury within the previous twelve months when compared to adolescent females.

Hypothesis 2.2. Adolescent females will exhibit significantly greater odds of reporting feeling sadness/hopelessness, as well as suicidal ideation, planning and attempts when compared to adolescent males, irrespective of injury.

Hypothesis 2.3. Adolescent females will demonstrate stronger associations between a single concussive event in the previous twelve months and reporting poorer psychological health and increased suicidality, whereas in adolescent males these associations will emerge only in context of multiple concussions.

Specific Aim 3. Longitudinally examine the influence of hormonal contraceptives on recovery time, concussion symptoms, cognitive function, and psychological health in collegiate females.

Hypothesis 3.1. Concussed collegiate females using hormonal contraceptives will exhibit faster recovery times, fewer symptoms, and lower overall symptom severity, when compared to females not using hormonal contraceptives.

Hypothesis 3.2. Concussed collegiate females using hormonal contraceptives will exhibit smaller post-injury deficits in cognitive performance, as indicated by objective measures of cognitive function, when compared to females not using hormonal contraceptives.

Hypothesis 3.3. Concussed collegiate females using hormonal contraceptives will exhibit smaller declines in psychological health, as indicated by self-reported emotional distress, when compared to females not using hormonal contraceptives.

LITERATURE REVIEW

This review of literature provides a comprehensive summary of the research on concussion, with special attention given to adolescents and young adults. The definition of concussion will be provided first, followed by a summary of the biomechanical and etiological aspects of concussive injury, as well as associated pathophysiology. Next, an overview of concussion epidemiology, common risk factors, and cumulative effects of repeated injury will be provided. This will be followed by an evaluation of concussion assessments, with emphasis on clinical symptoms, cognitive functioning, and psychological health. Key studies that have advanced our current understanding of sex-based differences in concussion outcomes will be thoroughly evaluated. The literature review concludes with a summary of pertinent gaps in the literature and the purposes of the proposed study.

Definition

The term "concussion" has an important historical underpinning. While cranial injury has been well documented in ancient Greek, Roman, and Arabic text, no early distinction was made between the transient effects of mild and severe traumatic brain injuries, with skull fracture the cornerstone of diagnoses.[11] Lanfrancus, a 13th century European physician, is often credited as the first to describe "commotio cerebri" (shaking of the brain) as a separate entity, independent of overt structural damage "contusio cerebri" (contusion of the brain).[12] This distinction was pivotal in the subsequent definition of concussion as a transient physiological state.

By the 17th century, several hypotheses emerged on the nature of concussive injury. Perhaps most prominent were the writings of Berengario da Carpi (c. 1460 – c. 1530) in which he postulated that concussion was the result of the soft brain being forced against the skull,[13] and later by Heister (c. 1683 – c. 1758) whom hypothesized that this force could injure "the nervous filaments in the interior of this precious organ,"[14] both linking the injury with observable behavioral outcomes. These early *hypotheses of brain commotion* have played an important role in our modern understanding and definition of concussion, drawing important attention to the clinical signs used to distinguish concussion from other forms of brain injury. However, the heterogeneity of symptom presentation, notable inconsistencies in altered consciousness, and the perplexity of underlying pathophysiology have made defining this injury very difficult.

Present day, the term "concussion" remains ill-defined, and a consensus has yet to emerge.[11] One of the earliest definitions was proposed by the Congress of Neurological Surgeons in 1964, and later recognized in the Traumatic Brain Injury Act of 1966, as "a

clinical syndrome characterized by immediate and transient impairment of neural functions, such as alteration of consciousness, disturbance of vision, equilibrium, etc. due to mechanical forces."[12,15] This definition has been heavily criticized by the scientific community for overemphasizing brainstem function and loss of consciousness (LOC) and failing to account for the role of other affected brain regions that may result in persistent symptoms.[16,17] In attempt to address these shortcomings, the 1997 American Academy of Neurology (AAN) introduced a grading system to distinguish levels of concussion by presence of LOC and duration of symptom presentation or abnormal mental status.[18] However, concussion grading systems have drawn stark criticism in recent years, and fail to demonstrate a strong evidence base.[19]

Perhaps the most widely accepted definition is in the most recent consensus statement from the 5th International Conference on Concussion in Sport.[20] The panel defined concussion as "a traumatic brain injury induced by biomechanical forces" that cannot be explained by substance use, other injuries, or comorbidities. The panel supplemented this definition with several clinical features: 1) may be caused by a direct blow to the head or periphery in which an impulsive force is transmitted to the brain; 2) typically results in rapid and transient neurological impairment that resolves spontaneously; 3) may induce neuropathological changes, but acute clinical symptoms largely reflect functional disturbance with no remarkable findings on standard brain imaging; and 4) the range of clinical symptoms may or may not involve LOC; and while most symptoms typically resolve within 10-14 days in adults and within 4 weeks in adolescents, symptoms may be prolonged in some cases.

In summary, important historical foundations have advanced our understanding and definition of concussion. The varied clinical signs and symptoms of concussion have made defining this injury very difficult. While several organizations have attempted to characterize the nature of concussion, a true consensus has yet to emerge.[11,12] Indeed, this is evidenced in contemporary literature in which the term "concussion" and "mTBI" are often used interchangeably. The inconsistencies in common nomenclature may impede accurate identification and diagnosis of concussion,[21] and hinder comparisons across research studies.[22] Importantly, emerging trends in the literature indicate the use of current terminologies may be rooted in the biomechanical and etiological context of injury. Whereby the term "concussion" is most commonly used in sports medicine communities to describe injuries as a result of sport or recreation, and the term "mTBI" more commonly used in other medical specialties to describe injuries sustained by other etiologies, such as motor vehicle accidents, or blast-related injury.[23,24]

Biomechanics and Etiology

The biomechanics of concussive brain injury can be broadly described as the transfer of kinetic forces to the head and transient deformation of underlying neural tissue.[25] Understanding the biomechanics of concussion requires knowledge about how biological responses are influenced by various loading conditions or etiological context (i.e., modality of injury), and how the mechanical properties of injury are moderated by key factors, such as tissue composition of the head and neck. In this section, a general overview of injury biomechanics across common modalities of injury will be provided, with special attention paid to potential sex-based moderators, where appropriate.

Denny-Brown & Russell[26] were among the first to deliver calculated blows to the head of animals and found that inducing a concussion was dependent upon movement characteristics of the head. In their experiments, concussion was more often induced when the head was destabilized (free to move) rather than when the head was fixed in position. This led the authors to conclude that concussion was likely due to the transfer of kinetic energy to the head (rather than through the head, when stabilized) causing inertial loading of force onto the brain within the skull. The pioneering work of Denny-Brown & Russell[27] paved the way for later studies on vector characteristics of concussive head impacts.

Vector characteristics of head impact trauma are most often categorized into linear (translational) and angular (rotational) forces. An inertial force applied linearly to the head accelerates and decelerates the brain along its center of gravity.[28] During acceleration, the relative movement of the brain lags behind that of the skull; conversely, during deceleration the brain continues to move when after the head has been abruptly halted.[28] In clinical context, this may be best exemplified by the coup-countercoup injury commonly observed following a front/rear-end motor vehicle accident (MVA). Normally, the cerebral spinal fluid and meningeal layers provide a protective cushion around the brain. However, when traumatic impact forces are applied, the brain will collide with the skull, resulting in a violent deformation or distortion of underlying neural tissue.[28] In contrast, an inertial force applied angularly to the head accelerates and decelerates the brain tangentially around its center of gravity. In clinical context, this type of concussive injury may be best exemplified by the twisting motion of the head during helmet-to-helmet contact commonly seen in American football. Rotational acceleration and deceleration forces create a swirling or

spinning of brain matter within the skull, causing micro-level shearing or stretching of axonal connections within the brain.[29,30]

While specific examples of injury mechanisms were provided above, it is important to note that both translational and rotational forces occur in varying degrees during concussion, whether incurred during MVA, sport, or most other contexts.[25] However, recent research has been shedding light on the unique oscillatory (wave-like) forces that produce concussion during blast-related injury. Blast-related concussions result from exposure to high speed pressure waves that result in catastrophic expansion and contraction of neural tissue as they pass through the brain.[31] Similar to conventional (non-blast-related injury), if pressure loading of force exceeds the stress threshold of brain tissue, widespread deformation of axons can lead to the disruption and separation of nerve fibers.[32] It is important to note that the biomechanics of blast-related injury are distinct from concussion in MVA, sport, etc. and further discussion of these injuries is beyond the scope of this literature review. However, non-blast-related head impacts that occur in military settings (e.g., combat training, falls) are governed by similar biomechanics as MVA, sport, or other contexts; thus, the concepts discussed in subsequent sections are applicable.

Several methods have been developed to examine concussive injury thresholds. Human anthropomorphic surrogates and computational models (finite element models; FEMs) are commonly employed to replicate injuries, particularly in contexts which *in vivo* measures are difficult to obtain. These models utilize theory of diffuse axonal injury, in which white matter bundles throughout the brain are affected during inertial loading of force.[30,31] While neither can directly quantify concussion or axonal injury in real-time, these methods can be used to predict tissue stress and strain (distortion) from documented

injuries. Several FEM investigations have aimed to estimate shear stress and strain thresholds of tissue in brain regions with densely pack white matter (thalamus, corpus collosum, brainstem). In thalamus, shear stress and strain rate thresholds at 50% likelihood of injury have been estimated to be 2.24 kPa and 24.0 s(-1), respectively.[33] In corpus collosum, shear stress and strain rate thresholds at 50% likelihood of injury have been estimated to be 3.51 kPa and 25.1 s(-1), respectively.[33] In brainstem, shear stress and strain rate thresholds at 50% likelihood of injury have been estimated to be 7.8 kPa[34] and 27.0 s(-1),[35] respectively. In general, results from FEM studies indicate that linear acceleration forces may lead to greater intercranial pressure; whereas rotational forces likely lead to greater shear stress on central brain structures.

In addition to brain injury surrogates and computational modeling, devices such as the Head Impact Telemetry System (HITS) have been used to obtain real-time data during sporting events. A sensor is typically fixed to mouthpiece or headwear to measure the direction (linear, rotational) and magnitude (acceleration, velocity) of head motion following impact.[33,34] Establishing the threshold of concussion with head telemetry would allow for better side-line determination of an injury event. Researchers have aimed to correlate head impact measures with injury events. Concussion thresholds in American football have been associated with linear magnitudes ranging 70*g* to 145*g*[36-39] and mean rotational acceleration estimates of 7688 rad/s^2.[40] In ice hockey, concussion thresholds have been associated with linear magnitudes ranging 30*g* to 53*g* and mean rotational acceleration estimates ranging 1307rad/s to 5419rad/s^2.[41-45] Investigators have also estimated concussion risk using HITS, and have generally shown that rotational forces are more predictive of injury.[46] Rotational acceleration greater than 6945 rad/s^2 may result in

a 75% risk for concussion, whereas rotational acceleration exceeding 7483 rad/s^2 may result in a 90% risk.[40] When factoring for impact location, research has shown 21.3% specificity of injury threshold at 96.1*g* linear magnitude and 5582.3 rads/s^2 rotational acceleration.[39] Although HITS have been pivotal in advancing our understanding of head impact tolerance, precise thresholds have been difficult to obtain due to numerous moderating factors.

The general overview of head motion characteristics and hypothesized thresholds provided in previous sections highlights the formidable challenges researchers face in reaching a comprehensive understanding of injury biomechanics. There are many aspects of injury kinematics, as well as human anatomy and physiology that may influence biological responses to concussion. Characteristics of the concussive blow, such as nature, magnitude, and direction of impact are key factors that influence resultant injury to neural tissues.[28] Variations in human anatomy and physiology, such as size, shape, and thickness of the scalp and skull; density and elasticity of underlying neural tissues; and relationships between the head-neck-body (mass, strength, mobility) may also play an important role in resultant injury.[28] Investigating biomechanical moderators of injury may also help to explain sex-based differences, as injury risk and outcomes appear to vary between sexes[47] (see *Overview of Epidemiology and Common Risk Factors: Sex*, pg. 105). Briefly, HITS studies often report greater head acceleration among females,[48,49] which some researchers attribute to sex-based differences in head-neck composition, strength, and mobility.[50] Youth also tend to experience greater risk of concussion and poorer outcomes following injury[51] (see *Overview of Epidemiology and Common Risk Factors: Age*, pg. 105). The relation between lower threshold-higher risk/poorer outcomes may be due to important

developmental factors, such as density and elasticity of neural tissues.[28,52] Concussion history may also be an important moderator, with some studies showing lower thresholds for subsequent injury and greater frequency of sub-concussive impacts associated with significant alterations in brain structure function, as well as poorer neurobehavioral health[53-56] (see *Cumulative Effects of Concussion*, pg. 109). Taken together, the moderating relationships between injury kinematics and human anatomy and physiology call attention to the heterogeneous nature of concussive injuries and uniqueness of each insult.

In summary, concussion is best described as mild form of traumatic brain injury, induced by rapid acceleration/deceleration of the head, resulting in deformation of underlying neural tissues. Although several studies have aimed to establish injury tolerance, the heterogeneous nature of concussion biomechanics present significant challenges in obtaining a precise threshold. However, extant research in this area has helped to explain how differing aspects of concussion biomechanics and human anatomy / physiology may influence concussion risk and outcomes. Continued technological advancements in computational modeling and head impact telemetry will help generate a substantive knowledge base of concussion biomechanics, and may aid improvements in safety equipment and return-to-activity management, particularly in sport.

Neuropathophysiology

The biomechanical insult to the brain during concussion results in a complex neurometabolic cascade of events leading to disruption of cerebral homeostasis. Alterations in cell permeability, ion flux, neurotransmitter release, cellular metabolism, and cerebral blood flow have been well-documented following concussive injury.[57] While concussion is largely characterized by functional disturbances of neuronal processes,

several important studies also demonstrate microlevel damage (shearing of axonal fibers) in lieu of gross structural abnormalities.[58] Furthermore, while evidence for sex-based differences in concussion neuropathology is somewhat limited, some studies demonstrate unique differences between males and females that may lead to differing outcomes.[59] Namely, the withdrawal of sex-based steroid hormones in females may result in heightened symptom severity and longer recoveries.[6,7,59,60] In this section, a general overview of concussion neuropathology is provided, and concludes with a summary of potential sex-based differences that may predispose females to poorer outcomes following injury.

The permeability of cell membranes (both neuron and glia) is immediately compromised upon concussive impact, and defects within the cell membrane allow for widespread ionic flux to occur.[57] The cells of the brain become flooded with sodium (Na+) and calcium (Ca2+), while potassium (K+) pours into the extracellular space.[61] This rapid shift in ionic homeostasis is accompanied by massive increases in extracellular concentrations of glutamate (primary excitatory neurotransmitter).[61] If left unchecked, the accumulation of extracellular glutamate can become toxic, triggering apoptosis (i.e., neuronal cell death) and structural breakdown of the neuron; which are likely key mechanisms of chronic neurodegeneration observed with repeated concussive injury[62] (see *Cumulative Effects of Concussion*, pg. 109). The survival of neurons is dependent upon the restoration of ionic homeostasis. In attempt to rectify acute ionic instability, Na+/K+ pumps are forced into overdrive, requiring large amounts of ATP.[57] To meet these nutrient demands the rate of glucose utilization (i.e., glycolysis) increases dramatically, placing the brain in a hypermetabolic state.[61] Furthermore, increasing levels of intracellular calcium

may persist beyond ionic disturbances, compromising mitochondrial function and exacerbating the downstream cellular energy crisis.[63]

Following initial hyperglycolysis, a hyper-to-hypometabolic shift occurs, marked by diminished cerebral blood flow (CBF) and glucose availability.[64] Research has shown that CBF may be reduced by as much as 50% following brain injury.[65] Although reductions in CBF are generally thought to be global, decreases may be more prominent with the cerebral hemispheres, relative to brainstem or cerebellum.[65] Further, dysfunctional CBF may be due to increased permeability of endothelial cell junctions that form the brain's intricate cerebrovascular system, potentially leading to an accumulation of fluid in the extracellular space (i.e., edema).[65] CBF is tightly coupled with neuronal activity, and reductions in CBF impair the neurons ability to meet glucose/nutrient demands. The mismatch in energy supply and demand results in a spreading "depression-like" energy crisis that interferes with healthy brain physiology.[61] This hypometabolic state and concomitant alterations in cerebral hemodynamics are thought to last several days to weeks following injury, leaving the brain more susceptible to injury during this acute recovery period.[57]

Although concussive injuries are largely characterized by functional disturbance of neuronal processes, growing evidence indicates that structural damage does occur. As discussed previously, shearing and stretching of axons occurs widespread in the brain.[29,30] At the microlevel, the shear stress that impact forces induce upon axonal fibers results in lesions, inflammation, demyelination, and ultimately degeneration.[66-68] Axonal damage further weakens the neurons ability to function normally, and the diffuse nature of concussive axonal damage generates significant interference between neural networks.

This is evidenced by numerous studies that show disrupted functional communication of brain networks with post-concussive axonal damage.[69] Interestingly, specific axon bundles (white matter tracts) appear more susceptible to injury than others. Researchers have shown that corpus collosum, corona radiata, longitudinal fasciculus, and the corticospinal tract appear to be most vulnerable to damage following concussion.[70-72] Moreover, concussive damage to these white matter tracts has been associated with significant declines in neurobehavioral health.[72,73] These impairments tend to resolve within the first few weeks following injury, suggesting that the brain has the ability to repair itself. However, this resilience appears to diminish with repeated injury, and may be due to the structural breakdown of axons and accumulation of protein fragments.[74] Indeed, research suggests that axonal damage is a key contributor of chronic neurodegeneration observed in repeated concussions[75,76] (see *Cumulative Effects of Concussion*, pg. 109).

Biological sex has been proposed as an important modifier of concussive injury outcomes.[59] However, relatively few studies have sought to examine potential sex-based differences in the neuropathophysiological processes following concussion. Animal models generally demonstrate better outcomes among females, with less cerebral edema, greater cerebral blood flow, and fewer structural alterations.[77] Although findings on sex-based differences in post-concussive functional and structural functional alterations remain largely inconclusive, research that shows inherent sex-differences in central white matter structures may provide some explanation for poorer outcomes among females.[78] More specifically, the cross-sectional area of corpus callosum fibers is smaller in females than males, which may heighten susceptibility to injury.[78,79] Damage to this structure impairs functional communication of brain networks, and may be an underlying mechanism of

increased perceived symptoms and greater neurobehavioral disturbances among females.[79] Although speculative, increased vulnerability to corpus callosum damage may suggest that females are also more susceptible to damage within other central connective tracts and nuclei. The hypothalamus, for example, is a small central brain region that is comprised of many small nuclei responsible in regulating autonomic functions.[80] Hypothalamic damage and autonomic nervous system dysfunction are commonly implicated in brain injury.[81] One important area of investigation is the function of the hypothalamic-pituitary-gonadal axis, which becomes suppressed after brain injury and leads to decreases in luteinizing hormone, follicle-stimulating hormone, testosterone, progesterone, and estrogen concentrations.[60,82] The *hormonal withdrawal hypothesis* asserts that reductions in sex hormones (progesterone in particular) following brain injury may be a key factor in worse outcomes among females.[83] Indeed, research has shown that significant withdrawal of sex hormones following brain injury is associated with poorer quality of life and greater symptom presentation in women.[83] Together, these findings indicate that females may not only be more susceptible to injury due to inherent differences in white matter structure, but may experience poorer outcomes due to unique neurochemical alterations following injury when compared to males.

In summary, the neuropathophysiology of concussion is characterized by widespread functional and structural alterations. Immediately following concussive impact there is catastrophic ionic imbalance, unchecked excitatory neurotransmitter release, and microstructural alterations that synergistically impair healthy brain functioning. Importantly, innate structural differences in central white matter architecture, as well as downstream disruption of neuroendocrine function may provide some explanation for

increased injury susceptibility and poorer outcomes in females (when compared to males) following concussive injury.

Overview of Epidemiology and Common Risk Factors

Concussive injuries are a growing public health concern in the United States and internationally.[84] Research indicates 100 to 300 per 100,000 people seek some form of medical attention for mTBI worldwide.[85] Furthermore, there has been considerable growth in concussion incidence in recent years, with estimates demonstrating a rise in concussion incidence from 569.4 per 100,000 in 2006 to 807.9 per 100,000 in 2012.[86] However, the true incident rate is likely higher, as most data is gathered from emergency department medical records and fail to capture those that are seen in other health care settings or fail to seek medical attention.[87] Thus, researchers suggest as many as 600 per 100,000 seek medical attention for mTBI per year (roughly 42 million people) worldwide,[85] and lifetime prevalence may be as high as 15% across the global population.[88,89] Despite challenges in estimating the global impact of concussive injuries, research in this area serves to identify important risk factors and potentially vulnerable populations.

Concussion is a particularly salient issue in sport and recreation, and the vast majority of epidemiological work has focused on adolescent and young adult athletes.[90] An estimated 1.6 to 3.8 million sport- and recreation-related concussions (SRRCs) occur each year in the United States (US).[91-93] Overall, studies show concussion rates range from .09 in limited-contact sports to 2.61 in collision sports per 1000 athletic exposures (AEs).[94-96] While concussion rates have risen steadily over the last decade (particularly among youth),[97] the reasons why remain somewhat elusive. Researchers suggest increased organized sport participation[98] and growing community awareness / knowledge of

concussion[99] may play a significant role. Nonetheless, epidemiological investigations on SRRC (despite being relatively narrow in scope) have been pivotal in enhancing our scientific understanding of important risk modifiers. For example, recent systematic reviews and meta-analyses on SRRC indicate that sex, age, and concussion history are the most predominant risk factors for incurring a concussive injury.[100,101]

Biological Sex. Epidemiological investigations on SRRC incidence demonstrate important differences between male and female athletes at both collegiate and high school levels of competition, with females consistently demonstrating a greater proportion of concussive injury [relative to all other sport injuries], higher injury rates (IR), and increased risk of concussive injury across comparable sports.[102-104] In a sample of both collegiate and high school athletes, Gessel and colleagues (2007)[102] observed a significantly higher proportion of concussive injuries among females (5.5-15.1%) when compared to males (2.9-9.4%) across softball/baseball, basketball, and soccer. Among collegiate athletes specifically, Covassin and colleagues (2016)[103] observed significantly higher injury rates when comparing females to males (IRs = 4.84 and 3.46 per 10000 AEs, respectively) across baseball/softball, basketball, ice hockey, and soccer. In a recent high school specific sample, O'Connor and colleagues (2017)[104] observed significantly increased concussion risk among females when compared to males (RR=1.56; 95% CI = 1.34,1.81). Importantly, when examining concussion rates by sporting event, the authors observed consistently higher concussive injury risk among females when compared to males in competition (RR = 1.46; 95% CI = 1.20-1.77) and during practice (RR = 1.75; 95% CI = 1.39-2.20).[104] These data clearly suggest that sex is an important factor to consider when understanding concussion rates/risk at both the collegiate and high school level; and further, these

differences likely exist irrespective of competition level. While the reasons behind higher injury rates and greater risk among females are not entirely understood, researchers speculate that sex-based differences in biomechanical vulnerability and neurochemical responses (as discussed in prior sections of this review), as well as sociocultural influences in symptom reporting (see *Current Knowledge: Sex-Based Differences in Concussion Outcomes*, pg. 121) may play an important role.

Age. The relation between age and concussion risk is not as clear as sex differences discussed above; however, extant research appears to show that adolescent youths may be at greater risk when compared to younger pre-pubescent children and adults.[93,103,105-107] When examining trends in SRRC incidence between 2001 and 2012, Coronado and colleagues (2015)[93] observed most significant increases among adolescents aged 10-19 years (>140%). In addition to analyzing sex differences in concussion incidence, Covassin and colleagues (2016)[103] also found that concussions accounted for a greater proportion of total sport-related injuries among high school athletes when compared to older collegiate counterparts. In a large cross-sectional population study of 50,352 adolescents and young adults aged 12-24 years, Gordon, Dooley, and Wood (2006)[105] found that younger age was associated with higher reporting of concussion. In a smaller, but more tightly controlled prospective cohort of football players, Guskiewicz and colleagues (2000)[106] observed significantly higher rates of injury among high school athletes (1.03 concussion per 1000 AEs) when compared to Division I-III NCAA athletes (0.49-0.69 concussions per 1000 AEs, respectively). In a more recent examination of collegiate and military academy athletes, van Pelt and colleagues (2019)[107] found that freshman (grade level) status was associated with greater odds of sustaining a concussion when compared to older athletes in

upper grade levels (OR: 3.05 [95% CI: 2.62-3.56]; d=.62). However, the authors noted that these findings were largely driven by academy training-related injuries, suggesting some specificity in injury setting and curtailing generalizability. In general, current evidence supporting the association between adolescent age and higher concussion risk is limited and relatively sparse. However, given the complexity and potentially vulnerable nature of the developing brain during adolescence,[108] further research in this area is warranted.

Concussion History. Similar to many other sport-related injuries, one of the best predictors in injury risk is history of prior injury.[101,109] With respect to SRRC, research has not only shown higher risk of concussive injury in those with general history of concussion, but also that the likelihood of incurring a subsequent injury increases after each concussive event.[106,107,110] In a study of high school and collegiate football players, Guskiewicz and colleagues (2000)[106] observed athletes that had sustained a concussion during practice or competition were 3-fold more likely to sustain a subsequent concussion during the same sport season, when compared to athletes with no prior concussion. Alarmingly, in the same study, the authors found ~20% of athletes were never withdrawn from sport participation following injury, and over ~30% returned to play on the same day of their concussion. In a follow-up study, Guskiewicz and colleagues (2003)[110] examined the relation between the number of previous concussions and risk of incident concussion among collegiate football players. In this study, the authors found athletes with one prior concussion were 1.5 times more likely to incur a concussion when compared to athletes with no history of concussion. Furthermore, athletes that reported two and three (or more) prior concussions were 2.8 and 3.4 times more likely to incur a concussion when compared to athletes with no history of concussion, respectively. The authors also reported over 90% of recurrent concussions

occurred within 10 days of the previous concussion. While the early pioneering work by Guskiewicz and colleagues has been pivotal in shaping our understanding of the influence of concussion history on injury risk, these studies are relatively narrow in scope and have focused exclusively on football athletes. A more recent investigation has sought to address these gaps by examining concussion risk factors in a large sample of 10,604 military cadets across multiple injury settings (varsity, club, and intramural sports; physical education class; academy training; recreation).[107] In this study, van Pelt and colleagues (2019) observed cadets reporting a history of concussion were nearly two times more likely to have incurred a concussion when compared to cadets with no history of concussion (OR: 1.98, 95% CI: 1.65-2.37). Importantly, the authors further observed the magnitude of risk remained fairly stable across injury settings (OR: 1.73 to 2.01). Together, these data clearly indicate that concussion history is a strong moderator for risk of subsequent concussion, irrespective of injury setting. Further, this risk is likely magnified with an increasing number of prior concussions. Research in this area has been crucial toward developing regulations and rules that prohibit athletes from return to play following suspected concussion,[111] and continued scientific efforts are beginning to shed light on the cumulative effects of concussive injury on clinical outcomes.[20]

Cumulative Effects of Concussion

Given the evidence that demonstrates increased risk in sustaining a concussive injury in those that report history of concussion, there is vested interest among scientists and clinicians to better understand the cumulative effects of concussion. Research in this area is themed around two important questions: 1) What are the consequences of repetitive

concussion on brain structure?; and 2) What are the consequences of repetitive concussion on neurobehavioral health? These questions will be addressed in the following section.

Studies using Diffusion Tensor Imaging (DTI), a Magnetic Resonance Imaging (MRI) technique, are currently leading the way in elucidating the chronic microstructural (white matter) alterations associated with repetitive concussive brain injury, *in vivo*.[112,113] *Diffusion* refers to the random movement of water molecules from an area of higher concentration to an area of lower concentration within a fluid medium.[114] Water molecules within neuronal axons demonstrate preferential direction of movement—a phenomenon termed *diffusion anisotropy*.[114] Measuring diffusion within an axon forms the basis of DTI.[114] Concussion-induced damage causes axons to swell or rupture, resulting in significant changes in the diffusion of water molecules.[112] Although this research is in early stages, existing studies demonstrate that concussion may be associated with long-term alterations in white matter integrity, with the majority of research focusing on (adolescent, young adult) athletes and military personnel.[115-125] However, extant research demonstrates inconsistent findings with respect to the most common measures of white matter integrity, including differences in *fractional anisotropy* (FA; index of longitudinal water diffusion within axons),[115-125] *axial diffusivity* (AD; index of horizontal water diffusion within axons),[115,117,119-122] and *mean diffusivity* (MD; index of overall water diffusion within axons),[115,117-120,123-125] particularly within corpus callosum, corona radiata, and bilateral corticospinal tracts. Furthermore, few existing studies have consistently demonstrated correlations between DTI measures and clinical symptoms.[116,117,119,120,122-125] Thus, although existing studies indicate significant alterations in neuronal microstructure are associated with repeated concussion, current DTI techniques are not yet “up to par” with

identifying individual (person) level changes in white matter integrity for clinical decision making.

Findings from *ex vivo* examination of human brain tissue (postmortem) have engendered considerable interest linking neurodegenerative processes with repeated concussion. Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease, and has been observed in brain tissue of athletes with history repetitive concussive trauma.[75,76,126-129] CTE pathology is best characterized by the hyper-phosphorylation of tau-protein (neurofibrillary tangles; NFTs).[76,130] At the cellular level, accumulation of NFTs within the synaptic cleft disrupts neuronal communication and can signal apoptotic mechanisms, ultimately leading to cell death.[130,131] As the disease progresses, these molecular processes ultimately lead to volumetric decreases in both cortical (grey matter) and axonal (white mater) architecture.[131-133] Although CTE has been sensationalized via popular press in recent years, there is considerable controversy in characterizing the condition. The lack of validated *in vivo* biomarkers and pathophysiological characteristics of CTE are significant limitations.[134] In addition, existing biological samples of the disease are complicated by selection bias, and examining the clinicopathological correlates in potential CTE candidates is often muddled by the presence of multiple premorbid and/or comorbid (e.g., developmental disorders, substance use) factors.[135] Nonetheless, emerging research on the neurodegenerative processes associated with repetitive concussion highlights the importance of examining potentially chronic neurobehavioral consequences that precede CTE pathology.

Given the recent growth of media attention linking concussion with chronic detriments in neurobehavioral health (concentration and memory difficulties, emotional instability),[136,137] long-term consequences of concussion have become a central concern among athletes,

coaches, and families. Consequently, health care professionals and researchers have sought to examine cumulative effects of concussion on cognitive function and other neurobehavioral health factors. Studies have consistently demonstrated significant declines in cognitive function in retired professional athletes across several computerized performance measures (memory recall, visuospatial ability, attention, and reaction time; see *Assessment and Management of Concussion*, pg. 114) when compared to age-matched, non-concussed controls.[138-146] However, findings on cumulative effects on cognitive function in younger athletes is less clear. While some studies have shown small additive effects of multiple concussions (typically deficits in verbal and visuospatial memory),[147,148] others demonstrate no effects of prior concussions on global or task-specific cognitive performance.[149-151] The inconsistency in extant literature has sparked debate over whether or not such cognitive test batteries are reliable and sensitive enough to detect cumulative effects of concussion.[151]

With respect to other important neurobehavioral health outcomes, researchers have also shown retired professional athletes with history of multiple concussions are at greater odds of reporting symptoms of depression and anxiety, as well as socio-emotional distress (i.e., feelings of isolation) and suicidality behaviors.[152,153] The term *suicidality* refers to suicidal ideation (serious thoughts about taking one's own life), suicide planning, and nonfatal suicide attempts (intentional self-harm).[154] Though psychological symptoms are not uncommon following a single concussive event (irrespective of age), brain imaging research has shown individuals with history of multiple concussions demonstrate similar anatomical and functional brain alterations in areas that are commonly associated with psychological disorders.[142,155,156] Despite evidence linking multiple concussions with

greater emotional turmoil in retired elite athletes, less attention has been paid to neurobehavioral outcomes following repeated concussion in younger populations. Yet, research demonstrates higher rates of mood disorders and socio-emotional distress among youths with a history of concussion, relative to uninjured counterparts.[157,158] Youth concussion has also been associated with greater risk of experiencing suicidal thoughts, planning, and attempts;[159,160] however, it remains unclear how these neurobehavioral health outcomes may be moderated by frequency of prior concussive injuries. Additional investigations are needed, particularly given the recent evidence linking multiple concussions with chronic alterations in neurobehavioral health and potentially fatal risk behaviors (i.e., suicidality) in youth.[137] Understanding the link between multiple concussions and neurobehavioral consequences would complement intervention efforts and psychological skills programs to prevent potentially fatal outcomes.

In sum, while there appears to be a substantive evidence base supporting greater risk of subsequent injury among those with history of concussion,[105-107,109] research linking multiple concussions and long-term neurobehavioral consequences remains underexplored. Foremost, very few investigations have sought to examine potential sex differences regarding cumulative effects of concussion on neurobehavioral health. Though existing studies in this area have shown that history of multiple concussions may affect cognitive functioning in males to a greater degree than females,[148] whereas history of multiple concussions may affect sleep and emotional-behavioral functioning to a greater degree in females when compared to males.[161] Further research is necessary to elucidate potential sex differences in neurobehavioral health among males and females with history of multiple concussions. Additionally, studies on cumulative effects of concussion have

predominantly focused on multiple "clinically recovered" concussions in older adults several years post-injury,[152,153] and less attention has been paid to youth that have sustained consecutive concussions within close temporal proximity (a single sport season or academic year).[162,163] Research suggests returning to sport within 7-10 days post-injury not only increases risk of subsequent concussion, but often results in delayed recovery – or prolonged and persistent symptoms.[164,165] Although the neurobehavioral consequences of repeated concussion are not fully understood, studies suggest the lack of appropriate recognition and proper injury management (i.e., underreporting or premature return-to-play) may lead to poorer recovery outcomes.[165,166] Thus, prompt recognition and proper management techniques are imperative for preventing potentially devastating long-term sequelae.

Assessment and Management of Concussion

The clinical assessment and management of concussion can vary considerably between individuals and injuries, and across clinical settings. The same committees / panels that have aimed to reach a consensus in defining concussive brain injury have also sought to establish assessment and management guidelines,[18,19,20] and each highlight the importance of evaluating specific functional outcomes (e.g., clinical symptoms, cognitive and sensorimotor functions) and monitoring neurobehavioral health,. Another common feature across existing guidelines is the recommended incorporation of baseline testing to enhance delineation of within-subject post-concussive detriments.[18,19,20] This is not always feasible in clinical settings outside those intimately tied with sporting arenas. In hospital settings, such as specialty clinics, normative data provides an important foundation for clinical decision making. Irrespective of setting, concussion management practices are

continuously evolving, and new assessment instruments and techniques are constantly emerging. Thus, the key focus of this section will serve to synthesize to common clinical, evidence-based assessments for screening and managing concussive injuries in adolescents and young adults, with emphasis on measures that align with the specific aims of the proposed series of experiments, pg. 90.

Concussion Symptoms. Prompt recognition of the early signs and symptoms of concussion is critical in proper management. During the acute phase of injury, concussed individuals typically experience headaches, dizziness/balance problems, nausea/vomiting, blurry vision, light or noise sensitivity, and disrupted sleep. [20,111,167] In the days to weeks following injury, many of these symptoms persist and recovery may be further complicated by disturbances in cognitive (e.g., concentration and/or memory difficulties) and emotional (e.g., irritability) health.[20,111,168]

Clinical instruments, such as the *Rivermead Post-Concussion Symptom Questionnaire* (RPQ),[169] *Sport Concussion Assessment Tool* (SCAT),[170] and Post-Concussion Symptom Scale (PCSS)[171] are among the most widely utilized self-report inventories designed to provide health care professionals with subjective information regarding symptom intensity (total number) and symptom severity (respective Likert Scale rating) in adolescents and adults following concussion. Although reporting of concussion-like symptoms at baseline is not uncommon,[172,173] research on the psychometric properties of these inventories demonstrates comparable validity in discriminating concussed and non-concussed subjects.[174-179] However, some concussion symptom inventories may differ with respect to measures of reliability. More specifically, studies show that test-retest reliability falls well below clinically acceptable levels for both the SCAT and PCSS,[180,181]

whereas other studies have observed greater consistency in test-retest scores among clinical and non-clinical samples using the RPQ.[169,179,182]

While these studies suggest that the RPQ may be more useful in tracking recovery, it is important to note that there are many factors that can influence the reliability of concussion symptom inventories.[183] Thus, current discrepancies in the aforementioned studies may be due to variations in research design, rather than characteristics of the inventories in question. Taken together, current evidence suggests that self-report symptom inventories may be useful in screening for suspected concussion, but should not be used as a standalone diagnostic nor in determining recovery.

Cognitive Function. Another key area of evaluation and management of concussive injury involve tests of cognitive function. Given the reliability and potential limitations of self-report inventories, health care professionals often rely on more objective measures of brain function to gain a better understanding of concussed individuals' health and recovery. Instruments such as the Standardized Assessment of Concussion (SAC)[184] are commonly employed in the immediate screening of concussion in sport. The SAC is an observer-rated inventory designed to evaluate cognitive function by assessing orientation, immediate memory, concentration, and delayed recall performance.[184] The SAC has proven to be clinically useful in classifying acutely concussed from non-concussed subjects, with 95% sensitivity and 76% specificity.[185] However, longitudinal research shows that participants rapidly return to baseline SAC values (typically within 48 hours),[185] and demonstrates poor test-retest reliability (ICC = .34-39, d = .07-.42).[180] Thus, the SAC may be useful in screening of concussion, but may have limited application in tracking symptoms outside the acute phase of injury.

In addition to observer-rated assessments, health care professionals commonly administer computer-based cognitive assessments, such as the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)[186] and CogState Brain Injury Test Battery[187] to more objectively evaluate post-concussive alterations in brain function. The ImPACT generates composite scores to quantify cognitive performance across domains of attention, problem solving ability, working memory, and speed of information processing.[186] While studies on the face validity of ImPACT suggests some clinical utility in screening concussive injuries,[188-190] additional research has found the ImPACT to be largely unreliable in repeat testing across cognitive domain measures, with the possible exception of visual motor speed (ICC = 0.66-0.72, d = 0.13-0.22).[190] The CogState is another commonly employed computer-based cognitive testing software designed to measure processing speed, attention, visual learning, working memory, as well as visual motor and executive functioning.[187] Construct validity and sensitivity of the CogState test battery for adequately assessing changes in cognitive function within the clinical population of concussion has been demonstrated in the scientific literature.[187,190] However, the CogState has also been shown to perform unreliably in test-retest settings, but similar to ImPACT, measures of performance speed tend to fair better.[191] Furthermore, in general, computer-based indices of neurocognitive impairments often fail to correlate with subjective clinical symptoms.[192] Moreover, while studies suggest that computerized neurocognitive assessments are sensitive to change in brain function following concussion, they are susceptible to a number of confounding factors (e.g., neuropsychiatric conditions, neurodevelopmental disorders)[193,194] that may compromise interpretation and render them less than clinically optimal, particularly outside the acute phase of injury.[190] To this end,

experts recommend a multifaceted approach using computerized indices of neurocognitive functioning in combination with other sources of data can enhance diagnostic sensitivity and tracking of recovery, while being mindful of the potential confounds that can influence outcomes measures.[195,196]

Though not widely used in the field of concussion, some researchers have implemented other neurobehavioral measures to enhance recovery management following injury.[20,107,197,198] For example, instruments such as the Behavioral Rating Inventory of Executive Function (BRIEF),[199] have been utilized by health care professionals, particularly when working with youth, to gain a better understanding of the cognitive-behavioral consequences following concussion. The observer-report version of the BRIEF is designed to be completed by either a parent/guardian or another person close to the child or individual being assessed. The observer completing the questionnaire is asked to choose the response (N= Never, S= Sometimes, or O = Often) that best characterizes their child or the individual, based on their observations. Items of the BRIEF are separated into nine, non-overlapping scales that are used to generate; one summary score (Global Executive Composite, *GEC*) and two summary sub-scores. The Behavioral Regulation Index (BRI) summary sub-score includes measures of inhibitory control, attention shifting, emotional control, and self-monitoring behaviors. The Metacognition Index (MI) summary sub-score includes measures of task initiation, working memory, task monitoring, and planning/organizing behaviors. In addition, the BRIEF includes three validity scales that are utilized to check the consistency of responses from the individual. While the BRIEF was not specifically developed to evaluate concussion, research has shown that it is clinically useful in classifying observer-rated detriments in executive functioning

following traumatic brain injury,[199,200] with high internal consistency (α = 0.80-0.98) and test-retest reliability (r = 0.82-0.88).[201] Incorporating parent observations not only provides health care professionals with valuable information on patient cognitive-behavioral functioning in daily life, but including such assessments may also serve to further engage caregivers (parents) in the management of their child's injury and recovery.[202,203]

Psychological Health. Elevated levels of psychological distress and mood disturbances are common among individuals recovering from concussion,[204-206] and research has shown that emotional-behavioral symptoms of concussion may coincide with decrements in specific cognitive performance measures (i.e., visual memory, reaction time).[207] As such, instruments such as the Beck Depression Inventory (BDI)[208] and the Brief Symptom Inventory (BSI)[209] have been utilized by researchers and health care professionals to gain a better understanding of the emotional-behavioral outcomes following concussive brain injury. There are several versions of the BDI available, each with minor semantic variation for items tailored toward appropriate age of the respondent. In general, the BDI is a short, self-report inventory that evaluates depressive symptoms including mood, pessimism, self-dissatisfaction, guilt, sense of failure, punishment, self-dislike, self-accusation, crying, irritability, indecisiveness, social withdrawal, and sleep difficulties. A 4-point Likert scale (0=never, 3=always) is used to self-rate how each item reflects respondents' characteristics, with a total score range of 0 – 60; higher scores indicating greater severity of depressive symptoms. Estimates of internal consistency for the BDI have been acceptable for healthy and depressed adolescents and adults (α = 0.83—0.95).[210] Estimates of test-retest reliability have also been acceptable (r = 0.73—0.96).[210]

With respect to concussion, a cutoff score of 19 has been shown to maximize sensitivity (87%) and specificity (79%) of elevated depressive symptoms following injury.[211]

The BSI was originally developed by Derogatis and Melisaratos (1983)[209] from the Symptom Check List with 90 items (SCL-90).[212] However, medical professionals determined the length of the inventory was cumbersome, particularly in clinical settings that often require repeat testing. Thus, the shortened Brief Symptom Inventory with 53 items was created using factor analysis following the scale structure of the SCL-90 (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety paranoid ideation, and psychoticism). To further reduce stress overload in patients and broaden the clinical application of the inventory, an abbreviated version with 18 items (BSI-18)[213] was developed to examine psychological distress across a wide range of clinical populations. The BSI-18 contains three six-item scales to evaluate somatization (SOMA), anxiety (ANX), and depression (DEP). Participants are asked to report on items of emotional-behavioral functioning, rated from (0 = Not at all) to (4 = Extremely), which best describes how they have been feeling during the last week. A total score over all items can be calculated representing general psychological distress (global severity index; GSI). Estimates of internal consistency for the BSI across the three subscales SOMA ($\alpha = .74$), ANX ($\alpha = .84$), DEP, ($\alpha = .79$), and GSI ($\alpha = .89$) have been shown satisfactory in healthy American sample of 18-60 years old.[213] Estimates of test-retest reliability have also been satisfactory (r = 0.68—0.82) in clinical populations without intervention.[214] The BSI-18 has also shown good internal consistency, good convergent validity with other measures of emotional-behavioral functioning, and low to moderate test-retest reliability in a large normative samples of high school and collegiate

athletes.[180,215] Moreover, the BSI-18 has demonstrated high internal consistency for GSI ($\alpha = 0.84$—0.91), ranging fair to good across somatization, anxiety, and depression subscales ($\alpha = 0.61$—0.84); moderate test-retest reliability for GSI and subscales ($r = 0.57$—0.67); and moderate concurrent validity in predicting functional, psychosocial, and psychological status ($r = 0.49$—0.68) in a brain injured cohort.[215] Thus, in addition to aforementioned concussion symptom inventories and measures of cognitive function, incorporating measures of psychological health may provide health care professionals with valuable information on patient emotional-behavioral functioning in daily life.

Current Knowledge: Sex-based Differences in Concussion Outcomes

In addition to providing guidelines for the assessment and management of concussion, recent consensus statements[20,111] also highlight the importance of considering individual characteristics that may modify the nature and outcomes of concussion. Biological sex is one such factor gaining interest among researchers and health care professionals. While there appears to be a substantive knowledge base on sex-based differences in prevalence (as previously discussed), less is known regarding the influence of sex on concussion recovery and long-term health outcomes. Prior works in the greater TBI literature appear to demonstrate poorer outcomes among females;[7] however, relatively few studies have exclusively examined the relation between sex and outcomes following less severe brain injuries, such as concussion.[59] Further, the majority of existing research in this area has focused on adults, with less attention paid to potential sex-based differences in concussion recovery outcomes among adolescents.[59] This section serves to provide a summary of existing studies that have aimed to explore the influence of sex on common measures of concussion outlined in the preceding section. Each subsection is organized

such that evidence for sex differences in baseline measures are discussed first, followed by post-injury phases of recovery. Given the important influence of age on concussion outcomes, each subsection seeks to address current evidence for adolescent and adult populations.

Concussion Symptoms. Numerous studies have examined the relation between sex and clinical symptoms following concussion. Among adolescents, studies have observed significant differences between males and females on self-reported concussion symptom inventories. However, current studies have been inconsistent across baseline, acute, and post-acute assessments. To date, limited evidence exists for sex differences in symptom reporting at baseline. Of the few existing studies, it appears older adolescent females (13-17 years) may endorse greater symptoms than their male counterparts;[172,216,217] whereas the inverse relation may be true among younger adolescents (10-12 years).[217] With respect to acute symptom reports, some studies have shown that adolescent females endorse higher number and greater severity of symptoms when compared to adolescent males,[218-220] while other studies have observed no such differences.[221,222] Additional research aiming to determine if particular symptom clusters (migraine-cognitive-fatigue, affective, vestibular-somatic, and sleep) differ between male and female adolescents has also been largely inconclusive, with a possible exception of greater affective endorsement among females at baseline.[217,222-225] In contrast, research examining adolescent sex differences in post-acute symptoms appears to be more consistent. Recent meta-analyses have revealed greater risk of reporting persisting symptoms and longer duration of symptom resolution among adolescent females (>1 month post-injury), when compared to adolescent males.[226,227] Despite the methodological strengths of meta-analyses, it is important to consider that the

majority of current studies have utilized cross-sectional designs and lack adequate control for potential baseline differences – which might influence acute and post-acute effects. Further, given the unreliability of symptom inventories beyond initial screening of concussion, it is not currently possible to draw any strong conclusions that adolescent females differ from males in duration of recovery, based on such measures. Thus, the influence of biological sex on severity, intensity, and duration of concussion symptoms in adolescents remains to be fully understood.

A greater number of studies have examined sex differences in concussion symptom reporting among young adults. At baseline, Covassin and colleagues (2013) observed higher rates of reporting concussion-like symptoms on the PCSS among females when compared to males.[223] Researchers have also observed similar trends in SCAT symptoms, with females endorsing higher mean and median total symptom scores, as well as significantly lower proportion of reporting no symptoms at baseline, relative to males (24.3% and 47.4%, respectively).[227] Studies examining specific baseline symptom clusters have found females are more likely to endorse affective and sleep symptoms than males, but findings for cognitive, somatic, and sensory symptom clusters have been inconsistent.[228,229] With respect to acute symptom reports, research has consistently shown females report a higher total number and greater severity of acute post-concussion symptoms than males.[223,230-233] Importantly, these findings appear to be stable across mode of injury and setting (sport, military, MVA, falls, etc.).[234,235] Researchers have observed mixed findings when examining acute symptom clusters; although, overall trends reveal greater endorsement of affective and vestibular-somatic symptoms (e.g., headache, dizziness) among females and greater endorsement of confusion among males during the

acute phase of concussion recovery.[208,227,229,236-238] To date, however, only one meta-analysis has sought to statistically examine specific symptoms and has revealed only confusion differed between the sexes, with females at lower odds of endorsing confusion than males.[227]

With respect to post-acute (chronic) concussion symptoms, large cohort studies have shown that females are more likely to endorse higher concussive symptoms than males at three months post-injury.[239] Other research has shown military females with history of mTBI reported greater post-concussive vestibular-somatic dysfunction than their male counterparts, even when controlling for important comorbidities (e.g., PTSD) and injury characteristics (e.g., blast exposure).[235,240] Recent systematic reviews have also revealed higher risk among females for elevated symptoms 12-18 months post-injury,[241] and greater odds of persisting symptoms at 3-6 years following most recent diagnosed mTBI.[242] Together, these findings indicate young adult females not only experience greater symptom burden in earlier phases of recovery, but may be more likely to experience persisting symptoms following concussion.

In sum, research has shown adolescent and young adult females may endorse greater concussion-like symptoms than males at baseline; though findings appear dependent upon age.[172,217,223,227,230-239] While trends appear stable across acute and post-acute phases of concussion in young adults, the available evidence is less clear among adolescents. Further, current findings regarding sex differences in specific symptom clusters are also variable, with the exception of potentially greater endorsement of affective and vestibular-somatic symptoms among females.[207,227,229,236-238] Together, irrespective of assessment timepoint, these findings suggest other factors (e.g., sociocultural pressures,

hormonal changes) may influence concussion reporting behaviors differently in females than in males. However, many studies examining the relation between sex and reporting of concussion symptoms have failed to control for other important potential moderators, such as concussion history, which may also influence concussive recovery outcomes. Although researchers and health care professionals should be aware of the potentially different symptom profiles between males and females, given the critical limitations of available evidence, our current understanding of sex based differences in symptom reporting among adolescents and young adults remains incomplete.

Cognitive Function. The majority of literature regarding sex-based differences in concussion/mTBI has focused on cognitive outcomes. The popularity of computerized neurocognitive tests (NCTs) in research and clinical settings has grown considerably over the last decade. NCTs provide valuable information on cognitive performance across measures of attention, learning, memory, and speed of information processing (previously discussed). This subsection aims to synthesize current literature evaluating potential sex-based differences in neurocognitive performance at baseline and following concussion. As will be discussed in detail below, some research indicates there may be sex-based differences in specific domains of neurocognitive functioning. However, current evidence has largely failed to find consistent patterns of performance between males and females.

Research examining sex differences in NCT performance at baseline often include samples that span high school and collegiate athletes. Among these studies, authors have found females tend to perform better on tasks of verbal memory[243,244] and visual motor processing speed[243] when compared to males. However, with respect to studies that have focused exclusively on adolescent or young adult athletes, findings are somewhat mixed.

Researchers have often failed to observe baseline sex differences in adolescent neurocognition.[217,245,246] In contrast, researchers examining sex differences in baseline NCT performance among collegiate athletes have observed better verbal memory among females when compared to males, but better visual memory performance among males when compared to females.[247] Researchers have speculated the inclusion of younger (pre-pubescent) adolescents may skew results, and have suggested hormonal differences between males and females may play a significant role in cognitive functioning, irrespective of injury status.[217]

Research aiming to examine sex differences in acute post-injury outcomes has also been somewhat inconsistent. Some studies have shown no differences between males and females in immediate post-concussive NCT performance,[236,248-250] whereas others have observed differences within specific cognitive measures. Among studies including both adolescents and young adults, studies have shown slower reaction times[230,231] and poorer verbal and visual memory scores[223,237] in females when compared to males. These findings have been corroborated by a recent meta-analysis demonstrating larger deficits in overall cognitive functioning among females 1-10 days post-injury when compared to males.[251] Interestingly, sex-based differences in cognitive outcomes following concussion may also be influenced by age. Tanveer and colleagues (2017) observed poorer visual memory ~3 days post-injury among adolescent females ≥14 years when compared to age-matched males, but no sex differences among adolescents ≤13 years.[238] Research has also shown greater acute differences on ImPACT test performance among adolescent females, as well as longer duration to return to baseline performance when compared to adolescent males.[220] While these findings suggest females may experience greater cognitive deficits following

concussion, other investigations using the SAC may indicate better post-injury immediate memory and delayed recall in females when compared to males.[252] Though additional research suggests these differences may be influenced by specific post-traumatic neurological symptoms (i.e., migraine) that may become chronic and delay recovery, particularly in females.[233]

Although researchers often observe longer recovery of self-reported symptoms (including cognitive) in females when compared to males,[226,227,239-242] evidence for protracted recovery among females using more objective measures of neurocognitive performance remains less clear. Henry and colleagues (2016)[253] prospectively examined sex differences in NCT performance in athletes age 14-23 years and reported no differences in recovery time, or at any specific assessment timepoint (at 1, 2, 3, and 4 weeks) on any ImPACT measure between males and females. In contrast, Majerske and colleagues (2008)[254] found a greater proportion of adolescent females (53.3%) demonstrated impaired visual memory and visual motor speed at 1-month follow-up when compared to adolescent males (26.3%). The authors further demonstrated a delay in returning to moderate-intensity physical activity predicted poorer cognitive outcomes at 1-month follow-up. Additional research on post-acute NCT performance in adults also demonstrates mixed findings. Some studies have shown better visual[255] and verbal memory[140] among females when compared to males, whereas other research has shown slower reaction times in females when compared to males.[256]

In sum, research on sex differences in cognitive functioning has largely failed to find consistent patterns of impairment between males and females at baseline and post-injury. However, trends in specific NCT measures have emerged, with research often

demonstrating better verbal memory performance among females and better visual memory performance among males.[140,243,244,247,255] Inconsistencies in current literature may be due to variability in research design between studies. Cross-sectional studies that demonstrate differences between males and females in post-concussive cognitive functioning cannot control for baseline differences. Interestingly, longitudinal studies that have controlled for baseline differences have also produced conflicting findings, but have illuminated important potential moderators (*time return to physical activity, severity of specific post-traumatic symptoms – migraine*)[233] that may differ between males and females, thereby influencing concussion recovery. Additional studies have also shown that variables such as *time to specialty care*[257] and *sleep quality*[161] may also moderate sex-based differences in cognitive recovery following concussion. Thus, evaluating differences between males and females on NCT performance can be very difficult. Nonetheless, continued efforts to longitudinally examine such differences are incredibly important, and informative for appropriate clinical decision making among health care professionals.

Psychological Health. Measures of psychological health are perhaps the most overlooked areas of clinical research regarding the effects of concussion on neurobehavioral health; this is particularly true among youth and young adults.[258] Yet, existing studies have consistently demonstrated higher rates of mood disorders and emotional-behavioral distress in concussed adolescents and young adults, relative to uninjured counterparts.[157,158,258,259] Furthermore, investigations on potential sex-based differences regarding concussion and psychological health outcomes are relatively sparse among adolescents and young adults. Nonetheless, this subsection aims to synthesize

current literature evaluating potential sex-based differences in psychological health at baseline and following concussion.

Sex differences in psychological health among adolescents and young adults have been well documented. In general, research has shown adolescent females report lower subjective well-being than males, and this gap appears to amplify into adulthood.[260,261] Adolescent and young adult females also appear to be more concerned about mental health issues than adolescent and young adult males, and perhaps more likely to report symptoms.[262] The gap between males and females regarding mental health diagnoses becomes more prominent following puberty, and continues to diverge into adulthood.[263,264] As such, researchers suggest that neuroendocrinological factors may contribute to greater emotional-behavioral problems among adolescent females, as well as increased likelihood of mental health diagnoses through adulthood when compared to age-matched males.[265,266] Emotional-behavioral problems are typically characterized in terms of *internalizing* and *externalizing* behaviors. The former refers to behaviors that are directed inward, through depression, anxiety, hypersensitivity, and somatic complaints; the latter refers to behaviors that manifest outward, by way of attention and concentration problems, irritability, lack of inhibitory control, and other impulsive behaviors.[266,267] Research shows adolescent and young adult females have greater tendency to 'internalize' emotional distress; whereas, adolescent and young adult males are more likely to 'act out' when experiencing psychological stressors.[268-270] Further, research indicates adolescent and young adult females may also have greater tendency to report non-fatal suicidal behaviors (ideation, planning, attempts) when compared to males, whereas males may be more likely to die by suicide than females.[271,272] Though prior research suggests that females are at greater odds

of reporting psychological distress and mental health diagnoses when compared to males,[273] the degree to which concussion compounds pre-existing emotional-behavioral problems is less clear.

Research on post-concussive psychological outcomes is relatively sparse, particularly among youth. Further, studies supporting sex-based differences in psychological health following concussive injury predominantly include evidence from specific items or clusters on concussion symptom inventories (discussed previously) or likelihood of post-traumatic psychiatric diagnoses, rather than discrete measures of emotional-behavioral functioning. Of the existing studies on sex differences in acute psychological outcomes following concussion, current evidence is mixed. Kontos and colleagues (2012)[229] found females endorsed greater affective symptoms 1—7 days post-concussion when compared to males, but no differences in other symptom clusters (cognitive, somatic, sleep). In a follow-up study,[207] the authors found no differences in concussion symptoms nor BDI scores between females and males at 2, 7, or 14 days following concussive injury. In contrast, Covassin, Schatz, & Swanik (2007)[237] found males reported more post-concussive sadness when compared to females at ~3 and 10 days following injury. Thus, scant evidence and inconsistent findings hinder any strong conclusions for potential sex differences in psychological function acutely following concussion.

Researchers have also examined sex differences in psychological health in post-acute phases of injury. However, it should be acknowledged many investigations in this area include the full range of TBI severity, with very few focusing exclusively on concussion or mTBI. Overall, current evidence suggests adolescent and adult females may

experience more severe emotional-behavioral symptoms and may be more likely to carry psychological diagnoses long-term following concussion.[235,259,274,275] Iverson and colleagues (2011)[235] evaluated sex differences in neurobehavioral symptom severity and psychological diagnoses in a large sample of post-TBI veterans and found females were more likely to report somatosensory, vestibular, and cognitive symptoms when compared to males, but interestingly no differences were observed on affective symptoms. Additionally, the authors reported that females were more likely to carry psychological diagnoses of depression and anxiety than males, but these effects were diminished to null when blast exposure was controlled in the analyses. Scott and colleagues (2015)[274] examined outcomes of psychological diagnoses, as well as psychosocial functioning (i.e., emotional-behavioral characteristics of externalization and internalization problems) among adults with childhood history of concussion and moderate/severe TBI and healthy controls. Though the authors demonstrated comparable odds of reporting psychological diagnoses (across conditions), the authors found greater odds of internalizing problem behaviors among females, and greater odds of externalizing problem behaviors among males, regardless of injury severity.[274] Interestingly, research has shown that increases in frequency of prior concussion is strongly correlated with increases in depressive symptoms (particularly rumination) in females, but not males.[275] Though fascinating, it remains unclear to what degree concussion exacerbates emotional-behavioral problems, as these patterns of behavior are also evident between females and males without history of brain injury.[259] However, additional research using advanced psychophysiological techniques to evaluate autonomic nervous system function as well as neural substrates of emotional processing are beginning to provide some insight.

More specifically, research has shown dysautonomia – namely, decreased parasympathetic activity – during the first week of injury predicts elevated depressive symptoms eighteen months post-concussion in females, but not in males.[276] Further, studies using EEG have shown females with history of multiple concussions demonstrated similar neural processing of emotion to uninjured females, whereas males with history of multiple concussions demonstrated blunted neural processing of emotion when compared to uninjured males.[277,278] Together, current evidence (though limited and tentative) indicates that concussion may differentially affect post-concussive psychological health and emotional-behavioral functioning between females and males, and these effects may be partially moderated by frequency of prior injury (as discussed in *Cumulative Effects of Concussion*, pg. 109). Additional investigations are needed, particularly given the growing body of evidence linking concussion with chronic psychological health problems and potentially fatal risk behaviors among youth and young adults.[137,157,158]

Summary. There is growing interest among researchers and clinicians for developing a better understanding of the influence of sex on concussion recovery and outcome. Current research on sex differences indicates that females may experience more severe symptoms and longer recoveries when compared to males. While several studies have aimed to examine sex differences in cognitive function following concussion, existing research remains inconclusive. Additionally, while some evidence indicates females may be at greater risk of decline in psychological health relative to males following concussion, investigations have largely failed to confirm sex differences in post-injury emotional-behavioral functioning that cannot be explained by potential differences at baseline. Furthermore, a growing body of evidence suggests potential sex-based differences in

concussion outcome may be due to important biological factors (e.g., hormonal differences); however, very few longitudinal investigations exist and our understanding of the influence of sex-based hormones on concussion outcomes remains incomplete and tentative. Thus, the series of proposed studies is intended to address important knowledge gaps in current literature, and specifically seeks to illuminate the relation between biological sex and key domains of brain function and neurobehavioral health.

METHODS

Experiment 1

Purpose. To examine the influence of biological sex on concussion symptoms, cognitive function, and psychological health following adolescent concussion.

Research Design. We will utilize a prospective cohort design to evaluate the influence of sex on dependent variables: self-reported concussion symptoms, computerized measures of cognitive function, parent-reported executive function, and self-reported depressive symptoms. Independent variables will include male and female sex, as indicated by participant medical records of physical examination.

Participants. Male and female adolescents (13 – 18 years of age) that present to a local Pediatric Concussion Clinic will be screened for inclusion. Adolescents with a history of a learning disability or developmental disorder, history of a psychiatric or mood disorder, and/or use of psychotropic medication will be excluded from the study. Additionally, adolescents with history of moderate-severe brain injury, or other neurological disorder (including migraines) will be excluded from the study. Male and female adolescents will be matched on key demographic and injury information, including age, body mass index, race/ethnicity, concussion history, and current injury characteristics

(e.g., injury modality, loss of consciousness, post-traumatic amnesia). Additionally, only those participants that completed the full battery of tests at initial and follow-up examinations will be included in the statistical analyses. All study procedures have been approved by the Institutional Review Board at Prisma Health-USC School of Medicine (Pro00075286). Waivers of Written Consent and Health Insurance Portability and Accountability Act (HIPPA) Authorization have been granted. However, adolescents and their parents/legal guardians will be verbally informed by the attending physician of all clinical research activities, and will be provided the opportunity to withdraw participation if they prefer.

Instrumentation. The National Institutes of Health provides an open-access resource for exploring several common data elements (CDEs; data elements common in multiple data sets across studies). Included are "domain-specific" CDEs for the clinical study of concussion. We will draw from the NIH-supported CDEs that span measures of clinical symptoms, cognitive function, and psychological health to guide clinical assessments:

- The *Demographic, Health, and Safety Questionnaire* is an extensive survey we will use to acquire basic demographic information, academic history, and personal/family medical history. This data enables the physician and study staff to identify and evaluate known risk factors that may potentially complicate recovery. Additionally, this screening questionnaire has been designed to ensure participants will have minimal to no risk of adverse reactions during examinations.
- The *Rivermead Post-Concussion Symptoms Questionnaire* (RPQ)[169] is a 16-item self-report survey that will assess the presence and severity of somatic, cognitive, and

emotional symptoms most commonly experienced following a mild traumatic brain injury. The RPQ is designed to compare post-concussive symptom burden with pre-injury status on a 5-point Likert scale, (0 = Not experienced) to (4 = A severe problem).

- The *CogState Brain Injury Test Battery* (CogState)[187] is a validated computerized assessment for rapid and reliable measure of cognitive function following traumatic brain injury. A modified version including one-back and two-back tests (working memory), a Groton maze learning test (executive function), and a Groton maze delayed recall test (visual memory recall) will be administered to assess post-concussive cognitive functioning.
- The *Behavior Rating Index of Executive Function* (BRIEF)[199] is an 86-item questionnaire aimed at assessing multiple sub-domains of executive function, including: inhibitory control, attention shifting, emotional control, self-monitoring, task initiation, working memory, planning, task monitoring, and organization behaviors. The parent-report version of the BRIEF requires either a parent/guardian to respond (N= Never, S= Sometimes, or O = Often) on items that best characterize their child, based on their daily observations. Test scores will be compared to age-adjusted normative values to provide insight into the child's executive functioning.
- The depression subscale of the *Beck Youth Inventories* (BYI-2)[208] is a 20-item self-report inventory designed to measure symptoms of depression in children and youth aged 7 to 18 years. The survey includes items related to negative thoughts about self, life, and the future, as well as feelings of sadness, guilt, and sleep disturbance. Participants are asked to choose between 4 statements, rated from (0 = Never) to (3 = Always), which best describes how they have been feeling during the last two weeks.

Study Procedures. Collaborating physicians at local concussion clinics have requested research assistance in developing and implementing an evidence-based clinical care protocol. We will leverage this partnership by recruiting adolescent patients that present to the Pediatric Concussion Clinic with suspected brain injury. The program is designed to prospectively study and monitor concussion recovery outcomes (physical, cognitive, psychological) using the most up-to-date evaluation and management tools, and is consistent with the recommendations outlined in the most recent *Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016.*[20] The data collected from patients will help to improve our understanding of the natural course of recovery, help to identify patients who may be at risk for more adverse outcomes, and improve the standard of care for patients with concussive injuries. No patient is denied medical care. However, data from patients outside the initial and follow-up evaluation windows described above will not be analyzed in the present study.

Participant survey data, including (1) *Demographic, Health, and Safety Questionnaire*; (2) RPQ; (3) BRIEF; and BYI-2 will be collected via HIPPAA-compliant Research Electronic Data Capture (REDCap; Vanderbilt University, 2019) online survey software approximately 24-48 hours prior to each in-clinic visit. CogState computerized cognitive tests will be completed during each clinic visit. In accordance with the Office of Research Integrity and Compliance, participant confidentiality will be insured by assigning each individual a unique and unidentifiable code. This code will be used on all collected records throughout the duration of the study and is maintained solely by the attending physicians. Only de-identified protected health information and assessment data are

provided to the research team. All de-identified data will be housed via approved and protected University of South Carolina servers at the Public Health Research Center. This process ensures participant confidentiality through each stage of analysis, data presentation, and publication.

Data Analysis. Statistical analyses will take place at the Public Health Research Center at the University of South Carolina. Data will be analyzed using the Statistical Package for the Social Sciences Version 26 (SPSS; IBM, Chicago, Illinois), with *a priori* alpha level of $p < .05$ for all analyses. Independent samples t-tests will be used for continuous data, and χ^2 tests will be used for categorical data to compare male and female demographics and injury characteristics. Concussion outcome variables (RPQ, CogState, BRIEF, BDI-Y) will be examined via 2 (group: male, female) x 2 (time: initial exam, follow-up exam) repeated measures ANOVAs. Outcome variables will be assessed for normality via visual inspection of q-q plots and the Shapiro-Wilk test. Mauchly's sphericity tests will be employed to evaluate violations in the assumption of homogeneity of variance. In the event of a violation, a Greenhouse–Geisser correction for sphericity will be applied. Post-hoc comparisons will be performed to identify the source of the interactions by means of independent samples t-tests with Bonferroni correction for multiple comparisons. To address concerns for potential baseline differences, age- and sex-adjusted normative data will be used to calculate T-Scores for each outcome measure, and will be included in ANOVA models. Partial eta squared statistics will be calculated to provide magnitude of effect on significant differences between male and female adolescents. Additionally, χ^2 tests will be used to compare the proportion of males and females with persistent symptoms at follow-up. Power analysis, *a priori*, calculated a participant number of 54 to have

adequate power for detecting medium effect size (Cohen's $f = 0.25$; $\eta p^2 = 0.14$), which is comparable to prior research.[230]

Experiment 2

Purpose. To cross-sectionally examine sex-based differences in psychological outcomes and the association between concussion history (stratified by number of prior injuries) within previous 12 months and suicidality using data from the 2017 National Youth Risk Behavior Surveillance System (YRBSS).

Research Design. We will utilize a retrospective cross-sectional design to evaluate the association between concussion history and dependent variables: self-reported sadness/hopelessness and suicidality (suicidal ideation, planning, and attempts). The independent variable will include frequency of concussion (within the previous 12 months). Sex will be imputed as covariate to evaluate potential interactions.

Participants. The 14,765 high school students that completed the National Youth Risk Behavior Surveillance System (YRBSS) in 2017 will be screened for analyses. Students that did not respond to questions subserving the dependent (concussion exposures), independent (sadness/hopelessness, suicidal ideation, suicide planning, suicide attempts, injurious suicide attempts), and/or selected confounding (sex, age, race/ethnicity, current alcohol use) variables will be excluded from the analyses.

Instrumentation. The YRBSS provides valid and reliable measures of risk behaviors that contribute to leading causes of death and disability among youth in the United States.[279] The YRBSS includes national, state, territorial, tribal government, and local school-based surveys of high school students in 9th through 12th grade. Variables of interest for purpose of the proposed study are described below:

- *Exposure Variable*: Concussion exposure was a new variable included in the 2017 national YRBSS. The question included in the survey was specific to the respondent's participation in sport or recreational activities. Students were prompted on the following definition of concussion: *A concussion is when a blow or jolt to the head causes problems such as headaches, dizziness, being dazed or confused, difficulty remembering or concentrating, vomiting, blurred vision, or being knocked out.* In the following question, students were asked: *During the past 12 months, how many times did you have a concussion from playing a sport or being physically active?* In addition, students were instructed to report their number of concussions (e.g., *0 times*, *1 time*, *2 times*, *3 times*, or *4 or more times*).
- *Dependent Variables*: The dependent variables selected for this study will include five questions from the 2017 national YRBSS regarding psychological health and suicidality. Students were prompted with the following description of suicidality: *Sometimes people feel so depressed about the future that they may consider suicide, that is, taking action to end their own life.* Self-reported indicators of psychological health and suicidality will include: 1) sadness/hopelessness; 2) suicidal ideation; 3) suicidal planning; 4) suicidal attempt 5) injurious suicidal attempt.
- *Covariates:* The covariates selected for this study will include questions to identify participants' biological sex (*What is your sex? Male or Female*); age (*How old are you?*); race/ethnicity (*Are you Hispanic or Latino?, What is your race?*); and current alcohol use (*During the past 30 days, on how many days did you have at least one drink of alcohol?*).

Study Procedures. The YRBSS administers a school-based survey biennially with the aim of monitoring the prevalence of priority health risk behaviors among youth. In 2017, a three-stage cluster sampling design was used to produce a nationally representative sample of public and private school students in grades nine through twelve. Weight factors were applied to each respondent record to adjust for nonresponse and oversampling of certain grades, sex, and racial/ethnic demographics. Parental permission was obtained at each collection site, and survey participation was voluntary. Respondents provided their information anonymously on computer-scannable answer sheets. An institutional review board at the CDC approved all procedures. A detailed description of YRBSS sampling methodology can be found elsewhere.[279] The CDC YRBSS dataset is openly available (online access) for research: https://www.cdc.gov/healthyyouth/data/yrbs/data.htm.

Data Analysis. Data from the 2017 YRBSS will be analyzed using Statistical Analysis System Version 9.4 (SAS Institute; Cary, NC) with *a priori* alpha level of 0.05. Chi-square statistics will be used to examine bivariate association between categorical dependent and exposure variables. The GENMOD procedure in SAS will be used to examine the association between concussion history and 1) sadness/hopelessness; 2) suicidal ideation; 3) suicidal planning; 4) suicidal attempt; and 5) injurious suicidal attempt. Adjusted odds ratios (aOR) with 95 % Confidence Intervals (CI) will be calculated. Five weighted binomial regression models will be used to examine each of the five associations of concussion history and suicidality using bifurcated responses (e.g., *yes* versus *no*). To evaluate the potential influence of multiple concussions, five additional models will include three levels of no concussion history (*0 times*; reference), one concussion (*1 time*), and multiple concussions (*2 or more times*). All binomial regression models conducted will

be adjusted for covariation on age, race/ethnicity, and current alcohol use. For each regression model, an interaction term for sex will be included to examine potential differences between males and females. Cramer's V statistics will be calculated to provide magnitude of effect on significant differences between male and female adolescents. Power analysis, *a priori*, calculated a participant number of 1979 to have adequate power for detecting small effect size (OR > 1.68; Cramer's V = 0.04), which is comparable to prior studies.[159,160]

Experiment 3

Purpose. To longitudinally examine the relation between hormonal contraceptive (HC) and concussion outcomes by evaluating length of recovery, concussion symptoms, cognitive function, and psychological health.

Research Design. We will utilize a quasi-experimental, matched-comparison group design to determine the effects of HC on the dependent variables: recovery time, symptom severity, cognitive function, and self-reported emotional distress. Independent variables will include regular HC use of any dose (HC+), and non-HC use or none at all (HC-).

Participants. Female student athletes who were evaluated during baseline assessments, incurred a concussion, and completed post-injury assessments (n = 1,025) will be screened for inclusion. Participants with a history of learning disability or developmental disorder, and/or history of a psychiatric or mood disorder will be excluded from analyses. Additionally, participants with history of moderate-severe brain injury, non-sport-related mild brain injury, or other neurological disorder (including migraines) will be excluded from analyses. Further, prior works[280] indicate the Mirena IUD releases localized hormones that do not circulate the blood stream as is the case with other implants or oral

contraceptive pills. Thus, females reporting the use of the Mirena IUD will also be excluded. Females using hormonal contraceptives (HC+) will be matched to 50 non-HC user controls (HC-) on key demographics, including: age, body mass index, race/ethnicity, sport contact level, and injury characteristics, including: concussion history, time since injury, loss of consciousness, and post-traumatic amnesia.

Instrumentation. Concussion assessments will include measures of clinical symptoms (Sport Concussion Assessment Tool Symptom Scale) cognitive function (Standardized Assessment of Concussion; Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)), and psychological health (Brief Symptom Inventory—18). Instruments used to evaluate clinical symptoms, cognitive function, and psychological health are described briefly below:

- The clinical symptom inventory of the *Sport Concussion Assessment Tool* (SCAT)[170] is a 22-item self-report survey designed to examine total number and severity of common symptoms following concussion. Participants report symptoms on a 7-point Likert scale, (0 = none) to (6 = severe).
- The *Standardized Assessment of Concussion* (SAC)[184] is an observer-rated inventory designed to screen cognitive function by assessing orientation, immediate memory, concentration, and delayed recall.
- The *Immediate Post-Concussion Assessment and Cognitive Testing* (ImPACT)[186] is a 25-minute computerized cognitive test battery that evaluates working memory, attention, speed of information processing, and multi-tasking performance. For task descriptions.

- The *Brief Symptom Inventory – 18* (BSI-18)[213] is a short and reliable instrument that measures emotional-behavioral functioning in three dimensions: somatization, depression, and anxiety. Participants are asked to report on items of emotional distress, rated from (0 = Not at all) to (4 = Extremely), which best describes how they have been feeling during the last week. A total score over all items can be calculated representing general psychological distress (global severity index; GSI).

Study Procedures. In an effort to address important knowledge gaps in the field of concussion, the National Collegiate Athletic Association (NCAA) and the US Department of Defense (DoD) developed a partnership known as the Grand Alliance: Concussion Assessment, Research, and Education (CARE) Consortium. The CARE Consortium has, in part, been designed to establish an important concussion research network and implement scientific investigations on the 6-month natural history of concussive injuries among collegiate student athletes and military service personnel. Most pertinent to this study, a key factor underlying this partnership stipulates "the need for information about concussion in sports other than American football, and *concussion in females*."[281] A full description of data collection protocols, baseline and post-injury assessment tools, as well as recovery management procedures can be found elsewhere.[281]

In brief, the CARE Consortium collected data on ~47,000 student athletes and military cadets between the 2014 and 2017 academic years. Timepoints of data collection include baseline and post-injury assessments (acute, subacute, chronic phases of recovery). Prior to the start of sport season, participant demographics and medical history were collected and include important information on age, sex, concussion history, as well as pre-existing conditions and medication status. Upon suspected concussion, athletes were

removed from play and managed in accordance with accepted guidelines[10,160] by the performance site's medical team. Included in concussion records is important information on injury characteristics (e.g., mechanism of injury, loss of consciousness, post-traumatic amnesia), as well as data from post-injury assessments that spans clinical symptoms, cognitive function, and psychological health. All National Collegiate Athletic Association (NCAA) student athletes and military cadets at participating academic institutions were eligible for the study following the provision of written informed consent. The institutional review board at each participating university approved all research activities.

We will utilize CARE Consortium data to evaluate differences in concussion outcomes (length of recovery, concussion symptoms, cognitive function, and psychological health) between females on and off HC at baseline, 24-48 hours post-injury, and at unrestricted RTP assessments. Length of recovery will be defined by the number of days between injury and when the student is granted unrestricted RTP.

Data Analysis. Data will be analyzed using the Statistical Package for the Social Sciences Version 26 (SPSS; IBM, Chicago, Illinois). Independent samples t-tests will be used for continuous data, and χ^2 tests will be used for categorical data to examine group demographics (age, race, socioeconomic status, sport) and injury characteristics (concussion history, loss of consciousness, amnesia), and to confirm matching procedures are successful. Independent samples t-tests will be used to evaluate differences in length of recovery between HC+ and HC- females. Concussion outcome variables (SCAT5, SAC, ImPACT, BSI-18) will be examined via 2 (group: HC+, HC-) x 3 (time: baseline, 24-48 hours, unrestricted RTP) repeated measures ANCOVAs. Given the growing literature on cumulative effects of concussion, the number of prior concussions will be used as the

covariate in our analyses. Each continuous outcome variable will be assessed for normality via the Shapiro-Wilk test, and Mauchly's sphericity tests will be employed to evaluate violations in the assumption of homogeneity of variance. In the event a violation occurs, a Greenhouse–Geisser correction for sphericity will be applied. Post-hoc comparisons will be performed to identify the source of the interactions by means of independent samples t-tests with Bonferroni correction for multiple comparisons. To evaluate the potential influence of baseline group differences on recovery profiles, we will calculate change scores for each outcome measure and analyze via 2 (group: HC+, HC-) x 2 (change score: baseline-to-24-48 hours, baseline-to-RTP) repeated measures ANCOVAs, again with number of prior concussions used as the covariate. An *a priori* alpha level of 0.05 will be set for all analyses. Partial eta squared statistics will be calculated to provide magnitude of effect on significant differences between HC+ and HC- females. Power analysis, *a priori*, calculated a participant number of 50 to have adequate power for detecting medium effect size (Cohen's $f = 0.25$; $\eta p^2 = 0.14$), which is comparable to prior research.[282]

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