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# CLINICAL AND DEMOGRAPHIC VARIABLES ASSOCIATED WITH COGNITIVE DEFICITS, SYMPTOM SEVERITY, AND DURATION AFTER CONCUSSIVE INJURY IN ADOLESCENTS: A RETROSPECTIVE STUDY

Seema S. Aggarwal

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DEFICITS, SYMPTOM SEVERITY, AND DURATION AFTER CONCUSSIVE  
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A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE  
DEGREE OF DOCTOR OF PHILOSOPHY IN NURSING  
THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON  
SCHOOL OF NURSING

BY

SEEMA S. AGGARWAL, PhD(c), MSN, RN, NP-C

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MAY, 2016

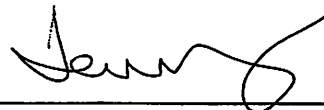
The University of Texas Health Science Center at Houston  
School of Nursing  
Houston, Texas

March 23, 2016

Date

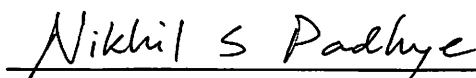
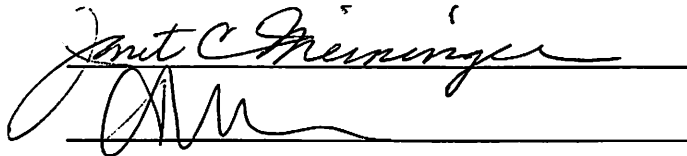
To the Dean for the School of Nursing:

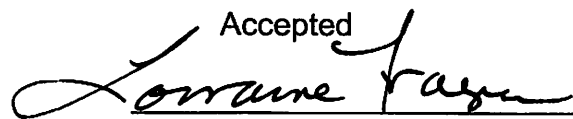
I am submitting a dissertation written by Seema Aggarwal and entitled " Clinical and Demographic Variables Associated with Cognitive Deficits, Symptom Severity, and Duration after Concussive Injury in Adolescents: A Retrospective Study". I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Nursing.



Terri Armstrong, PhD, Committee  
Chair

We have read this dissertation  
and recommend its acceptance:



Accepted  
  
Dean for the School of Nursing

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Seema Aggarwal

Clinical and Demographic Variables Associated with Cognitive Deficits, Symptom Severity, and Duration after Concussive Injury in Adolescents: A Retrospective Study

May, 2016

**Abstract**

**Background:** Concussions in adolescents are a public health concern with the growing popularity of high school sports. Recent legislation mandates that athletes who are suspected of a concussion be cleared to return-to-play by a clinician. More research is needed to develop a concussion predictive model to identify populations at risk for more severe and prolonged symptoms and long-term neurologic deficits.

**Aims:** The aims of this study were to (1) examine the effect of race and gender on neurocognitive and symptom scores and (2) determine which clinical (e.g., number of concussions, migraine history, learning disabilities/ attention deficit disorders) and demographic factors (e.g., age, gender, race/ ethnicity, health insurance, mechanism of injury/ sport, education) predict prolonged recovery times.

**Methods:** This was an observational cohort study of clinical data reviewed retrospectively in adolescents aged 13 to 19 years who were evaluated for an acute concussion ( $\leq 10$  days from injury) at a university-based concussion clinic between January 1, 2012 to August 1, 2015. Multivariate analysis of variance was used to examine the role of gender and race on Immediate Post-concussion Assessment and Cognitive Testing composite scores. Logistic regression, Kaplan-Meier analysis, and Cox regression proportional hazards model were utilized to examine predictors of concussion recovery times.

**Results:** The sample (N = 118) was primarily male (71.2%) with a median age of 16 (range 13-19 years old). Ethnic minorities (Blacks and Hispanics) constituted 40% of the sample. Univariate analyses revealed that females had slower reaction times than males ( $p = .04$ ) and minority females performed significantly worse on verbal memory ( $p = .04$ ) than other groups. Predictors of protracted recovery included ADHD ( $p < .001$ ) and prior concussion history ( $p = .03$ ). Predictors of shorter recovery times included student athletic insurance ( $p = .02$ ) and public insurance (Medicaid or Chips) ( $p = .03$ ) as compared with private or no insurance.

**Conclusions:** The findings showed that there was a gender difference on reaction time and there was an interaction of race and gender on verbal memory after a concussion. This study also identified key risk factors that may be used prognosticate concussion recovery times in adolescents.

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### **Summary of the Study**

The proposal entitled, “Clinical and Demographic Variables Associated with Cognitive Deficits, Symptom Severity, and Duration after Concussive Injury in Adolescents: A Retrospective Study” was a study conducted to examine risk factors for concussion severity and duration. Approval for this study was sought from the Committee for the Protection of Human Subjects (CPHS) at the University of Texas Health Science Center at Houston’s Institutional Review Board and approval was attained in July, 2015.

The retrospective study was conducted on cases from January 1, 2012 to August 1, 2015 from a university-based concussion clinic in the ethnically/ racially diverse metropolitan city of Houston, Texas. The specific aims of the study were to:

1. Examine the effect of race and gender on neurocognitive and symptom scores and
2. Determine which clinical (e.g., number of concussions, migraine history, learning disabilities/ attention deficit disorders) and demographic factors (e.g., age, gender, race/ ethnicity, health insurance, mechanism of injury/ sport, education) predict prolonged recovery times.

This was an observational cohort study of clinical data reviewed retrospectively in adolescents aged 13 to 19 years who were evaluated for an acute concussion. Once inclusion, exclusion, and sample selection criteria were applied, the study sample was N = 118. Descriptive statistics were used to analyze demographic and clinical characteristics of the sample by gender and race. General linear models were used to examine the relationship between gender and race and the composite scores of the Immediate Post-concussion Assessment and Cognitive Testing [ImPACT] computerized battery. Logistic regression and Cox proportional hazard regression was conducted to examine predictors of

concussion recovery time. The variables of interest for the Cox proportional hazard regression were clinical (e.g., number of concussions, migraine history, learning disabilities/ attention deficit disorders) and demographic factors (e.g., age, gender, race/ ethnicity, health insurance, mechanism of injury/ sport, education).

Three manuscripts were written on topics that were pertinent to the dissertation study. Manuscript A presented and discussed the methods and results of this retrospective study. The primary changes from the dissertation proposal was the addition of examining baseline concussion data, when available, and the descriptive data evaluating school type (public vs. private), the number of days from injury to presentation in clinic, and noting which subjects were on medication for Attention Deficit Hyperactivity Disorder (ADHD) prior to concussive injury. Manuscript B was a systematic review of the impact of gender on concussion outcomes in adolescents and young adults. Results from the systematic review are presented along with a discussion on the findings from the literature. Manuscript C describes the Concussive Vulnerability framework and depicts how a concussive injury occurs and the potential recovery pathways of concussion. Appendices A-D contain supplemental information from the studies including CPHS approval from the University of Texas Health Science Center, the study operations protocol, information on the coding of study variables, and training certificates.

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OCTOBER, 2016

### **Proposal and Specific Aims**

There are approximately 1.7 million traumatic brain injuries (TBIs) that occur in children and adults annually, of which 75% are mild traumatic brain injuries (mTBIs), also termed concussions (Centers for Disease Control, 2003). Concussions in children commonly occur from falls, motor vehicle accidents, and sports. Common concussion symptoms include headaches, nausea, dizziness, light and noise sensitivity, emotional changes, and cognitive difficulties. Concussion symptoms typically resolve within 10 days; however approximately 10-15% of concussions result in persistent symptoms lasting longer than 10 days (McCrory et al., 2013). Concussion diagnosis rates in high school athletes have increased significantly from 2006 to 2012 by 0.23 to 0.51 concussions/1000 athletic exposures (Rosenthal, Foraker, Collins, & Comstock, 2014). Concussions result in lost school and work time during recovery and may reduce quality-of-life (QOL) (Pieper & Garvan, 2014). Risk factors for more severe and/ or prolonged concussion symptoms (>10 days) may include pediatric age, female gender, mechanism of injury, previous concussion history, migraine history, psychiatric history, learning disabilities, and attention deficit disorders (Committee on Sports-Related Concussions in Youth, 2014; Giza et al., 2013; Harmon et al., 2013; McCrory et al., 2013).

The focus of this study will be on concussions in the adolescent population. High school athletes have a higher incidence of concussions compared to college athletes (Clay, Glover, & Lowe, 2013). High school females have a higher incidence of concussions compared to high school males when playing comparable sports with the same rules (Castile, Collins, McIlvain, & Comstock, 2012). Studies are mixed with respect to whether female gender is a risk factor for worse concussion symptom severity

and for longer recovery time (Giza et al., 2013). Another potential risk factor for longer recovery time that has not been well-studied in concussions is race/ ethnicity. One study found that compared to Whites, Black concussed college athletes had significantly worse cognitive decline on at least one component of ImPACT concussion symptom computerized testing at 7 days post-concussion despite similar baseline scores (Kontos, Elbin, Covassin, & Larson, 2010). More studies are needed to ascertain the role of race/ ethnicity with respect to recovery from concussion. Hence, this study will evaluate the impact of gender and race/ ethnicity on concussion outcomes.

The specific objective of this proposal is to examine demographic (e.g., gender, race/ ethnicity, health insurance, mechanism of injury/ sport, years of education) and clinical factors (e.g., concussion history, migraine history, learning disabilities/ attention deficit disorders) on symptom severity and duration and neurocognitive performance in adolescents ages 13-19 years old diagnosed with a concussion within 10 days of injury. Our long-term goal is to reduce the severity and neurologic and psychosocial sequelae of concussion symptoms in adolescents. The rationale for this proposal is to contribute further data on concussion recovery and prognosis in persons at risk for more severe and/ or prolonged concussions in order to personalize the therapeutic approach.

Aims to be addressed in this retrospective medical review include:

**Aim 1:** To describe the clinical (e.g., concussion history, migraine history, learning disabilities/ attention deficit disorders) and demographic factors (e.g., gender, race/ ethnicity, health insurance, mechanism of injury/ sport, years of education, socio-economic status) of adolescents referred to a concussion clinic for acute concussion symptoms.

Aim 2: To examine the relationship between the demographic variables of gender and race/ ethnicity and the components of composite ImPACT concussion symptom test scores (e.g., self-reported post-concussion symptoms scale, verbal memory, visual memory, visual motor speed, and reaction time) within 10 days of concussive injury.

Hypothesis: Females have worse acute post-concussion ImPACT scores than males and minorities have worse ImPACT scores than whites.

Aim 3: To determine which clinical (e.g., number of concussions, migraine history, learning disabilities/ attention deficit disorders) and demographic factors (e.g., gender, race/ ethnicity, health insurance, mechanism of injury/ sport, education) predict longer duration (>14 days from injury) of concussion symptoms as measured by the composite ImPACT concussion symptom test scores.

Hypothesis: Clinical and demographic factors will contribute to longer duration of symptoms with females, minorities, and those with multiple concussions having the longest duration of symptoms (> 14 days from injury) as measured by ImPACT.

### **Background and Significance**

Concussion is defined as a functional and not structural injury to the brain caused by a non-life-threatening traumatic blow resulting in a set of symptoms (Borich et al., 2013; McCrory et al., 2013). Computed Tomography (CT) Scans and Magnetic Resonance Imaging (MRI) are abnormal in TBIs, but are usually normal in patients with concussions. Thirty percent of all concussions are sports-related concussions (SRCs) in children and adolescents ages 5 to 19 years (Harmon et al., 2013). Sports-related concussions (SRCs) can affect athletes of all ages and skill levels and are becoming more common. Adolescents may be more vulnerable to concussions because they can take

longer than adults to recover and may experience devastating lasting effects from repeated concussions due to critical neural development disruption (Choe, Babikian, DiFiori, Hovda, & Giza, 2012; Grady, 2010).

There were 7.7 million U.S. high school students who participated in sports during the 2012-2013 school year. SRCs constitute approximately 8.9% to 13.2% of total injuries among U.S. high school athletes (Halstead, Walter, Council on Sports, & Fitness, 2010; Marar, McIlvain, Fields, & Comstock, 2012). The total incidence of concussion in U.S. high school students is almost 25 per 100,000 athletic exposure (Guerriero, Proctor, Mannix, & Meehan, 2012; Laker, 2011). Among U.S. high school sports, the primary cause of SRCs with respect to sports in males is football at 56.8% and in females is soccer at 11.8% (Laker, 2011).

High school adolescents comprise the majority of emergency department (ED) visits for SRC visits. For example, in 2008 there were approximately 44,000 ED visits in the U.S. attributed to SRCs. Out of these ED visits for SRCs, 58% were in adolescents ages 14 to 18 years, 17% were in 11- to 13-year olds, and 8% were in 19- to 23-year olds (Zhao L, 2011). The total number of ED visits for concussions in the U.S. in 2010 was approximately 118,000 in children ages 1-17 years old for concussion ICD-9 codes 850.0 and 850.11 (Agency for Healthcare Research and Quality, n.d.). Recent media attention on the potential long-term neurological damage of concussions has contributed to a sharp increase in emergency department (ED) visits due to public awareness. As an example, a recent study revealed a 92% rise in ED visits for evaluation of SRCs in 3,878 children ages 0 to 19 years at a level I trauma center in the U.S. from 2002 to 2011 (Hanson, Pomerantz, & Gittelman, 2013). However, physician office visits are estimated to be



significantly higher than ED visits and account for most concussion evaluations (Centers for Disease Control, n.d.).

The estimated expenditure of concussions in the U.S. in the year 2000 was \$12 billion, including indirect costs such as time lost from work (Centers for Disease Control, n.d.). In 2006, the average hospital cost for adolescents ages 15-to 17-years-old diagnosed with concussion averaged over \$18,000 per patient (Edwards, 2010). State laws are now in place in most states that require physician clearance for young athletes to return-to-play after a suspected concussion. Therefore, cumulative health costs for SRCs are expected to grow with the increase in ED visits and latest requirements for physician clearance. Hence, determining who is at highest risk for prolonged and severe symptoms of concussion will help reduce treatment costs and morbidity.

### **Concussion Recovery Risk Factors**

There are several concussion risk factors that may affect concussion recovery that will be addressed by this study including gender, race/ ethnicity, health insurance status, multiple concussions, migraine history, mechanism of injury or sport, education, learning disabilities, attention deficit disorders, and health insurance status.

**Gender.** In addition to pediatric age, gender may be a risk factor for persistent concussive symptoms. There is growing evidence that females may be at higher risk for concussive injury compared with males when playing similar sports with similar rules. For example, some studies have demonstrated that female soccer players have a 1.5 to 2.5-fold increase in concussion risk and female basketball players have a 1.5 to 3-fold increase in concussions compared with male players (Abrahams, Mc Fie, Patricios, Posthumus, & September, 2013; Makdissi et al., 2013). It is unclear why females may at

higher risk for a concussion than males. Some explanations that have been proposed include compared with males, females have a smaller head to neck ratio, weaker neck muscles, and greater angular head acceleration (Eckner, Oh, Joshi, Richardson, & Ashton-Miller, 2014). It is unclear whether female gender is a risk factor for more severe concussion symptoms. Several studies have shown that females report worse post-concussion symptoms compared with males (Berz et al., 2013; Broshek et al., 2005; Covassin, Elbin, Bleecker, Lipchik, & Kontos, 2013; Covassin, Elbin, Harris, Parker, & Kontos, 2012; Zuckerman et al., 2014); whereas other studies have not demonstrated a gender difference in post-concussion symptom reporting (Frommer et al., 2011; Kontos, Covassin, Elbin, & Parker, 2012; Preiss-Farzanegan, Chapman, Wong, Wu, & Bazarian, 2009; Zuckerman et al., 2012). Some researchers believe concussion symptom differences may reflect gender reporting behavior differences in that females may readily report their concussion symptoms compared with males (Dick, 2009). In fact, some studies have demonstrated that females report more symptoms at pre-concussion baseline compared with males (Covassin, Elbin, Harris, et al., 2012; Leach, Bay, & Valovich McLeod, 2013; Register-Mihalik, Mihalik, & Guskiewicz, 2009; Zuckerman et al., 2014). However, other studies have not shown any pre-concussion symptom reporting differences based on gender (Brooks et al., 2014; Covassin, Elbin, Larson, & Kontos, 2012; Covassin, Schatz, & Swanik, 2007; Kontos et al., 2012; Zuckerman et al., 2012). In terms of symptom type, a few studies have determined that females may experience worse post-concussion headaches than males (Bramley et al., 2015; Covassin, Elbin, Bleecker, et al., 2013; Mihalik et al., 2013). With respect to neurocognition, several studies found that females had significantly worse post-concussion neurocognitive

performance than males (Broshek et al., 2005; Covassin, Elbin, Bleecker, et al., 2013; Covassin, Elbin, Harris, et al., 2012; Covassin et al., 2007); however another study did not indicate difference in neurocognition among males and females (Zuckerman et al., 2012).

Research has shown that females may have prolonged recovery times as compared with males by a few days (Zuckerman et al., 2014) to over a month (Bramley et al., 2015; Kostyun & Hafeez, 2015). Furthermore, Kostyun & Hafeez (Kostyun & Hafeez, 2015) found that adolescent females required more treatment interventions and academic accommodations after a concussion compared to their male counterparts. More research is needed to elucidate reasons for these gender differences. This study seeks to determine whether gender is a risk factor for worse concussion outcomes.

**Race/ Ethnicity.** Multiple studies have reported higher incidence and poorer health outcomes among Blacks and Hispanics for diseases such as obesity, HIV/ AIDS, asthma, diabetes, cardiovascular, and cancer (Brennan Ramirez, 2008; Price, Khubchandani, McKinney, & Braun, 2013). Moderate to severe TBIs are distinguished from mild TBIs/ concussions by the presence of intracranial hemorrhage detected by routine CT or MRI and frequently result in permanent complications or death. TBI incidence is highest among ethnic minorities. For example, American Indians/ Alaska Natives suffer the highest incidence of death due to TBI followed by Blacks compared to all other ethnic/ racial groups (Coronado et al., 2011). TBI incidence reported in EDs is highest among non-Whites compared to Whites (Jager, Weiss, Coben, & Pepe, 2000). TBI rates among ethnic minorities are expected to rise as the US minority population exceeds the non-Hispanic White population by 2060 (U.S. Census Bureau, 2012). Racial/

ethnic differences have been shown to be present with respect to TBI outcomes as they related to the psychosocial (e.g. QOL, community integration), treatment (e.g. rehabilitation, medication, etc.), and functional domains (e.g. mortality, repeat TBI risk); these differences were apparent in both the adult and pediatric populations (Gary, Arango-Lasprilla, & Stevens, 2009).

Conversely, there are few studies that have evaluated concussions in minorities, many of whom participate in sports. One study found that high school and college Black athletes performed worse in at least one neurocognitive testing component compared to Whites 7 days after a concussion despite similar baseline scores (Kontos et al., 2010). There is a lack of data on the percentages of minorities who play high school sports; however, both the National Football League (NFL) and National Basketball Association (NBA) are composed of approximately 70% minorities (Lapchick, 2014). As pointed out earlier, 75% of all TBIs are concussions and given the rising number of concussion ED visits and growing popularity of high school sports, as described previously, more research is needed to ascertain concussion risk factors in order to identify populations at risk for more severe and prolonged symptoms and long-term neurologic sequelae. Because of the limited data on concussions and out of concern for the presence of health disparities, the Institute of Medicine (IOM) recently published a report on sports-related concussions in youth and recommended that the National Electronic Injury Surveillance System- All Injury Program (NSEISS-AIP) database include race/ ethnicity, gender, socio-economic status and concussion outcomes (e.g. mechanism of injury, symptoms, etc.) in all injured persons with concussions ages 5 to 21 years old (Committee on Sports-Related Concussions in Youth, 2014).

**Health Insurance/ Socio-Economic Status.** Health insurance status is correlated with better health outcomes (Centers for Disease Control, 2011). In 2007, there were an estimated 6.5 million uninsured children and in 2014, even with the passage of the Affordable Care Act in 2010, there were an estimated 4 million uninsured children (Ward, Clarke, Freeman, & Schiller, 2014). Under-insurance is defined as insurance that does not adequately cover an individual's health needs (Kogan et al., 2010). In 2007, there were approximately 14.1 million under-insured children (Kogan et al., 2010). Schoen and colleagues (2014) determined that the number of underinsured persons <65 years old grew from 29.9 million in 2010 to 31.7 million in 2012 (Schoen, Hayes, Collins, Lippa, & Radley, 2014). It is estimated that a third of Texans ages 19-64 years old were underinsured in 2014 (Collins, Rasmussen, Beutel, & Doty, 2015). More data is needed on the current rates of underinsured children and how under-insurance affects children's health outcomes. Health disparities among TBI patients with respect to clinical outcomes has been identified particularly among minority children (Brown, 2010) and adults (Schiraldi et al., 2015). Some studies have determined that ethnic minorities and lack of insurance were predictors of discharge to rehabilitation among adult TBI patients (Asemota, George, Cumpsty-Fowler, Haider, & Schneider, 2013; Kane, Wright, Fu, & Carlson, 2014). Gardizi and colleagues (2014) found that adult TBI patients who had public insurance had worse disability compared with those who had private insurance even after controlling for education, race, and mechanism of injury (Gardizi, Hanks, Millis, & Figueroa, 2014). Jimenez and colleagues (2015) determined that children with TBI who had Medicaid had worse functional outcomes and lower cognitive scores compared with non-minority children (Jimenez et al., 2015). A recent study found that

the only predictor of poor cognitive outcomes among adult mTBI patients was socio-economic status (Rabinowitz et al., 2015). Additional studies are needed to determine insurance status and socio-economic status among adolescents with mTBI and whether these variables are associated with concussion symptoms and worse cognition.

**Multiple Concussions.** As mentioned earlier, a common cause of concussion is sports. Athletes are at high risk for repeated brain trauma due to high risk of collision between players, impact with play equipment, and surface contact. There are a growing number adolescent athletes participating in sports. For example, there were a total of 7.7 million US high school athletes in the 2013-2014 school year with 82,000 more high school athlete participants compared to the 2012-2013 school year (National Federation of State High School Associations, 2014). Studies have shown that multiple concussions (Guskiewicz et al., 2005) or repeated head impacts (Bazarian et al., 2014) can result in debilitating long-term motor (De Beaumont et al., 2013) and cognitive deficits and depression (Hart et al., 2013) in retired adult professional football players. It remains unknown how many concussions an athlete can sustain before having permanent long-term neurologic sequelae. In fact, adolescents with SRCs may be at higher risk for worse neurological outcomes with repeated concussions compared to adults who sustain repeated concussions (Choe et al., 2012). MRI studies have shown that the brain is not fully mature until approximately age 25 years (Lenroot & Giedd, 2006). Animal experimental studies in rats have demonstrated that myelination of white matter tracts continues throughout adolescence and that unmyelinated white matter tracts are more easily disrupted compared to myelinated white matter tracts after an experimental

concussion (Giza & Difiori, 2011). More studies are needed to evaluate the long-term neurological deficits in adolescent athletes with multiple concussions.

**Migraine History.** Migraine headaches are a risk factor for prolonged concussion symptoms lasting >10 days (Harmon et al., 2013). A common concussion symptom is migraine-type headache. Females in the general population have significantly higher rates of migraine headaches compared to males with a peak prevalence in females during their child-bearing years (Borsook et al., 2014). Females athletes in one study were found to have a five times greater risk for personal and/ or family history of migraine headaches compared to male athletes (Covassin, Elbin, Crutcher, & Burkhart, 2013). In addition, a recent review article found racial/ ethnic differences among migraine sufferers with Native Americans having the highest overall prevalence rates and Hispanic females having the highest prevalence rate of chronic migraines (Loder, Sheikh, & Loder, 2015). Therefore, the race/ ethnicity and gender should be studied further as risk factors for prolonged concussion recovery.

**Mechanism of Injury/ Sport.** Adolescents who experience concussion as a result of a motor vehicle may have worse concussion outcomes compared to injury from football and soccer (Seiger, Goldwater, & Deibert, 2014). With respect to SRCs, football has the highest rate of concussion compared to other sports including soccer and basketball (Lincoln et al., 2011). However, as stated earlier, females have a higher incidence of concussion compared to males when playing similar sports. Sport play positions have been associated with higher rates of concussion including running backs, quarterbacks, wide receivers, and defensive backs in football (Harmon et al., 2013) and goalies in soccer (Daneshvar, Nowinski, McKee, & Cantu, 2011).

**Years of Education.** Education is a significant predictor of higher health status in adult TBI patients (Willemse-van Son, Ribbers, Verhagen, & Stam, 2007). A recent meta-analysis found that adolescent athletes with concussion who have more years of education have been shown to have fewer neuropsychological deficits compared to those with less education (Dogan, Horswill, & Geffen, 2013).

**Learning Disabilities and Attention Deficit Disorders.** Learning disabilities and attention deficit disorders (ADD/ADHD) may complicate the diagnosis of concussion in that neurocognitive baseline scores are often lower than students without these issues (Zuckerman, Lee, Odom, Solomon, & Sills, 2013). Learning and attention deficit disorders may be associated with protracted recovery of concussion (Harmon et al., 2013). Hence, it is imperative that the healthcare provider be aware of these deficits when interpreting concussion symptom data.

### **Summary of Gaps**

Concussion clinicians and researchers have identified potential risk factors for more severe and protracted recovery from concussions. However, more research is needed to substantiate these risk factors. While there is substantial evidence that indicates that gender may be a risk factor for incurring a concussion, studies are mixed as to whether female gender predicts more severe symptoms, worse cognition, and prolonged recovery times. There have been few studies that have evaluated the role of race/ethnicity and health insurance status in patients with mild TBIs. Furthermore, more research is needed in adolescents who have had multiple concussions and whether they may have future neurologic sequelae. Other factors that may be associated with worse



concussion outcomes and need further study include migraine history, mechanism of injury/ sport, years of education, and learning disabilities/ attention deficit disorders.

### **Importance of proposed research to health and nursing**

Identifying concussed adolescents who are at most at risk for worse symptoms, poor cognition, and protracted recovery will aid in early treatment measures. Currently, the primary treatment for acute concussion symptoms include physical and cognitive rest, as described earlier. However, other forms of treatment interventions including medication for symptoms and rehabilitation measures (e.g., vestibular rehabilitation) may be needed sooner in adolescents at risk for protracted recovery. Nurses (e.g., school nurses) are key front-line health professionals who can quickly identify adolescents at risk for worse concussion outcomes and refer them for appropriate evaluation and treatment with a concussion specialist. Hence, a predictive model is needed by nurses to direct the patient to the appropriate provider in an expedient manner.

### **Conceptual Model**

The Concussive Vulnerability Model (CVM) was based on a synthesis of current literature in order to describe the factors contributing to the development of concussion and protracted recovery (see Figure 1). Concussive vulnerability is defined as the propensity of an individual to sustain a brain injury caused by biomechanical forces that culminates in a pattern of symptoms due to microstructural and cellular damage that may result in long-term neurologic impairment (Prins, Alexander, Giza, & Hovda, 2013; Shenton et al., 2012; Umile, Sandel, Alavi, Terry, & Plotkin, 2002). The CVM builds upon the Dynamic Recursive Model for Sports Injury (Meeuwisse, Tyreman, Hagel, & Emery, 2007). Conceptual elements utilized from this model include the predisposed host, external risk

factors, the inciting event or impact, injury, removal from activity, and repeat participation (Meeuwisse et al., 2007). There are two major components of the CVM: the process of concussion development and the cycle of concussive vulnerability. The process of concussion development entails a predisposed host who experiences a concussion after an impact in a risk-taking environment or taking a risk-taking activity. The host is typically diagnosed by reporting concussion symptoms, neuropsychological testing, and physical exam, and is then removed from the risky environment or activity (e.g., sports). After receiving individualized treatment, typically rest, the host usually recovers within 7 to 10 days. However, some individuals with predisposing risk factors may experience persistent symptoms or permanent neurologic sequelae if he/ she returns to the risk-taking environment or activity without making a full recovery. The cycle of concussive vulnerability begins once the predisposed host has a concussion. If the host prematurely enters the risk-taking environment or activity, then he/ she is vulnerable to persistent or permanent neurologic damage. The host exits this cycle of vulnerability once he/she completely recovers from the concussion. This study seeks to identify certain risk factors in the predisposed host that are correlated with worse performance on neuropsychological testing and protracted recovery (>14 days).

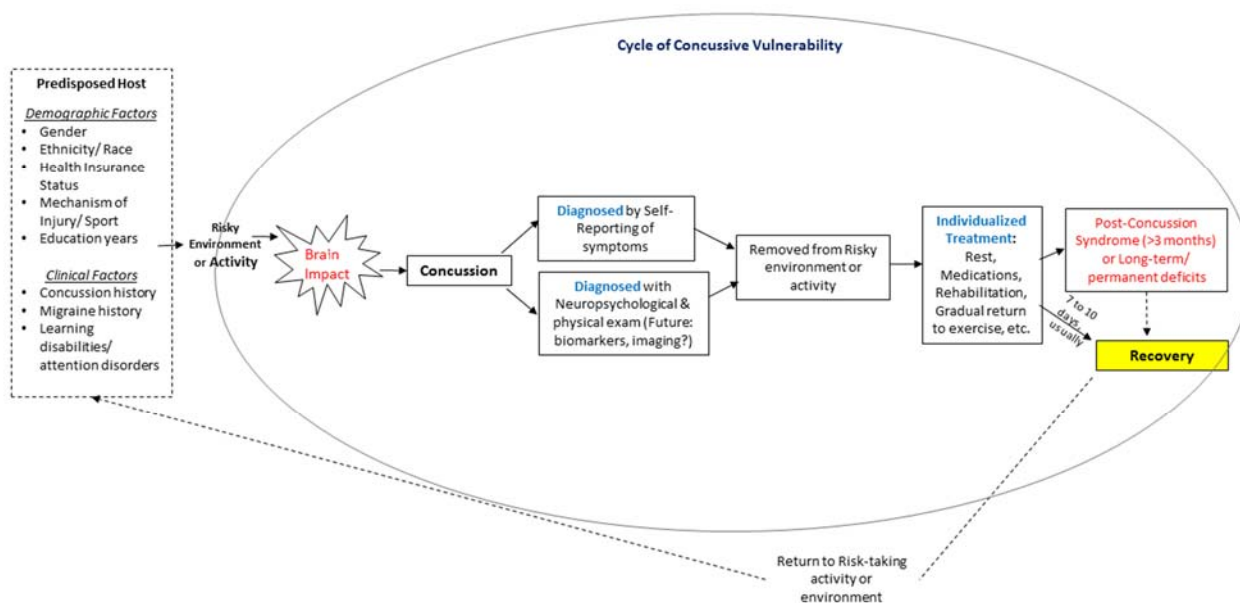


Figure 1. The Concussion Vulnerability Model (condensed).

## Innovation

As described earlier, there is conflicting evidence as to whether females are at higher risk for persistent concussion symptoms. In addition, few studies have evaluated racial/ ethnic differences or health insurance status with respect to concussion outcomes. Given that the adolescent population is vulnerable to sports-related concussions and the high treatment cost of concussions, more information is needed to ascertain which subgroups of adolescents are at highest risk for poor concussion outcomes.

This proposal seeks to evaluate who is at highest risk for prolonged and more severe symptoms and cognitive decline among adolescents. A predictive model is needed by clinicians, neuropsychologists, nurses, and athletic trainers in order to classify an individual's risk for protracted concussion recovery. The results of this proposal will

inform future research and treating healthcare providers as to whom to aggressively treat in order to prevent neurological sequelae from concussions.

## **Methods and Design**

### **Research Design**

This study will be a retrospective observational cohort design of clinical data.

### **Setting**

The electronic medical record and paper charts of patients treated at the University of Texas Sports Medicine Institute Concussion Program in Houston, Texas will be reviewed.

### **Sampling and Inclusion Criteria**

Houston- area adolescents ages 13 to 19 years old with concussion/ mTBI diagnosis (ICD-9 codes 850.0 to 850.9; ICD-10 codes S06.0X), who were treated between January 1, 2012 to August 1, 2015 at University of Texas Houston Sports Medicine Institute Concussion Program, will be included as part of a retrospective chart review. The dates were selected based on the availability of ImPACT computerized concussion test data. Patients with acute post-injury ImPACT test scores within 10 days of concussive injury and at least one ImPACT test performed >10 days will be included in this study or clearance to return to play/ normal activities by the health care provider. Sample size will be chosen based on the number of patients meeting inclusion/ exclusion criteria. Approximately 225 patients were seen between years 2012 to date (May, 2015). Of the total concussion clinic population, it is estimated that 50% were Hispanic, 25% were Black, 25% were Caucasian, and <1% were other races/ ethnicities; with respect to gender, there were approximately 50% males and 50% females. Based on the PI's clinical experience, it is expected that

approximately 50% (100 patients) will not be eligible based on inclusion and exclusion criteria. The racial/ ethnic and gender identification provided by the patient or patient's family as designated in the electronic and paper chart will be used in this study. Power analysis for multiple regression demonstrates that with a moderate effect size ( $R^2 = 0.15$ ) with 9 predictors to achieve a power of 0.80 and alpha of .05, a minimum estimated sample size of 98 charts (Polit & Beck, 2012). It is anticipated that 10% of eligible charts will have missing data; therefore, approximately 108 charts will need to be reviewed. If there are significantly more charts than power analysis, then charts will be randomized using a computer generated program.

**Exclusion Criteria.** Patients with a psychiatric diagnosis (e.g. depression, anxiety, mood disorders), who are identified by the healthcare provider or neuropsychologist in the patient chart, will be excluded due to higher symptom reporting (Lange, Iverson, & Rose, 2011).

### **Data Collection**

The data will be collected from electronic and/ or paper clinic records from January 1, 2012 to August 1, 2015. The PI will identify the charts to be reviewed based on inclusion criteria and completeness of records. Data will be collected by the PI on the following demographic and clinical variables: age, gender, race/ ethnicity, primary language, education, concussion history, migraine history, mechanism of injury/sport, history of learning disabilities/ Attention Deficit Disorders (ADD/ ADHD), health insurance status, and zip code. Ethnicity categories will be as follows: Hispanic or non-Hispanic. Racial categories will be as follows: White, Black, Asian, American Indian/ Alaska Native, Native Hawaiian/ Pacific Islander, and Other. Health insurance will be classified as follows:

public (government), private (commercial), student athletic or none. Outcome measures will include the: (1) duration of concussion symptoms which will be obtained from the chart or the last date of Immediate Post-concussion Assessment and Cognitive Testing (ImPACT) computerized test, (2) total symptom scores on the Post-Concussion Symptoms Scale (PCSS), a component of the ImPACT concussion testing described in more detail in the next section, and (3) verbal memory, visual memory, visual motor, and reaction time scores on the ImPACT computerized test.

Typically, pre-season baseline ImPACT concussion symptom data is collected in adolescent athletes prior to the start of the athletic season and the same data is collected for comparison during the acute phase of concussion (usually within 10 days) and routinely (usually weekly) as deemed necessary by the neuropsychologist or health care provider. When the ImPACT symptom scores return to baseline scores within 2 standard deviations (usually by 14 days after concussive injury), as automatically calculated by the ImPACT computerized system, the healthcare provider or neuropsychologist will typically clear the patient to return to sports and remove other activity restrictions. If baseline data is not available, ImPACT normative data for the age, gender, education level, and special education (learning disabilities and ADD/ ADHD) may be used instead. The PI will collect baseline ImPACT data, the documented date of concussion, the acute post-concussive injury data, and the date of the last post-concussive injury test. De-identified patient data will be coded and entered into a spreadsheet in Microsoft Windows Excel (version 2013).

### **Instrument**

The Immediate Post-concussion Assessment and Cognitive Testing (ImPACT) computerized concussion symptom test battery consists of the following composite

scores: Post-Concussion Symptoms Scale (PCSS) and 4 neurocognitive modules including verbal memory, visual memory, visual motor speed, and reaction time. The instrument is well-studied, widely used, and is valid in patients 10-59 years old (ImPACT Applications Inc., 2007). The ImPACT test takes approximately 25–30 min to complete and is composed of three sections.

**Demographic data.** The first section contains a self-report demographic questionnaire including age; gender; and self-reported history of alcohol and drug use, learning disabilities, neurological and psychiatric disorders, migraine headaches, previous concussions, and mechanism of injury/ sport information. This data is compared to the patient's medical history and integrated into the patient's medical record by the neuropsychologist or healthcare provider.

**Self-reported concussion symptoms severity checklist.** The second section contains the PCSS and has an ordinal 7-point Likert-type response format for severity with response options from 0 (none) to 6 (severe). The symptom domains include 6 cognitive symptoms, 4 emotional/ mood symptoms, 3 sleep disturbance symptoms, and 9 somatic symptoms. Scores from 0 to 132; lower scores indicate fewer symptoms. The PCSS was initially developed as a separate symptoms checklist and was subsequently included as a composite score on the ImPACT computerized test.

Evidence of PCSS reliability includes Cronbach's  $\alpha$  of .88 to .94 (ImPACT Applications Inc., 2007), suggesting adequate internal consistency, and test-retest correlation of .80 with a 4-day interval in high school and collegiate athletes with concussion (ImPACT Applications Inc., 2007), suggesting adequate stability of the instrument per the a priori criteria. Evidence of PCSS validity includes predictive validity

for predicting post-concussion syndrome, a syndrome of intense symptom severity and prolonged duration, [AUC = .377,  $p = .03$ ] (Barlow, Schlabach, Peiffer, & Cook, 2011) and concurrent validity with the ImPACT processing speed [ $r = .70$ ] (Schatz & Putz, 2006), indicating support for instrument validity. The PCSS demonstrated adequate sensitivity to change by change scores that were calculated from data used to compute the test-retest coefficient ( $SEM = 3.3$ , change =  $\pm 4$  points) (ImPACT Applications Inc., 2007).

**Neurocognitive battery.** The third section of the test consists of four neuropsychological tests including verbal memory, visual memory, visual motor speed, and reaction time. This section of the test requires the participant to answer a series of questions by following a series of written and visual prompts that require the participant to click the mouse or type in an appropriate answer. Lower scores on verbal memory, visual memory, and visual motor speed composite scores and higher scores for reaction time compared to baseline scores and/ or norms indicate cognitive impairment.

The ImPACT test has adequate evidence of reliability and validity of neurocognitive performance related to concussion. The ImPACT neurocognitive subscales have estimates of 1-year test-retest reliability measured by intra-class coefficients (ICCs) of 0.62 to 0.86 in high school athletes (Elbin, Schatz, & Covassin, 2011). The ImPACT neurocognitive subscales demonstrate evidence of convergent validity with the Symbol Digital Modalities Test, Trail Making Tests and the Digit Symbol subtest of the Wechsler scale, CogSport, and HeadMinder (Iverson, Lovell, & Collins, 2005; Schatz & Putz, 2006). The ImPACT has a sensitivity of 90% and specificity of 82% (Schatz, Pardini, Lovell, Collins, & Podell, 2006).



## Data Analysis

The objective of the study is to conduct an exploratory analysis of demographic and clinical concussion risk factors and concussion symptom severity and duration and neurocognitive performance in adolescents with concussions, ages 13-19 years old, within 10 days of injury. IBM SPSS Statistical Package (version 23) for Windows will be utilized for statistical analyses. The PI and statistician will perform the data analysis. Records that have missing data and do not meet statistical analysis assumptions, described below, will not be included in the statistical analyses.

**Aim 1. To describe the clinical (e.g., concussion history, migraine history, learning disabilities/ attention deficit disorders) and demographic factors (e.g., age, race, gender, health insurance, mechanism of injury/ sport, years of education, socio-economic status) of adolescents referred to a concussion clinic for acute concussion symptoms.**

Descriptive statistics will be calculated for each demographic and clinical factor that include measures of central tendency and dispersion of continuous variables (e.g., years of education), and frequencies and proportions of categorical variables (e.g., race/ ethnicity, gender). The reliable change index (RCI) will also be described by gender and race/ ethnicity groups.

**Aim 2. To examine the relationship between the demographic variables of race/ ethnicity and gender and the components of composite ImpACT concussion symptom test scores (e.g., self-reported post-concussion symptoms scale, verbal memory, visual memory, visual motor speed, and reaction time) within 10 days of concussive injury**

General linear models (GLM) will be utilized to determine the differences on the total PCSS score, and the four ImPACT scores including the verbal memory, visual memory, visual motor, and reaction time scores between racial/ ethnic and gender categories. Covariates will include years of education and presence of learning disabilities/ attention deficit disorders. Significance level will be set at  $\alpha = .05$ . Model residuals will be examined for normality, linearity, and homogeneity of variances. In order to control for type I error, we will also do a multivariate analyses of variance of the variables and continue to evaluate separate outcomes.

**Aim 3. To determine which clinical (e.g., number of concussions, migraine history, learning disabilities/ attention deficit disorders) and demographic factors (e.g., age, race, gender, health insurance status, mechanism of injury/ sport, education) predict longer duration (>14 days from injury) of concussion symptoms as measured by the composite ImPACT concussion symptom test scores.**

Hierarchical logistic regression will be utilized to determine whether the clinical (concussion history, migraine history) and demographic (age, race, gender, mechanism of injury/ sport, education years, health insurance) factors predict duration of symptoms >10 days. Demographic factors will be entered first (e.g., gender, race, education). In the second block, mechanism of injury/ sport will be added. In the third block, migraine history (coded for yes or no), number of concussions, and learning disabilities/ attention deficit disorders will be added. Significance level will be set at  $\alpha = .05$ .

### **Study Limitations and Alternative Plans**

There are a few potential issues with the feasibility of the study methods. The primary difficulty with conducting a retrospective chart review is the possibility of

missing data related to data collection. In order to avoid these issues, first an overestimate by 10% of the minimum number of charts indicated by power analysis will be obtained. Next, the PI will carefully check for missing data prior to data collection. Third, the PI will pause after every 5 data entries and double-check the data to ensure completion and save the data in the spreadsheet. Another potential issue is obtaining a sufficient number charts on minority patients. A potential way to handle this issue is to aggregate the data into minorities and non-minorities during the data analysis. Selection bias is a potential issue in a retrospective chart review. Thus, exclusion criteria were limited and all charts meeting inclusion criteria will be included. Finally, a problem with using self-report symptoms data is that self-report data may be inaccurate. Therefore, the PI will be using ImPACT neurocognitive test scores as an objective measure to evaluate evidence of concussion.

## **Human Subjects**

### **Inclusion of minority groups and female gender**

The focus of this retrospective chart review is to identify differences with respect to race/ ethnicity and gender. Thus, the PI will be including all charts that meet inclusion criteria.

### **Risks, benefits and procedures to protect the rights of human subjects**

Protection, privacy, and confidentiality of the data from the human subjects involved will be maintained to the highest standard throughout the study. IRB approval will be obtained from the University of Texas Houston Health Science Center.

**Potential Benefits**

While there may be no direct benefit to the patients whose charts will be reviewed, the researcher's goal for this study is to provide meaningful information that will benefit the health of future patients by furthering the scientific and medical knowledge of concussions.

**Potential Risks**

Risks to the patients may include breach of patient confidentiality and privacy.

**Protection Against Risks**

Utmost precautions will be taken by the PI to ensure a confidentiality breach will not occur. Study data collection will be restricted to the variables described in this proposal. All study data will be stored on an institution central server and access will be limited to the PI and researchers involved in this study. All data will be de-identified (e.g., patient names, MRNs, etc.) and each case will be assigned a unique study number and no subject identifiers will be entered on the spreadsheet. No connection between the study number and the actual patient identifiers will be stored in the study database ensuring that data analysis will be performed on completely de-identified data.

**Data Storage and Destruction**

The data will be kept for 7 years or until publication of data is completed, at which time the data will be permanently removed from the server.

**Timeline**

DATA COLLECTION TIMELINE	
DATE	ACTIVITY
August, 2015	Dissertation Committee Approval (D-1), Obtain IRB Approval
September, 2015	Finalize Dissertation proposal
October, 2015	Dissertation proposal approval by Committee (D-2), Begin dissertation data collection
November, 2015	Complete dissertation data collection
December, 2015	Complete data entry and begin data analysis
January, 2016	Complete data analysis, write dissertation
February, 2016	Revise dissertation
March, 2016	Dissertation defense

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March, 2016

Arthur MacNeill Horton, Jr.  
Editor-in-Chief  
*Applied Neuropsychology:Child*

Dear Dr. Horton:

I am writing to submit our manuscript entitled “Clinical and Demographic Variables Associated with Cognitive Deficits, Symptom Severity, and Duration after Concussive Injury in Adolescents: A Retrospective Study” for consideration for publication in *Applied Neuropsychology:Child*. In this manuscript, we demonstrate the relationship and interaction of race and gender on the Immediate Post-concussion Assessment and Cognitive Testing [ImPACT] computerized battery. We also examine predictors of protracted concussion recovery. Few concussion studies in adolescents report race/ethnicity or contain ethnically/ racially diverse samples; thus their results may not be generalizable. We believe this manuscript is appropriate for publication in your journal because it concerns assessment of risk factors for severe or prolonged recovery of mild traumatic brain injuries in adolescents.

We appreciate your consideration of our manuscript for review. We look forward to your response. Please feel free to contact me at [Seema.S.Aggarwal@uth.tmc.edu](mailto:Seema.S.Aggarwal@uth.tmc.edu).

Sincerely,

Seema Aggarwal, PhD(c), RN, NP-C  
University of Texas Houston Health Science Center

**Manuscript A**

**Clinical and Demographic Variables Associated with Cognitive Deficits, Symptom  
Severity, and Duration after Concussive Injury in Adolescents: A Retrospective  
Study**

## Introduction

There are approximately 1.7 million traumatic brain injuries (TBIs) that occur in children and adults annually, of which 75% are mild traumatic brain injuries (mTBIs), also termed concussions (Centers for Disease Control, 2003). Thirty percent of all concussions are sports-related concussions (SRCs) in children and adolescents ages 5 to 19 years (Harmon et al., 2013). Sports-related concussions (SRCs) can affect athletes of all ages and skill levels and are becoming more common. To date, there is no effective method of concussion prevention. While protective equipment such as helmets may aid in the prevention of severe head trauma (e.g., skull fracture and brain hemorrhage), there is not enough evidence that indicates that helmets reduce concussion rates or severity (Bonfield, Shin, & Kanter, 2015; Lloyd & Conidi, 2015). Once a concussion occurs, the brain is highly vulnerable to subsequent injury, which may result in long-term neurologic damage (Giza & Kutcher, 2014; Harmon et al., 2013). Furthermore, adolescents may experience worse concussion outcomes than adults due to potential disruption of critical neural development (Choe, Babikian, DiFiori, Hovda, & Giza, 2012; Grady, 2010). Studies have determined that undiagnosed or untreated concussions can lead to Post-Concussion Syndrome (PCS), a syndrome of prolonged concussion symptoms, or in rare cases, Second-Impact Syndrome (SIS), severe or fatal brain damage that may occur from a second impact shortly after sustaining an initial concussion (Blume & Hawash, 2012; Weinstein, Turner, Kuzma, & Feuer, 2013). Recent legislation in most U.S. states requires the immediate removal of a school-aged athlete with a suspected concussion from a school-sponsored athletic event and clearance to return-to-play (RTP) by a healthcare provider (National Conference of State Legislatures, 2014). Thus, swift

identification and removal of a concussed individual is necessary to avoid a repeat brain injury (Giza, 2014).

Currently, there are no blood tests or standard imaging techniques (e.g. Computed Tomography (CT) Scans and Magnetic Resonance Imaging (MRI) that can detect the microcellular damage of concussion. Typically, concussion diagnosis is based on a constellation of reported symptoms, physical exam findings, and neuropsychological (also known as neurocognitive) testing. Unfortunately, concussed individuals may not recognize the sometimes subtle symptoms of concussion (Fedor & Gunstad, 2014) or may not be inclined to report their symptoms (e.g., fear of missing athletic competitions) (Kroshus, Garnett, Hawrilenko, Baugh, & Calzo, 2015). Studies have identified potential risk factors for more severe and/ or prolonged recovery (>10 days) such as pediatric age, female gender, previous concussion history, migraine history, learning disabilities, and attention deficit disorders (Committee on Sports-Related Concussions in Youth, 2014; Giza et al., 2013; Harmon et al., 2013; McCrory et al., 2013). However, these studies are limited by small sample sizes, racially/ ethnically non-diverse samples, or have not been replicated. Furthermore, the interaction between race and gender has not yet been studied in concussed adolescents. More research is needed to substantiate these risk factors in diverse populations and to develop a concussion predictive model that would be helpful for health care professionals (i.e. physicians, neuropsychologists, nurses, coaches, and athletic trainers) to expediently identify who is at risk for worse and/ or longer duration of concussion symptoms, and to personalize the management of concussions.



## Background

Concussion is defined as a functional and not structural injury to the brain caused by a non-life-threatening traumatic blow that results in a set of physical, emotional, and cognitive symptoms (Borich et al., 2013; McCrory et al., 2013). A concussion occurs when axons and smaller blood vessels in the brain are sheared due to the transmission of biomechanical forces to the brain from an impact. The axonal and micro-vessel injury sets off a chain of neuronal events called the neuro-metabolic cascade, whereby communication between neurons is impaired due to neurotransmitter dysfunction and altered cerebral blood flow and glucose metabolism (Giza & Hovda, 2014).

Concussions in children usually occur from falls, motor vehicle accidents, and sports. Common concussion symptoms include headaches, nausea, dizziness, light and noise sensitivity, emotional changes, and cognitive difficulties. Concussion symptoms typically resolve within 10 days; however approximately 10-15% of concussions result in persistent symptoms lasting longer than 10 days (McCrory et al., 2013). Concussion diagnosis rates in high school athletes have increased significantly from 2006 to 2012 from 0.23 to 0.51 concussions/1000 athletic exposures (Rosenthal, Foraker, Collins, & Comstock, 2014). Concussions often result in missed school, academic learning difficulties (Baker et al., 2015; Ransom et al., 2015), and may reduce quality-of-life (QOL) during recovery (Pieper & Garvan, 2014).

There were 7.7 million U.S. high school students who participated in sports during the 2012-2013 school year. SRCs constitute approximately 8.9% to 13.2% of total injuries among U.S. high school athletes (Halstead, Walter, Council on Sports, & Fitness, 2010; Marar, McIlvain, Fields, & Comstock, 2012). The total incidence of concussion in

U.S. high school students is almost 25 per 100,000 athletic exposures (Guerriero, Proctor, Mannix, & Meehan, 2012; Laker, 2011). Among U.S. high school sports, the primary cause of SRCs in males is football at 56.8% and soccer in females at 11.8% (Laker, 2011).

High school adolescents comprise the majority of emergency department (ED) visits for SRC visits. For example, in 2008 there were approximately 44,000 ED visits in the U.S. attributed to SRCs. Out of these ED visits for SRCs, 58% were in adolescents ages 14 to 18 years, 17% were in 11- to 13-year olds, and 8% were in 19- to 23-year olds (Zhao L, 2011). The total number of ED visits for concussions in the U.S. in 2010 was approximately 118,000 in children ages 1-17 years old for concussion ICD-9 codes 850.0 and 850.11 (Agency for Healthcare Research and Quality, n.d.). Public awareness of the potential dangers of concussive injuries from heightened media coverage may have contributed to an increase in ED concussion evaluations. For example, there was a 92% rise in ED visits for the evaluation of SRCs in 3,878 children ages 0 to 19 years at a U.S. level I trauma center from 2002 to 2011 (Hanson, Pomerantz, & Gittelman, 2013). Healthcare provider visits are estimated to be significantly higher than ED visits and account for most concussion evaluations (Centers for Disease Control, n.d.).

The estimated expenditure of concussions in the U.S. in the year 2000 was \$12 billion, including indirect costs such as time lost from work (Centers for Disease Control, n.d.). In 2006, the average hospital cost for adolescents ages 15-to 17-years-old diagnosed with concussion averaged over \$18,000 per patient (Edwards, 2010). Cumulative health costs for SRCs are expected to grow with the increase in ED visits and latest requirements of healthcare provider clearance for student athletes to RTP. Hence,

determining who is at highest risk for worse concussion recovery is necessary for reducing treatment costs and morbidity.

### **Aims**

The focus of this study was to identify risk factors that negatively affect concussion recovery in the adolescent population. High school athletes have a higher incidence of concussions compared with college athletes (Clay, Glover, & Lowe, 2013). High school females have a higher incidence of concussions than high school males when playing comparable sports with the same rules (Dick, 2009). Studies are not definitive with respect to whether female gender is a risk factor for worse concussion symptom severity and longer recovery time (Giza et al., 2013). Furthermore, females may report more symptoms at baseline and this may affect clinical interpretation of post-concussion symptom scores. Another potential risk factor for longer recovery time that has not been well-studied in concussions is race/ ethnicity. One multi-site study found that compared with Whites, Black concussed college athletes had significantly worse cognitive declines on at least one component of the Immediate Post-concussion Assessment and Cognitive Testing [ImPACT] computerized battery at seven days post-concussion despite similar baseline scores (Kontos, Elbin, Covassin, & Larson, 2010). More studies are needed to evaluate the role of gender and race/ ethnicity on concussion recovery.

The specific objective of this study was to examine the impact of demographic (e.g., age, gender, race/ ethnicity, health insurance, socio-economic status, mechanism of injury/ sport, years of education) and clinical factors (e.g., concussion history, migraine history, learning disabilities/ attention deficit disorders) on recovery in adolescents ages 13-19 years old diagnosed with an acute concussion within 10 days of injury. The results

of this study are expected to contribute to the development of a predictive model that identifies demographic and clinical risk factors of prolonged recovery; thereby, allowing for expeditious identification and treatment of concussion in vulnerable populations.

The aims and hypotheses of this study were as follows:

**Aim 1:** To describe the clinical (e.g., concussion history, migraine history, learning disabilities/ attention deficit disorders) and demographic factors (e.g., age, gender, race/ ethnicity, health insurance, socio-economic status, mechanism of injury/ sport, years of education) of adolescents referred to a concussion clinic for acute concussion symptoms.

**Aim 2:** To examine the relationship and interaction between the demographic variables of gender and race/ ethnicity and the composite ImPACT test scores (e.g., verbal memory, visual memory, visual motor processing speed, reaction time, and self-reported symptoms scores) (a) within 10 days of concussive injury and (b) at baseline, if data is available.

Hypotheses: (a) Females have worse acute/ initial post-concussion ImPACT scores than males and Minorities have worse acute/ initial ImPACT scores than Whites. With respect to interaction between race and gender, Minority females will have worse concussion scores than other race/ gender groups.

(b) There will be no difference by race or gender on baseline scores.

**Aim 3:** To determine which clinical (e.g., number of concussions, migraine history, learning disabilities/ attention deficit disorders) and demographic factors (e.g., age, gender, race/ ethnicity, health insurance, mechanism of injury/ sport, education) predict longer duration (greater than the sample's median number of days from injury) of concussion symptoms as determined from clinical chart notes and/or measured by the composite ImPACT test scores.

Hypothesis: Females, Minorities, and those with prior concussions will have the longest concussion resolution times.

### **Theoretical Framework**

I developed the Concussive Vulnerability Model (CVM) based on a synthesis of current literature in order to describe the factors contributing to the development of concussion and protracted recovery (see Figure 1). Concussive vulnerability is defined as the propensity of an individual to sustain a brain injury caused by biomechanical forces that culminates in a pattern of symptoms due to microstructural and cellular damage that may result in long-term neurologic impairment (Prins, Alexander, Giza, & Hovda, 2013; Shenton et al., 2012; Umile, Sandel, Alavi, Terry, & Plotkin, 2002). The CVM builds upon the Dynamic Recursive Model for Sports Injury (Meeuwisse, Tyreman, Hagel, & Emery, 2007). Conceptual elements utilized from this model include the predisposed host, external risk factors, the inciting event or impact, injury, removal from activity, and repeat participation (Meeuwisse et al., 2007).

There are two major components of the CVM: the process of concussion development and the cycle of concussive vulnerability. The process of concussion development entails a predisposed host who has a concussion after experiencing an impact in a risk-taking environment or participating in a risk-taking activity; thus, the cycle of concussive vulnerability begins once the concussion occurs. This study specifically examined the risk factors of gender, ethnicity, socio-economic status, health insurance, education, migraine history, attention and learning disorders, and previous concussion history. The host is typically diagnosed by reporting concussion symptoms, neuropsychological testing, and physical exam, and is then removed from the risky

environment or activity (e.g., sports). After receiving individualized treatment, typically rest, the host usually recovers within 7 to 10 days. However, some individuals with predisposing risk factors may experience persistent symptoms or permanent neurologic sequelae if he/ she prematurely returns to the risk-taking environment or activity without making a full recovery. The host exits the cycle of concussive vulnerability once he/she completely recovers from the concussion. This study sought to identify specific risk factors, described below, in the predisposed host that were associated with worse concussion outcomes.

### **Concussion Recovery Risk Factors**

There are several concussion risk factors that may affect concussion recovery that were addressed by this study including gender, race/ ethnicity, health insurance, socioeconomic status, prior concussions, migraine history, mechanism of injury, education, learning disabilities, and attention deficit disorders.

**Gender.** Gender may be a risk factor for persistent concussive symptoms and worse baseline symptoms. There is growing evidence that females may be at higher risk for concussive injury compared with males when playing similar sports with similar rules. For example, some studies have demonstrated that female soccer players have a 1.5 to 2.5-fold increase in concussion risk and female basketball players have a 1.5 to 3-fold increase in concussions compared with male players (Abrahams, Mc Fie, Patricios, Posthumus, & September, 2013; Makdissi et al., 2013). It is unclear why females may be at higher risk for a concussion than males. Some explanations may include females have a smaller head to neck ratio, weaker neck muscles, and greater angular head acceleration than males (Eckner, Oh, Joshi, Richardson, & Ashton-Miller, 2014). Several studies have

shown that females report more severe post-concussion symptoms compared with males (Berz et al., 2013; Broshek et al., 2005; Covassin, Elbin, Bleecker, Lipchik, & Kontos, 2013; Covassin, Elbin, Harris, Parker, & Kontos, 2012; Zuckerman et al., 2014); whereas, other studies have not demonstrated a gender difference in post-concussion symptom reporting (Frommer et al., 2011; Kontos, Covassin, Elbin, & Parker, 2012; Preiss-Farzanegan, Chapman, Wong, Wu, & Bazarian, 2009; Zuckerman et al., 2012). The World Health Organization task force on concussions performed a systematic review on examining gender differences on concussion outcomes and determined that gender was not a predictor of post-concussion symptoms in children and adults (Cancelliere, Donovan, & Cassidy, 2015). Some researchers believe concussion symptom differences may reflect gender reporting behavior differences. Specifically, females may be more willing to report their concussion symptoms compared with males (Dick, 2009). In fact, some studies have demonstrated that females report more symptoms at pre-concussion baseline compared with males (Covassin, Elbin, Harris, et al., 2012; Leach, Bay, & Valovich McLeod, 2013; Register-Mihalik, Mihalik, & Guskiewicz, 2009; Zuckerman et al., 2014). However, other studies have not demonstrated baseline symptom reporting differences by gender (Brooks et al., 2014; Covassin, Elbin, Larson, & Kontos, 2012; Covassin, Schatz, & Swanik, 2007; Kontos et al., 2012; Zuckerman et al., 2012). In terms of symptom type, a few studies have determined that females may experience worse post-concussion headaches than males (Bramley et al., 2015; Covassin, Elbin, et al., 2013; Mihalik et al., 2013). In addition, several studies determined that females have worse post-concussion neurocognitive performance than males (Broshek et al., 2005; Covassin, Elbin, et al., 2013; Covassin, Elbin, Harris, et al., 2012; Covassin et al., 2007); however,

another study did not indicate a gender difference in neurocognition (Zuckerman et al., 2012). Research has indicated that females may have prolonged recovery times as compared with males by a few days (Zuckerman et al., 2014) to over a month (Bock et al., 2015; Bramley et al., 2015; Kostyun & Hafeez, 2015; Miller et al., 2015).

Furthermore, Kostyun & Hafeez (2015) found that adolescent females required more treatment interventions and academic accommodations after a concussion than adolescent males ( $N = 266, p < .001$ ). More research is needed to evaluate whether gender is a risk factor for worse concussion recovery and baseline symptoms.

**Race/ Ethnicity.** Multiple studies have reported higher incidence and poorer health outcomes among Blacks and Hispanics for diseases such as obesity, HIV/ AIDS, asthma, diabetes, cardiovascular, and cancer (Brennan Ramirez, 2008; Price, Khubchandani, McKinney, & Braun, 2013). Moderate to severe TBIs are distinguished from mild TBIs/ concussions by the presence of intracranial hemorrhage detected by routine CT or MRI and frequently result in permanent complications or death. TBI incidence is highest among ethnic minorities. For example, American Indians/ Alaska Natives suffer the highest incidence of death due to TBI followed by Blacks compared with other ethnic/ racial groups (Coronado et al., 2011). TBI incidence reported in EDs is highest among non-Whites compared with Whites (Jager, Weiss, Coben, & Pepe, 2000). TBI rates among ethnic minorities are expected to grow as the U.S. minority population is expected to exceed the non-Hispanic White population by 2060 (U.S. Census Bureau, 2012). Minorities have been shown to have worse TBI outcomes as they related to the psychosocial (e.g. QOL, community integration), treatment (e.g. rehabilitation, medication, etc.), and functional domains (e.g. mortality, repeat TBI risk); these



differences were apparent in both the adult and pediatric populations (Gary, Arango-Lasprilla, & Stevens, 2009).

There are few studies that have evaluated concussions in minorities. As mentioned earlier, one study found that high school and college Black athletes performed worse on at least one of the ImPACT composite scores compared with Whites ( $N = 96$ ) a week after a concussion ( $OR = 2.39$ ,  $95\% CI = 1.04 - 5.50$ ,  $p = .04$ ) despite similar baseline scores (Kontos et al., 2010). There is a lack of data on the percentages of minorities who play high school sports. Because of the limited data on concussions and concern for health disparities, the Institute of Medicine recently published a report on SRCs in youth and recommended that the National Electronic Injury Surveillance System- All Injury Program (NSEISS-AIP) database include race/ ethnicity, gender, socio-economic status and concussion outcomes (e.g. mechanism of injury, symptoms, etc.) in all injured persons with concussions ages 5 to 21 years old (Committee on Sports-Related Concussions in Youth, 2014). None of the gender concussion studies described in the previous section reported race/ ethnicity of their study samples. Thus, more concussion research is needed in racially/ ethnically diverse population of adolescents.

**Health Insurance/ Socio-Economic Status.** Health insurance status is correlated with better health outcomes (Centers for Disease Control, 2011). In 2007, there were an estimated 6.5 million uninsured children and in 2014, even with the passage of the Affordable Care Act in 2010, there were an estimated 4 million uninsured children (Ward, Clarke, Freeman, & Schiller, 2014). Under-insurance is defined as insurance that does not adequately cover an individual's health needs (Kogan et al., 2010). In 2007, there were approximately 14.1 million under-insured children (Kogan et al., 2010).

Schoen and colleagues (2014) determined that the number of underinsured persons < 65 years old grew from 29.9 million in 2010 to 31.7 million in 2012 (Schoen, Hayes, Collins, Lippa, & Radley, 2014). It is estimated that a third of Texans ages 19-64 years old were underinsured in 2014 (Collins, Rasmussen, Beutel, & Doty, 2015). More data is needed on the current rates of under-insured children and how under-insurance affects children's health outcomes. Health disparities among TBI patients with respect to clinical outcomes has been identified among minority children (Brown, 2010) and adults (Schiraldi et al., 2015). Some studies determined that minority race and lack of insurance were predictors of adult TBI patients not being discharged to post-TBI rehabilitation therapy (Asemota, George, Cumpsty-Fowler, Haider, & Schneider, 2013; Kane, Wright, Fu, & Carlson, 2014). Gardizi and colleagues (2014) found that adult TBI patients who had public insurance had worse disability compared with those who had private insurance even after controlling for education, race, and mechanism of injury (Gardizi, Hanks, Millis, & Figueroa, 2014). Jimenez and colleagues (2015) determined that children with TBI who had Medicaid had worse functional outcomes and lower cognitive scores compared with non-minority children (Jimenez et al., 2015). Rabinowitz et al. (2015) found that the only predictor of poor cognitive outcomes among adult mTBI patients was socio-economic status. A recent study in patients ages 9 to 18 years old diagnosed with PCS (concussion symptoms lasting > 3 months) found that insurance type (private vs. other) was not a predictor of PCS (Morgan et al., 2015). However, 80% of the study sample ( $N = 40$ ) had private insurance and the other forms of health insurance were not clearly identified; furthermore, Whites constituted 90% of the sample. Additional studies are needed to examine health insurance type/ SES in a racially/ ethnically diverse

population of adolescents with concussions and whether these factors are associated with prolonged recovery.

**Prior Concussions.** As mentioned earlier, a common cause of concussion is sports. Athletes in contact sports are at risk for repeated brain trauma due to high risk of collision between players. There are a growing number adolescent athletes participating in sports. For example, there were 82,000 more U.S. high school athletes in the 2013-2014 school year compared with the 2012-2013 school year (National Federation of State High School Associations, 2014). Studies have shown that multiple concussions (Guskiewicz et al., 2005) or repeated head impacts (Bazarian et al., 2014) can result in debilitating long-term motor (De Beaumont et al., 2013), cognitive deficits, and depression (Hart et al., 2013) in retired adult professional football players. It remains unknown how many concussions an athlete can incur before developing permanent long-term neurologic sequelae. Adolescents who have had multiple concussions may be at higher risk for worse neurologic damage compared with adults (Choe et al., 2012). MRI studies have shown that the brain is not fully mature until approximately age 25 years (Lenroot & Giedd, 2006). Animal experimental studies in rats have demonstrated that myelination of white matter tracts continues throughout adolescence and that unmyelinated white matter tracts are easily damaged compared with myelinated white matter tracts after an experimental concussion (Giza & Difiori, 2011). Numerous studies have found declines on baseline neurocognitive scores and higher symptom reporting among male and female high school and college athletes who have sustained multiple concussions (Brooks et al., 2014; Covassin, Elbin, Kontos, & Larson, 2010; Iverson, Echemendia, Lamarre, Brooks, & Gaetz, 2012; Leach et al., 2013; Mannix et al., 2014;

Register-Mihalik et al., 2009; Schatz, Moser, Covassin, & Karpf, 2011). Several studies have also determined there is an association between multiple concussions and worse neurocognition and symptom scores during the acute phase of post-concussive injury ( $\leq 10$  days) (Covassin, Moran, & Wilhelm, 2013; Covassin, Stearne, & Elbin, 2008; Guskiewicz et al., 2003; Iverson, Gaetz, Lovell, & Collins, 2004; Macciocchi, Barth, Littlefield, & Cantu, 2001). However, there has only been one study that has examined the impact of prior concussions on protracted recovery. Wojcik (2014) performed a study in concussed patients ages 7 to 61 years old ( $N = 85$ ) and determined that prior concussion history was a predictor of PCS (median of 4.6 weeks;  $p < .001$ ). However, there have been no studies to date that has evaluated the relationship between prior concussion history and protracted recovery in the adolescent population. Furthermore, race/ ethnicity was not reported in any of these studies. Thus, more research is needed to examine the relationship between prior concussions and concussion recovery times in a racially/ ethnically diverse adolescent population.

**Migraine History.** Migraine headaches are another potential risk factor for prolonged concussion symptoms lasting  $>10$  days (Harmon et al., 2013). A common concussion symptom is migraine-type headache. Females in the general population have significantly higher rates of migraine headaches than males with a peak prevalence in females during their child-bearing years (Borsook et al., 2014). Females have double the risk for personal and/ or family history of migraine headaches compared with males (Burch, Loder, Loder, & Smitherman, 2015; Genizi, Khourieh Matar, Zelnik, Schertz, & Srugo, 2016). In addition, a recent review article found racial/ ethnic differences among U.S. migraine sufferers with Native Americans (17.7%) and Whites (15.5%) having the

highest overall prevalence and Hispanic females (2.26%) having the highest prevalence of chronic migraines, defined as  $\geq 15$  headache days per month, compared with White females (1.2%) (Loder, Sheikh, & Loder, 2015). Therefore, migraine history was examined in a racially/ ethnically diverse sample of adolescents as a risk factor for prolonged concussion recovery.

**Mechanism of Injury/ Sport.** Adolescents who experience a concussion as a result of a motor vehicle accidents may have worse concussion outcomes compared with concussions sustained during football and soccer (Seiger, Goldwater, & Deibert, 2015). Athletes who play football have the highest rates of concussion compared with athletes who play other sports including soccer and basketball (Lincoln et al., 2011). However, as stated earlier, females have a higher incidence of concussion compared with males when playing similar sports. Player positions have been associated with higher rates of concussion including running backs, quarterbacks, wide receivers, and defensive backs in football (Harmon et al., 2013) and goalies in soccer (Daneshvar, Nowinski, McKee, & Cantu, 2011). The role of mechanism of injury (MOI) on concussion recovery, particularly with respect to sports vs. non-sports injuries, has not been well-studied. Thus, this study examined MOI in relation to concussion recovery time.

**Years of Education.** Education is a significant predictor of higher health status in adult TBI patients (Willemse-van Son, Ribbers, Verhagen, & Stam, 2007). A recent meta-analysis found that adolescent athletes with concussion who have more years of education have fewer neuropsychological deficits compared to those with less education (Dougan, Horswill, & Geffen, 2013). The present study focused on the relationship

between the years of education on concussion recovery in a sample of racially/ ethnically diverse adolescents.

**Learning Disabilities and Attention Deficit Disorders.** Learning disabilities (LD) and Attention deficit hyperactivity disorders (ADHD) may complicate the diagnosis of concussion. Neurocognitive baseline scores are often lower than students without these diagnoses (Zuckerman, Lee, Odom, Solomon, & Sills, 2013). An estimated 5% of U.S. children ages have ADHD (Centers for Disease Control, 2013) and approximately 5% of U.S. students (Pre-Kindergarten to 12<sup>th</sup> grade) have learning disabilities (National Center for Education Statistics, 2013). Learning and attention deficit disorders have been associated with worse baseline neurocognition and higher symptom reporting in high school and college athletes (Elbin et al., 2013; Zuckerman et al., 2013). ADHD has been associated with higher concussion risk and rates in adolescent and college athletes (Alosco, Fedor, & Gunstad, 2014; Biederman et al., 2015; Iverson, Atkins, Zafonte, & Berkner, 2014). A recent study determined that ADHD was a significant predictor of protracted concussion recovery lasting  $\geq 28$  days in patients ages 6 to 18 years old ( $N = 126$ ,  $p < .05$ ); the subjects' race/ ethnicity was not reported in this study (Miller et al., 2015). There have been no studies to date that have examined the relationship between LD and ADHD and concussion recovery times in a racially/ ethnically diverse adolescent population; thus more studies are needed.

## **Methods**

### **Design**

This study was a retrospective observational cohort design of clinical data obtained from January 1, 2012 to August 1, 2015. The electronic medical record and paper charts of

patients treated at a large university- based concussion clinic in Houston, Texas were reviewed. The research protocol was approved by the university institutional review board for the protection of human subjects prior to data collection.

### **Study Sample**

Adolescents ages 13 to 19 years old with concussion/ mTBI diagnosis were included as part of the retrospective chart review. The dates were selected based on the availability of ImPACT computerized concussion test data. Patients with ImPACT test scores obtained within 10 days of concussive injury and who had at least one ImPACT test performed  $\geq 10$  days and/ or a clinical chart note that indicated the patient was recovered (e.g., cleared to RTP) were included in this study. Sample size was chosen based on the number of charts meeting inclusion/ exclusion criteria. The racial/ ethnic and gender identification provided by the patient or patient's family as designated in the medical chart was used in this study. For a retrospective chart review (Gearing, Mian, Barber, & Ickowicz, 2006), power was initially estimated by using a rule of thumb of 10 charts per variable for multivariable modeling used in Aim 2 (Fletcher, Fletcher, & Wagner, 1996) and logistic and Cox regression used in Aim 3 (Vittinghoff & McCulloch, 2007); this meant that Aims 2 and 3 required a minimum of 70 charts and 90 charts, respectively. However, a more robust method of estimating power was determined with a G\*Power 3.1 calculation; thus, for a multiple regression design with 9 predictors and alpha of .05 demonstrated that using a moderate effect size ( $R^2 = 0.15$ ) and power of 0.80 could be achieved from 114 charts (Faul, Erdfelder, Lang, & Buchner, 2007). Patients with a psychiatric diagnosis (e.g. depression, anxiety, mood disorders), who were diagnosed by a healthcare provider, as documented in the patient chart, were excluded due to potential for confounding related to

higher symptom scores and prolonged recovery (Iverson et al., 2015; Lange, Iverson, & Rose, 2011; Morgan et al., 2015; Ponsford et al., 2012). Charts with missing data were excluded from the study.

### **Data Collection Procedure**

Charts were reviewed based on inclusion criteria and completeness of medical records and ImpACT data. Data were collected on the following demographic and clinical variables: age, gender, race/ ethnicity, primary language, education, psychiatric history, concussion history, migraine history, MOI/sport, history of LD/ ADHD and if on ADHD medication, health insurance status, and zip code. Ethnicity categories were as follows: Hispanic or non-Hispanic. Race categories were as follows: White, Black, Asian, American Indian/ Alaska Native, Native Hawaiian/ Pacific Islander, and Other. Health insurance that paid for the subject's health provider concussion visit was classified as follows: none, public (e.g., Medicaid, Chips), student athletic insurance, and private (commercial). Student athletic health insurance is offered by the school district to students participating in school sports for a nominal fee in the event that they do not have other forms of health insurance if/ when they are injured during a school-sponsored sporting event. Outcome measures that were collected included the: (1) duration of concussion symptoms that was obtained from the clinical chart notes and ImpACT data (2) baseline (if available) and acute/ initial post-concussion scores (e.g., "Post-concussion #1" scores) on verbal memory, visual memory, visual motor processing speed, reaction time, and PCSS symptom composite scores on ImpACT (web-based application, 2012 version). The dates collected were as follows: date of concussion, dates of first and last post-concussive injury ImpACT tests, and date when the patient was cleared to RTP and/ or participate in normal activities



(e.g., recovered) per healthcare provider notes. De-identified patient data was coded and entered into a spreadsheet in Microsoft Windows Excel (version 2013).

### **Sample selection procedure**

Among 233 charts that met inclusion criteria, 123 were randomly selected using a random sample generated in the statistical software program, R (version 3.2.3) for Windows (R Core Team, 2013). De-identified chart numbers were randomized with a 1:1 acceptance ratio. The selected charts were included in this study.

### **Instrument**

The Immediate Post-concussion Assessment and Cognitive Testing (ImPACT) computerized concussion battery consists of the following composite scores: Post-Concussion Symptoms Scale (PCSS) and 4 neurocognitive modules including verbal memory, visual memory, visual motor processing speed, and reaction time. For ease of discussion, visual motor processing speed will be referred to simply as visual motor. The instrument is well-studied, widely used, and is valid in patients 10-59 years old (ImPACT Applications Inc., 2007). The ImPACT test takes approximately 25–30 min to complete.

**Self-reported concussion symptoms severity checklist.** The PCSS has 22 items and an ordinal 7-point Likert-type response format for severity with response options from 0 (none) to 6 (severe). The symptom domains include 6 cognitive symptoms, 4 emotional/mood symptoms, 3 sleep disturbance symptoms, and 9 somatic symptoms. Scores from 0 to 132; higher scores indicate more symptoms. The PCSS was initially developed as a separate symptoms checklist and was subsequently included as a composite score on the ImPACT computerized test. Evidence of PCSS reliability includes Cronbach's  $\alpha$  of .88 to .94 (ImPACT Applications Inc., 2007), suggesting adequate internal consistency, and test-

retest correlation of .80 with a 4-day interval in high school and collegiate athletes with concussion (ImPACT Applications Inc., 2007), suggesting adequate stability of the instrument per the a priori criteria. Evidence of PCSS validity includes predictive validity for predicting PCS, [AUC = .377,  $p = .03$ ] (Barlow, Schlabach, Peiffer, & Cook, 2011) and concurrent validity with the ImPACT visual motor processing speed [ $r = .70$ ] (Schatz & Putz, 2006), indicating support for instrument validity. For ease of discussion, PCSS scores will simply be referred to as ImPACT symptom scores.

**Neurocognitive battery.** The neuropsychological component of the ImPACT includes verbal memory, visual memory, visual motor processing speed, and reaction time tests. This section of the test requires the participant to answer a series of questions by following a number of written and visual prompts that require the participant to click the mouse or type in an appropriate answer. Lower scores on verbal memory, visual memory, and visual motor composite scores and higher scores on reaction time compared with baseline scores and/ or norms indicate cognitive impairment. The ImPACT test has adequate evidence of reliability and validity of neurocognitive performance related to concussion (ImPACT Applications Inc., 2007). The ImPACT neurocognitive subscales have estimates of 1-year test-retest reliability measured by intra-class coefficients (ICCs) of 0.62 to 0.86 in high school athletes (Elbin, Schatz, & Covassin, 2011). The ImPACT neurocognitive subscales demonstrate evidence of convergent validity with the Symbol Digital Modalities Test, Trail Making Tests and the Digit Symbol subtest of the Wechsler scale, CogSport, and HeadMinder (Iverson, Lovell, & Collins, 2005; Schatz & Putz, 2006). The online version of ImPACT has a sensitivity of 91.4% and specificity of 69.1% for detecting a concussion in athletes ages 13 to 21 years old (Schatz & Sandel, 2013).

## Data Analysis

Statistical analysis was performed with IBM SPSS Statistical Package (version 23) for Windows. To meet the criteria of Aim 1, descriptive statistics were calculated by gender and race for each demographic and clinical factor and included measures of central tendency and dispersion of continuous variables and frequencies and proportions of categorical variables. Differences between groups by gender and race on demographic (age, education, primary language, health insurance, median income, MOI) and clinical (migraine history, concussion history, LD/ADHD) factors were determined by independent samples *t*-test for continuous variables and by chi-square or Fisher's exact tests (if cell counts were 5 or less) for categorical variables. The study sample was evaluated with respect to gender and race/ ethnicity. Distributions of outcomes were examined for normality. The significance level was set at  $\alpha = .05$ .

For Aim 2, baseline and post-concussion differences between groups by gender and race on concussion outcomes were determined by independent samples *t*-tests. General linear models (GLM) were utilized to examine the differences on the ImPACT composite scores including the verbal memory, visual memory, visual motor, reaction time, and symptom scores between racial/ ethnic and gender categories at baseline, when available, and post-concussion. Model residuals were examined for normality, linearity, and homogeneity of variances. In order to control for type I error, I performed a multivariate analyses of variance (MANOVA) of the variables in addition to evaluation for separate outcomes. Continuous outcome variables exhibiting a skewed distribution were transformed prior to conducting independent samples *t*-tests and MANOVA to satisfy the prerequisite assumptions of normality. The reliable change indices (RCIs)

were described for subjects who had baseline data by gender and race/ ethnicity groups. The RCI is a method of examining whether a change in an individual's test score from baseline to post-concussion is clinically significant and depends on the reliability of the measure (Jacobson & Truax, 1991). The RCIs at the 80% confidence interval (CI) that is utilized with ImPACT raw scores are as follows: 8.75 points on verbal memory, 13.5 points on visual memory, 4.98 points on visual motor speed, 0.06 points on reaction time, and 9.6 points on PCSS symptoms score (Iverson, Lovell, & Collins, 2003). However, it is important to note that clinical judgment is needed for the interpretation of the clinical significance of individual RCIs, particularly with respect to reported symptom scores (ImPACT Applications Inc., 2007).

To address Aim 3, multivariable hierarchical logistic regression was utilized to determine whether the clinical (concussion history, migraine history, LD/ADHD) and demographic (age, race, gender, MOI (sport vs. non-sport), education years, health insurance) factors predicted the dichotomized duration of symptoms (less than or greater than the median time of resolution). Race and gender were added after all other clinical and demographic variables in order to determine how they added to the predictive model. Survival (or time-to-event) analysis was performed utilizing the Kaplan-Meier method with a log-rank test and Cox proportional hazards regression model. The Kaplan-Meier method with log-rank test is useful for comparing survival curves in two or more groups. The Cox proportional hazards regression model allows for the analysis of the effect of several risk factors or predictors on the event of interest, recovery. The Cox proportional hazards regression model is advantageous over logistic regression because it accounts for survival time and missing data on the outcome, also termed censored data (Singh &

Mukhopadhyay, 2011). There was sufficient data in this sample to determine which variables predicted the event of concussion resolution (days). There was no loss to clinic follow-up in this sample; hence the data were complete. The proportional hazards assumption was satisfied for all plots.

## Results

Figure 2 is a flowchart of chart selection in this study. A total of 825 patients were seen in the clinic from January 1, 2012 to August 1, 2015. There were 591 charts that did not meet inclusion criteria; 120 of these records had inaccurate or missing race data. Many patients were inaccurately classified as “Other” as the default race/ ethnicity when this data was missing from the patient’s chart; hence, this limited the chart review to patients whose races were complete in the patient’s chart and correctly classified. A total of 233 charts that met inclusion criteria were randomized, as described in the Methods section, and 123 charts were selected for review. Further inspection of the charts revealed that 5 of these charts did not meet inclusion criteria. Thus, 118 charts were included in this study.

### Description of the Sample

The total sample ( $N = 118$ ) was composed of 71.2% males and 28.8% females (see Table 1). The sample ( $N = 118$ ) consisted of 61% Whites (non-Hispanic) (42% males, 19% females), 24% Hispanics (14% males, 10% females), and 15% Blacks (non-Hispanic) (14 % males, <1% females). Hispanics and Blacks (non-Hispanic) were aggregated as ethnic minorities because there was only one Black female; this was a problem for statistically examining the interaction of race and gender. Thus, ethnic minorities constituted 40% of the sample (46/ 118), of which 73.9% were males and 26.1% were females (see Table 2). There were no White or Black subjects who had an ethnicity of

Hispanic in this sample. Thus, for ease of discussion in this paper, race/ ethnicity will be referred to only as race, and classification will be as follows: Hispanic, Black, and White. For comparison purposes, the sample that was not selected from the randomization selection process is displayed in Table 3. Compared with the selected sample, the unselected sample had more Hispanic males (60.7% vs. 86%) and fewer Hispanic females (39.3% vs.14%). The percentages of Whites and Blacks in the unselected sample were similar to the selected sample.

There were no significant differences ( $p > .05$ ) between males and females on demographic or clinical variables (see Table 4). However, there were several differences on demographic and clinical variables by race. Compared with Whites, Minorities were older by a year ( $M = 16.15$ ,  $SD = 1.35$  vs.  $M = 15.49$ ,  $SD = 1.49$ ;  $t(116) = -2.45$ ,  $p = .016$ ), had more education years by nearly a year ( $M = 9.63$ ,  $SD = 1.12$  vs.  $M = 9.03$ ,  $SD = 1.46$ );  $t(116) = -2.34$ ,  $p = .021$ ), were more likely to attend public middle or high school ( $\chi^2(1, N = 109) = 18.96$ ,  $p < .001$ ), had more bilingual Spanish/English speakers ( $p < .001$ , Fisher's exact test), had lower estimated median incomes,  $\chi^2(3, N = 118) = 48.07$ ,  $p < .001$ , had higher percentages of public and student (athletic) insurance ( $p < .001$ , Fisher's exact test), had less headache history particularly with respect to migraines ( $p = .03$ , Fisher's exact test), and experienced fewer non-sport concussions,  $\chi^2(1, N = 118) = 6.01$ ,  $p = .014$ . There was no statistical differences between groups in subjects who had prior concussions or LD and ADHD. There were 6 out of 13 or 46.2% of ADHD subjects who were taking prescribed ADHD medication prior to their concussion. The most common causes of concussions in males were football (66.7%) and motor vehicle accidents (7.1%); whereas concussions in females were most frequently caused by soccer

(44.1%), basketball (20.6%), and volleyball (14.7%). Males had more non-sport concussions than females (11.9% vs. 8.8%) and Whites had more non-sport concussions than Minorities (16.7% and 2.2%). There was no difference by race or gender on the number of days from concussive injury to the initial concussion clinic evaluation ( $p > .05$ ); 75% of subjects were examined within 5 days post-injury (see Table 4).

### **The Influence of Race and Gender on Post-Concussion Outcomes.**

I hypothesized that females will have worse acute/ initial post-concussion ImPACT scores than males and Minorities will have worse acute/ initial ImPACT scores than Whites. Furthermore, with respect to interaction between race and gender, I hypothesized that Minority females will have worse concussion scores than other race/ gender groups. In order to examine these hypotheses, a MANOVA was conducted (see Table 5). Since Box's M test of equality covariance matrices was significant and sample sizes varied across groups, particularly by gender, Pillai's trace statistic was used since it is more robust to violation of assumptions. The assumption of homogeneity of variance, as indicated by Levene's test of equality, was met. Reaction time and symptoms scores were transformed utilizing natural log and square root, respectively, in order to reduce skewness. Univariate tests indicated that effect of gender was statistically significant for reaction time ( $F(1,114) = 4.22, p = .04, \eta_p^2 = .036$ ). As depicted in Figure 3, females had slower reaction times compared with males after concussion. Univariate tests indicated that the interaction of gender and race was statistically significant for verbal memory ( $F(1,114) = 4.92, p = .03, \eta_p^2 = .041$ ). As depicted in Figure 4, Minority females performed worse than White females, White males, and Minority males on verbal memory. Multivariate tests for the main effects of gender ( $F(5,110) = 1.77, p = .13, \eta_p^2 =$

.07) and race ( $F(5,110) = 2.04, p = .08, \eta_p^2 = .09$ ) and the interaction of race and gender ( $F(5,110) = 2.01, p = .08, \eta_p^2 = .08$ ) were not statistically significant. In summary, my hypothesis that females would perform worse on ImPACT scores was confirmed for only one composite score of reaction time. My hypothesis that Minorities would perform worse on ImPACT scores was not true in this study sample. Finally, my hypothesis that Minority females would perform worse on ImPACT was confirmed only for verbal memory; this finding is further examined in the next section.

Exploratory descriptive findings are as follows. Post-concussion outcome variables, including resolution times and ImPACT scores, by race and gender are shown in Table 6. Reaction time and symptoms scores were transformed prior to running independent samples *t*-test utilizing natural log and square root, respectively, in order to reduce skewness. Sample statistics including means, standard deviations, medians, and ranges were provided on untransformed raw scores. Minorities had significantly fewer mean days to concussion resolution compared with Whites ( $M = 21.2, SD = 22.89$  vs.  $M = 31.61, SD = 38.62, p = .046$ ); the median days to resolution was 13 vs. 18.33 days, respectively. There was no statistically significant difference in resolution days by gender. Females had higher mean symptom scores ( $M = 24.94, SD = 22.6$ ) than males ( $M = 18.28, SD = 17.95$ ) and Minorities had lower mean symptom scores ( $M = 17.72, SD = 19.45$ ) than Whites ( $M = 21.78, SD = 19.45$ ). However, there was no statistical difference by gender or race on mean post-concussion outcomes ( $p > .05$ ) using independent samples *t*-tests.

Post-concussion outcomes variables by combined race and gender categories are presented in Table 7. Minority males and females had a shorter mean concussion



resolution days ( $M = 20.29$ ,  $SD = 23.85$  and  $M = 23.75$ ,  $SD = 20.71$ , respectively) compared with White males ( $M = 33.18$ ,  $SD = 44.82$ ) and White females ( $M = 28.05$ ,  $SD = 20.71$ ), respectively. On verbal memory, White females ( $M = 82.45 \pm 12.92$ ) had the highest scores and Minority females had the lowest scores ( $M = 72.08$ ,  $SD = 21.03$ ) compared with White and Minority males ( $M = 75.52$ ,  $SD = 13.87$  and  $M = 78.50$ ,  $SD = 12.76$ ). Minority females had slower reaction times ( $M = .78$ ,  $SD = .28$ ) compared with White females ( $M = .73$ ,  $SD = .12$ ), White males ( $M = .69$ ,  $SD = .15$ ), and Minority males ( $M = .68$ ,  $SD = .22$ ). Minority females had higher symptom scores ( $M = 27.55$ ,  $SD = 27.60$ ) compared with White females ( $M = 23.68$ ,  $SD = 20.02$ ), White males ( $M = 20.94$ ,  $SD = 19.34$ ), and Minority males ( $M = 14.36$ ,  $SD = 15.11$ ). Normative percentile categories on post-concussion ImPACT cognition scores for the study sample ( $N = 118$ ) are presented in Table 8. Most subjects performed in the low-average (10<sup>th</sup> to 25<sup>th</sup> percentile) to average range (26<sup>th</sup> to 75<sup>th</sup> percentile) after a concussion.

#### **The influence of primary language.**

Because Minority females performed significantly worse on verbal memory compared with other gender and race categories, I wanted to examine the influence of primary language (bilingual English/ Spanish vs. English only) on verbal memory. In order to determine whether primary language influenced verbal memory scores, language was added to the analysis (Table 9). The assumptions of independence of observations and homogeneity of variance and covariance were met. Univariate analyses indicated the interaction of gender and race remained statistically significant for verbal memory ( $F(1,113) = 4.4$ ,  $p = .04$ ,  $\eta_p^2 = .037$ ). Specifically, Minority females performed worse than White females, White males, and Minority males on verbal memory regardless of

primary language (see Figures 5 and 6). Multivariate tests indicated that the interaction of gender and race ( $F(5,109) = 1.69, p = .20, \eta_p^2 = .06$ ) and main effects for gender ( $F(5,109) = 1.82, p = .12, \eta_p^2 = .08$ ), race ( $F(5,109) = 1.48, p = .30, \eta_p^2 = .05$ ), and language ( $F(5,109) = 1.96, p = .09, \eta_p^2 = .08$ ) were not statistically significant.

#### **Comparison of baseline and post-concussion scores.**

Half of the subjects ( $N = 59/118$ ) had baseline ImPACT scores available that were used to compare their post-concussive ImPACT scores. I hypothesized that there will be no difference by race or gender on baseline ImPACT scores. A doubly multivariate analysis was conducted to determine if there was a difference between subjects on baseline and post-concussion ImPACT scores (see Table 10). Since Box's M test of equality covariance matrices was significant and sample sizes varied across groups, particularly by gender, Pillai's trace statistic was used. The assumption of homogeneity of variance was met. Univariate analysis with a Greenhouse-Geisser correction determined that there was a statistically significant difference between groups by race on baseline and post-concussion visual motor scores ( $F(1,56) = 11.51, p < .001, \eta_p^2 = .171$ ) with Minorities performing worse than Whites (see Figure 7). There was no significant interaction between race and time suggesting that Minorities performed worse than Whites on both baseline and post-concussion visual motor scores (see Figure 8). Statistically significant multivariate effects were found for the main effects of race ( $F(5,52) = 3.20, p = .014, \eta_p^2 = .009$ ) and time ( $F(5,52) = 3.46, p = .249$ ). There were no significant multivariate or univariate effects by gender ( $p > .05$ ). In summary, my hypothesis that there would be no difference by race or gender on baseline ImPACT

scores was not supported for race on the visual motor test. Minorities performed significantly worse than Whites at baseline and post-concussion on the visual motor test.

Exploratory findings are as follows. Table 11 presents the score means and percentages of subjects by gender and race who exceeded the RCI at the 80% CI on the composite ImpACT scores. Examination of the means shows worse overall performance on all ImpACT scores from baseline to post-concussion among all groups. The RCI scores that exceeded the 80% CI are displayed for ImpACT verbal memory, visual memory, visual motor, and the symptoms scores. A paired-samples *t*-test was conducted to evaluate the change in means on baseline and post-concussion ImpACT scores (Table 12). Reaction time and symptoms scores were transformed utilizing natural log and square root, respectively, in order to reduce skewness. There was a significant change in means from baseline to post-concussion on verbal memory ( $p = .003$ ), visual memory ( $p = .009$ ), reaction time ( $p < .001$ ), and symptoms ( $p < .001$ ). These results suggest that there was a significant difference between baseline and post-concussion ImpACT scores. To assess the clinical significance of the test scores, the difference between the baseline and post-concussion ImpACT scores were compared using the RCIs, as described in the analysis section. Table 13 displays the percentage of subjects who exceeded 1, 2, 3, and 4 of the RCIs, meaning that they performed clinically worse on at least 1, 2, 3, or 4 of the composite ImpACT scores. Most of the study sample ( $N = 44$ , 74.6%) exceeded at least 1 RCI at the 80% CI. There were significantly fewer females than males ( $N = 10$  vs.  $n = 49$ ); thus I could not adequately compare RCI results by gender. Most males and females exceeded at least 1 RCI ( $N = 36$ , 73.5% and  $N = 8$ , 80%, respectively). There were more Whites who exceeded 2, 3, or 4 or more RCIs ( $N = 17$ , 51.5%;  $N = 13$ , 39.4%;  $N = 9$ ,

27.3%, respectively) compared with Minorities ( $N = 13$ , 50%;  $N = 6$ , 23.1%;  $N = 3$ , 11.5%, respectively).

### **Predictors of Concussion Recovery**

I hypothesized that predictors of protracted concussion recovery will include female gender, Minority race/ ethnicity, and history of prior concussions. As described in the data analysis section, two different statistical approaches were utilized to evaluate predictors of resolution time: logistic regression and survival analysis. As shown in Table 6, the median number of days to concussion resolution for the total sample was 17 days; hence, the dependent variable of concussion resolution  $> 17$  days was utilized in the logistic regression analysis. When the first 7 predictors of age, prior concussions, mechanism of injury, headache history, LD/ ADHD, health insurance, and education years were considered, they did not significantly predict concussion resolution,  $\chi^2 (13, N = 118) = 16.20, p = .24$ . The step of adding race and gender to the logistic regression was not significant,  $\chi^2 (2, N = 118) = 3.44, p = .18$ ; nor was there significant improvement to the overall model,  $\chi^2 (15, N = 118) = 19.64, p = .19$ . As presented in Table 14, the odds ratios suggested that the ADHD group had 13.6 times higher odds of protracted concussion recovery ( $> 17$  days) than those without ADHD only (OR = 13.63, 95% CI = 1.48 - 125.42,  $p = .02$ ). The student (athletic) insurance group had 95.1% and public insurance group had 93.9% lower odds of protracted recovery post-concussion than those who had private or no insurance (OR = .06, 95% CI = .004 - .88,  $p = .04$  and OR = .05, 95% CI = .003 - .79,  $p = .03$ , respectively).

The Cox proportional hazards regression model indicated that 3 out of 9 variables had significant prognostic value for concussion resolution time ( $p \leq .05$ ). As depicted in

Table 15, prior concussions and ADHD decreased hazard ratios and were less favorable with respect to concussion resolution (HR = .564, 95% CI = .332 - .959,  $p = .03$  and HR = .221, 95% CI = .095 - .514,  $p < .001$ , respectively). Student (athletic) and public insurance were found to increase hazard ratios and were favorable towards concussion resolution (HR = 3.98, 95% CI = 1.25 - 12.65,  $p = .02$  and HR = 3.33, 95% CI = 1.09 - 10.15,  $p = .03$ , respectively). Kaplan-Meier plots for race, gender, prior concussions, LD/ADHD, and health insurance are depicted in Figures 9-14. The log-rank tests for aggregated race ( $p = .06$ ; see Figure 9) and non-aggregated race ( $p = .10$ ; Figure 10) were not significant. Figure 9 demonstrates that Minorities had a trend of shorter concussion resolution times than Whites. Even though the log-rank test was not significant, the independent samples  $t$ -test demonstrated that resolution times were significantly different by race ( $p = .046$ ; see Table 5). Figure 10 shows the following trends: Hispanics had the shorter resolution times than Blacks and Whites and Whites had the longest resolution times. The log-rank test for gender ( $p = .725$ ; see Figure 11) was not significant; however, the trend indicated that males had longer resolution times than females. The log-rank test for prior concussion ( $p = .104$ ; see Figure 12) was not significant; however, prior concussion was a significant predictor in the Cox proportional hazards regression model ( $p = .03$ ). The Kaplan-Meier plot indicated that subjects with one or more concussions tended to take longer to recover than those without prior history of a concussion. The log rank tests were significant for LD/ADHD with ADHD subjects having the longest recovery times ( $p = .004$ ; see Figure 13). The overall trend was that persons without LD/ADHD had the shortest resolution times; however, as shown in Figure 13, there was a subject without LD/ADHD with a prolonged recovery time who

had a history of prior concussion. Finally, the log-rank test for health insurance type was significant indicating that subjects who had public or student insurance had shorter recovery times than those who had private or no insurance ( $p = .004$ ; see Figure 14). In summary, my hypotheses that gender and race would be predictors of protracted recovery were refuted. However, my hypothesis that prior concussions would be a predictor of protracted recovery was supported. ADHD was another significant predictor of prolonged resolution times in this study. Student athletic and public health insurances were predictors of shorter recovery times.

### **Discussion**

I was interested in evaluating whether specific risk factors in a concussed adolescent were associated with poor concussion recovery. There is conflicting evidence as to whether females are at higher risk for more severe or persistent concussion symptoms, worse cognition, and prolonged recovery. In addition, there is a lack of concussion data on race and the interaction with gender. Furthermore, there are few studies that have examined the effect of SES and health insurance on concussion outcomes. Finally, more data was needed on the effect of demographic and clinical risk factors such as age, education, MOI, migraine headache history, prior concussions, and LD/ ADHD on concussion recovery in a racially diverse sample of adolescents.

### **Summary of Major Findings**

The study sample ( $N = 118$ ) was composed of more males than females, with an approximate ratio of 70:30, and Whites outnumbered Minorities by an estimated ratio of 60:40. There were no statistical differences by gender with respect to demographic and clinical factors. However, there were significant differences by race. Specifically,

Minorities in this sample were older and had more education by a year, attended public school, were more likely to have public or student athletic insurance, were in the lower income quartiles, were more likely to be bilingual, had no migraine headache history, and experienced significantly fewer non-sport concussions than Whites. The most common cause of concussions among males was football and females was soccer. When I examined post-concussion ImPACT composite scores, multivariate analysis was not significant, but univariate analysis revealed a significant gender difference on reaction time with females having significantly delayed reaction times on ImPACT than males. Thus, my hypothesis that females would perform worse than males on ImPACT scores was confirmed for only one composite score of reaction time. Furthermore, in assessing the univariate effects of the interaction of race and gender, Minority females performed worse on verbal memory. Over half of the Minority females (6/11) in this study sample were bilingual Spanish/ English speakers; therefore, I added language to the statistical model and determined that Minority females performed worse on verbal memory whether their primary language was bilingual Spanish or English. Hence, my hypothesis that Minority females would perform worse on ImPACT was confirmed only for the verbal memory. I also evaluated a subset of the study sample ( $N = 59$ ) that had baseline ImPACT data and compared it with post-concussion ImPACT data. As expected, compared with baseline data, this sample performed worse on all of the post-concussion ImPACT composite scores. Nearly 75% of the study sample exceeded at least one RCI at the 80% CI. Multivariate and univariate analysis in this subgroup ( $N = 59$ ) demonstrated that Minorities had worse performance on visual motor processing speed than Whites. However, the difference on visual motor scores by race was not significant with time

indicating that Minorities performed worse than Whites both pre- and post-concussion. My hypothesis that there would be no difference by race on baseline ImPACT scores was not true for the visual motor test.

With respect to recovery time, the mean and median recovery time for the sample ( $N = 118$ ) was approximately  $M = 28$ ,  $SD = 34$  days and 17 days, respectively. Minorities recovered significantly faster than Whites. Minorities had significantly shorter median recovery times than Whites (13 vs. 18 days). There was no statistically significant difference in recovery time by gender. ADHD and prior concussions were significant predictors of concussion resolution times; whereas, having public or student insurance predicted significantly shorter resolution times. Thus, my hypothesis that prior concussions would be a predictor of protracted recovery was supported.

### **Effect of Gender**

This study indicated that females from a racially diverse sample exhibited slower post-concussion reaction times than males. My results were consistent with Broshek et al. (2005) who demonstrated that high school and college females had slower post-concussion reaction times than males on CRI, a web-based test that evaluates simple and complex reaction times ( $N = 155$ ,  $p < .05$ ). Colvin et al. (2009) also determined that females ages 8 to 24 years old had slower post-concussion reaction times on ImPACT than males ( $N = 234$ ,  $p < .05$ ). However, other studies found no differences on post-concussion ImPACT reaction time composite scores in collegiate females (Covassin, Elbin, et al., 2013; Covassin et al., 2007). These studies did not report race and it remains unknown whether their results would remain the same in a racially diverse sample. I did not identify any gender differences on post-concussion ImPACT verbal memory, visual



memory, visual motor, or symptoms scores. However, some studies indicated that compared with males, high school and college females had worse post-concussion verbal memory (Covassin, Elbin, et al., 2013) and visual memory (Covassin, Elbin, et al., 2013; Covassin, Elbin, Harris, et al., 2012; Covassin et al., 2007) composite scores on ImPACT. Conversely, Zuckerman et al. (2012) did not detect differences in high school females on post-concussion ImPACT verbal or visual memory scores. Again, none of these prior studies reported race and it remains unknown whether racially diverse samples perform differently on these post-concussion ImPACT composite scores. When I considered the interaction between race and gender, I identified verbal memory differences as described in the next section on the influence of race/ ethnicity on concussions.

I was unable to replicate findings in previous studies that determined that adolescent females had significantly worse symptom scores, and/ or longer resolution times than males. My findings were similar to studies that did not find post-concussion gender differences in adolescents on symptom scores (Frommer et al., 2011; Zuckerman et al., 2012) and resolution time (Frommer et al., 2011; Morgan et al., 2015). There may be other clinical factors in females that may influence post-concussion outcomes that my sample did not have. For example, a study by Wunderle, Hoeger, Wasserman, and Bazarian (2013) suggested that females who sustained a concussion during the luteal phase of their menstrual cycle reported worse concussion symptoms as measured by the Rivermead Post-concussion Questionnaire and lower QOL. My study was retrospective and menstrual cycle information was not available for my review. Factors such as family, school, team, peer, or coaching expectations may also play a role on concussion symptom

reporting and recovery. For example, Chrisman, Quitiquit, and Rivara (2013) performed a qualitative study examining concussion reporting attitudes in male and female high school athletes and found that athletes may under-report symptoms to avoid disappointing team-mates and coaches. An observational cohort study examining concussion symptom reporting in 328 male and female collegiate athletes found that 26.5% of the sample felt pressured to under-report their concussion symptoms by either coaches, teammates, fans, or parents in the prior athletic season; there were no differences by gender ( $p > .05$ ) (Kroshus et al., 2015). While it remains unknown whether the subjects in my study under-reported their symptoms, my analysis of the chart notes revealed the concussion specialist cleared the patient to RTP or normal activities based on a variety of factors including self-report of symptoms, physical exam, neurocognitive scores, academic performance, and parent and/ or coach interviews. Thus, I am fairly confident that the concussion resolution times were accurate in this study.

### **Effect of Race**

Race has not been well-studied in concussion outcomes. My study found that Minority females performed worse on verbal memory regardless of primary language and more education years. This result was partially consistent with a retrospective study performed by Ott, Schatz, Solomon, and Ryan (2014) in adolescents ages 13 to 18 years old who found that bilingual Hispanic adolescent athletes ( $N = 12, 653$ ) were outperformed by English-speaking adolescent athletes ( $N = 12, 644$ ) on ImPACT verbal memory, visual memory, visual motor processing speed, and reaction times ( $p < .001$ ). Previous studies found that adult Minorities performed worse on TBI neurocognitive measures (e.g., ANAM4 TBI\_MIL) than Whites (Gasquoine, 2009; Ivins et al., 2015).

Acculturation level may play a significant role in explaining some of these differences. Acculturation may affect verbal fluency and varies based on parents' educational levels, language spoken in the environment, and length of exposure to language in the dominant culture (French & Llorente, 2008; Llorente, 2008). My results with baseline and post-concussion data ( $N = 59$ ) indicated that Minorities performed worse on visual motor processing speed than Whites pre- and post-concussion. Thus, some researchers have called for the development of norms by race on neuropsychological tests. However, some argue that norming neuropsychological tests by race may lead to false negative rates and cite the difficulty of generating multiple norms for individuals of different races (Gasquoine, 2009). Kontos et al. (2010) did not detect baseline differences in their sample of Black and Whites male collegiate athletes, but did find similar post-concussion differences as to my findings on visual motor processing speed ( $N = 96, p = .014$ ) with Blacks performing worse than Whites. Their sample did not include adolescents, females, or Hispanics who may perform differently. My study highlights the importance of having baseline data in Minorities in order to more accurately interpret post-concussion scores. However, it should be noted that clinicians typically do not have baseline data in non-athletes and normative data may be useful by race in these instances.

With respect to shorter concussion resolution times, other studies demonstrated that Hispanics may fare better on certain health outcomes. A prior TBI study found that Hispanics reported more symptoms than Whites and Blacks, but had higher functional recovery scores ( $N = 1339, p > .05$ ) (Arango-Lasprilla et al., 2012). These findings are similar to other health conditions. For example, previous oncology studies on the influence of race/ ethnicity on symptoms found that Hispanics had higher functional

scores compared with Whites, Blacks, and Asians (Im et al., 2007). Even though Minorities in my sample had significantly shorter recovery times ( $p < .05$ ), survival analysis of the data did not reveal race as an independent predictor of concussion recovery times. A potential explanation for shorter recovery times in Minorities may be the influence of cultural attitudes and social support. For example, Blacks and Hispanic families have strong cultural beliefs about spirituality and family support to overcome illness (Tseng & Streltzer, 2007). However, there may be individual variation and these generalizations regarding culture may not apply to individuals. More research is needed to understand why Minorities in this sample had shorter recovery times than Whites.

### **Effect of Socio-Economic Status/ Health Insurance Type**

Minorities in this sample were more likely to be from lower income households and possess public (Medicaid, Chips) and student athletic insurance than Whites. My analysis indicated that SES factors such as insurance type may influence concussion recovery. My finding that insurance type was a predictor of shorter resolution times was not consistent with those of Morgan et al. (2015) who determined that insurance type did not predict PCS. Their study had a small sample size ( $N = 40$ ) composed of primarily Whites possessing private insurance with only 8 subjects having other unspecified forms of insurance. My study is the only known study to date that has examined private, public, student athletic, and no insurance in relation to concussion recovery times in a racially/ ethnically diverse sample. There have been a few TBI studies that have also examined insurance type and TBI recovery. Kane et al. (2014) found that adult TBI patients who carried public insurance (Medicare/ Medicaid) were more likely than those with private insurance to be discharged to post-hospital rehabilitation therapy ( $N = 6061$ , OR = 1.65,

95% CI = 1.33-2.05). Other studies have found that privately insured children may have disproportionately higher out-of-pocket expenses than publicly insured children (DeVoe et al., 2011; Kreider et al., 2016); this may be a hindrance to privately-insured patients from seeking acute and follow-up medical care after a concussion. It is difficult to determine why adolescents with public or student insurances had shorter concussion resolution times in this study. However, there may be other factors that may need to be considered such as whether insurance type influences health outcomes differently in adolescents with chronic vs. acute (e.g., concussion) health conditions. There may be cultural attitudes that influence adolescents with public or student insurance to comply with the treatment management recommendations by the healthcare provider thereby improving recovery. For example, athletes from lower SES may strongly identify with their athletic role because their athletic career may lead to future financial opportunities such as athletic scholarships and professional sport careers; hence, they may be more motivated to follow concussion management protocols. Studies in athletes recovering from sport-related anterior cruciate ligament (ACL) reconstructive surgery demonstrated that subjects with a high degree of self-motivation more strongly adhere to rehabilitation recommendations and this leads to improved surgical outcomes (Christino, Fantry, & Vopat, 2015). It is unknown whether athletes of particular races/ ethnicities or lower SES identify more strongly identify with the athletic role and are more motivated to recover from sports injuries such as concussions.

### **Effect of Attention Deficit/ Hyperactivity Disorder**

The results of this study were similar to Miller et al. (2015) who determined that ADHD predicted prolonged recovery lasting longer than a month ( $N = 126$ ,  $aOR = 3.87$ ,

95% CI = 1.13 – 13.24). However, they did not report race/ ethnicity of their sample and the age ranged from 6 to 18 years old; younger age may have been a potential confounder. My study confirmed ADHD as a predictor of longer recovery times in a racially/ ethnically diverse sample of adolescents. A consideration in adolescents with ADHD is the influence of neurostimulant medication on concussion outcomes. As stated in the results section, less than half of the ADHD patients in this study sample were on a prescribed neurostimulant medication for ADHD prior to their concussive injury. A recent German study in 2,128 children ages 3 to 17 years old demonstrated a 34% risk reduction of brain injuries in newly diagnosed ADHD patients who were taking prescribed ADHD medications (Mikolajczyk et al., 2015). Given that ADHD has been associated with prior history of concussions, these study results may suggest an indirect beneficial role of ADHD medications in adolescent athletes. Another recent case crossover and case-control study found that at baseline the unmedicated ADHD group ( $N = 22$ ) performed worse on reaction time ( $p < .001$ ) than when they were taking their ADHD medication and worse on motor processing speed ( $p < .001$ ) than the control group ( $N = 22$ ) (Littleton et al., 2015). It is unknown whether post-concussion outcomes are better in medicated vs. unmedicated ADHD patients. More research is needed on the influence of ADHD medication on concussion outcomes in a U.S.-based racially/ ethnically varied sample.

### **Effect of Prior Concussions**

My study findings were similar to Wojcik (2014) who determined that prior concussion history was a significant predictor of protracted concussion recovery ( $N = 85$ , OR = 18.22, 95% CI = 8.86 – 37.48.  $p < .001$ ). However, their study had a small sample

size, did not report race/ ethnicity, and had a wide age range of 7 to 61 years old and age may be a confounder with respect to concussion recovery times. My study confirmed prior concussion history as a predictor of longer recovery times in a racially/ ethnically diverse sample of adolescents. As described earlier, prior concussion history has been associated with worse baseline and post-concussion neurocognition and symptoms. Generally, adolescents experiencing protracted recovery require more academic accommodations and cannot return to play until he/she has recovered thereby affecting his/ her ability to function normally for an extensive amount of time. It remains unknown how many concussions are considered too many before causing permanent neurologic damage. Some researchers are concerned that repetitive concussions lead to cumulative neurologic damage over time. Recent studies have utilized novel brain imaging techniques (e.g., high resolution T1-weighted and diffusion tensor MRI) and neuropsychological tests in adults who have had multiple prior concussions, and have identified neuro-degenerative changes and neurocognitive declines (List, Ott, Bukowski, Lindenberg, & Floel, 2015; Strain et al., 2015). It is imperative to understand the neurologic effects of prior concussions in adolescents who may potentially experience long-term physical symptoms, behavioral, and cognitive disability and be less functional compared with their peers of the same age. Similar brain imaging studies are needed in racially/ ethnically diverse populations to compare the adolescents and adults who have experienced repetitive concussions. These studies will offer more clues to determine if there is a threshold as to the number of concussions an athlete can sustain before there is permanent brain degeneration. This information will help parents and their adolescent

children understand the short and potential long-term effects of prior concussions on brain recovery at such a young age.

### **Limitations**

There were a number of limitations in this study. First, the retrospective design of this study had the inherent risk of incomplete or missing data on variables of interest. For example, I used estimated medians of income based on zip codes and health insurance type as indicators of SES. There was only one Black female in this sample, which forced me to aggregate Black and Hispanic data so that I could examine the interaction between gender and race. Thus, I could not determine how Blacks and Hispanics differed on concussion outcomes. In addition, I had baseline data for half of the subjects and the analyses indicated that baseline data may be critical to interpreting neurocognitive differences by ethnicity/ race. Information bias may have been another issue due to missing race data in this study. Furthermore, self-reported symptoms are subjective and may be influenced by the subject wanting to RTP. Next, a confounding factor on which I did not have data was the level of compliance to clinician treatment recommendations. It is unknown whether the Minority group strongly adhered to these recommendations compared with Whites, and whether this explained their shorter resolution times. Another consideration is the referral pattern of concussion patients to this clinic is unknown and I do not know to what extent this clinic sample represented the target population. Finally, I may have had insufficient power to detect differences by race and gender on ImPACT scores as indicated by small effect sizes and wide confidence intervals. I was conservative in my initial sample size estimates in assuming more covariates than used.



My assumption of a medium effect size was overly optimistic. My results suggest that a smaller effect size should be used for power estimates in future studies.

### **Future Directions and Research**

This study provided significant insights into the relationship of demographic and clinical factors and concussion recovery. However, a prospective study that is aimed at recruiting more Black females and other non-aggregated ethnic/ racial groups is needed to discern the effects of ethnicity/ race on concussion outcomes. There have been no prior studies that I know of that have examined the effect of insurance type on concussion recovery in adolescents. Further research is needed to examine the psycho-social aspects of concussion recovery including SES, sports culture, racial/ ethnic culture, individual coping mechanisms, academic assistance, and social support. I would like to explore the role of SES by evaluating concussion outcome differences between Minorities and Whites stratified by income quartiles. Future survival analysis should evaluate whether school type (e.g., private vs. public school) is a predictor of protracted recovery. Research utilizing newer brain imaging techniques may prove to be useful in determining the number of concussions and athlete can sustain prior to experiencing permanent neurologic damage. More research is needed on the influence of ADHD and the role of ADHD medication on concussion risk and recovery. In addition, the effect of prescribed neurostimulant medications pre- and post-concussion should be examined with respect to recovery time. The definition of protracted concussion recovery may differ based on the presence of clinical factors such as prior concussion history or ADHD. A larger sample estimated with a small effect size for power analysis and a population-based sample should be obtained for the next study. Furthermore, the role of motivation and athletic

identity has not been studied in concussion recovery in adolescent athletes but may provide some valuable insights into the concussion recovery process. I believe that my study highlighted which subgroups of adolescents are at highest risk for protracted recovery; thereby, providing direction for future concussion research aimed at developing a concussion predictive model.

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Table 1

*Demographics by Race and Gender (N=118)*

Gender	Whites <sup>a</sup>	Hispanics	Blacks <sup>a</sup>	Total Sample
Males, <i>n</i> (%)	50 (69.4%)	17 (60.7%)	17 (94.4%)	84 (71.2%)
Females, <i>n</i> (%)	22 (30.6%)	11 (39.3%)	1 (5.6%)	34 (28.8%)
Total, <i>n</i> (%)	72 (100%)	28 (100%)	18 (100%)	118 (100%)

*Note.* <sup>a</sup>Non-Hispanic ethnicity.

Table 2

*Demographics by Aggregated Race and Gender (N=118)*

Gender	Whites	Minorities <sup>a</sup>	Total Sample
Males, <i>n</i> (%)	50 (69.4%)	34 (73.9%)	84 (71.2%)
Females, <i>n</i> (%)	22 (30.6%)	12 (26.1%)	34 (28.8%)
Total, <i>n</i> (%)	72 (100%)	46 (100%)	118 (100%)

*Note:* <sup>a</sup>Minorities included Hispanics and Non-Hispanic Blacks.

Table 3

*Demographics of Sample that was Randomized Out of the Sample by Race and Gender (N=110)*

Gender	Whites <sup>a</sup>	Hispanics	Blacks <sup>a</sup>	Total Sample
Males, <i>n</i> (%)	38 (72%)	32 (86%)	18 (90%)	88 (80%)
Females, <i>n</i> (%)	15 (28%)	5 (14%)	2 (10%)	22 (20%)
Total, <i>n</i> (%)	53 (100%)	37 (100%)	20 (100%)	110 (100%)

*Note.* <sup>a</sup>Non-Hispanic ethnicity.

Table 4

*Demographic Characteristics of Subjects (N= 118)*

Characteristic	Total Sample (n=118)	Males (n=84)	Females (n=34)	Gender difference ( <i>p</i> value)	Whites (n=72)	Minorities (n=46)	Race difference ( <i>p</i> value)
Age <sup>a</sup> , <i>M</i> ( <i>SD</i> )	15.75 (±1.47)	15.80 (±1.43)	15.62 (±1.58)	.55	15.49 (±1.49)	16.15 (±1.35)	.016*
<i>Range</i> ( <i>years old</i> )	13-19						
<i>Mdn</i> ( <i>years</i> )	16.00	16.00	15.00		15.50	16.00	
Education years <sup>a</sup> , <i>M</i> ( <i>SD</i> )	9.26 (±1.39)	9.30 (±1.33)	9.18 (±1.55)	.67	9.03 (±1.46)	9.63 (±1.12)	.021*
<i>Range</i> ( <i>years</i> )	6-13						
<i>Mdn</i> ( <i>years</i> )	9						
Middle or High School Type <sup>b,c</sup> , <i>n</i> (%)				.06			<.001***
Public	79 (72.5%)	49 (62%)	25 (83.3%)		33 (52%)	31 (88.5%)	
Private	30 (27.5%)	30 (38%)	5 (16.7%)		31 (48%)	4 (11.5%)	
Primary language <sup>d</sup> , <i>n</i> (%)				.52			<.001***
English	101 (85.60%)	73 (86.9%)	28 (82.4%)		72 (100%)	29 (63%)	
Bilingual (Spanish)	17 (14.4%)	11 (13.1%)	6 (17.6%)		-	17 (37%)	
Health insurance <sup>d</sup> , <i>n</i> (%)				.41			<.001***
None	5 (4.2%)	3 (3.6%)	2 (5.9%)		3 (4.2%)	2 (4.3%)	

Characteristic	Total Sample	Males	Females	Gender Difference	Whites	Minorities	Race Difference
Public	22 (18.6%)	13 (15.5%)	9 (26.5%)		1 (1.4%)	21 (45.7%)	
Student	15 (12.7%)	12 (14.3%)	3 (8.8%)		1 (1.4%)	14 (30.4%)	
Private	76 (64.4%)	56 (66.7%)	20 (58.8%)		67 (93.1%)	9 (19.6%)	
Median Income <sup>b,e</sup> , <i>n</i> (%)				.33			<.001***
1 <sup>st</sup> Quartile (≤\$38,561.00)	33 (28%)	24 (28.6%)	9 (26.5%)		6 (8.3%)	27 (58.7%)	
2 <sup>nd</sup> Quartile (\$38,561.01 - \$56,700.50)	26 (22%)	16 (19%)	10 (29.4%)		13 (18.1%)	13 (28.3%)	
3 <sup>rd</sup> Quartile (\$56,700.51 - \$90,567.00)	34 (28.8%)	23 (27.4%)	11 (32.4%)		29 (40.3%)	5 (10.9%)	
4 <sup>th</sup> Quartile (≥\$90,567.01)	25 (21.2%)	21 (25%)	4 (11.8%)		24 (33.3%)	1 (2.2%)	
Headache history <sup>d</sup> , <i>n</i> (%)				.19			.03*
None	89 (75.4%)	66 (78.6%)	23 (67.6%)		52 (72.2%)	37 (80.4%)	
Non-migraine headache	20 (16.9%)	14 (16.7%)	6 (17.6%)		11 (15.3%)	9 (19.6%)	
Migraine, personal and family	9 (7.6%)	4 (4.8%)	5 (14.7%)		9 (12.5%)	-	



Learning disability/ ADHD <sup>b,f</sup> , <i>n</i> (%)	25 (21.2%)	21 (25%)	4 (11.8%)	.11	17 (23.6%)	8 (17.4%)	.42
Prior Concussions <sup>b</sup> , <i>n</i> (%)				.35			.28
None	83 (73.3%)	57 (67.9%)	26 (76.5%)		48 (66.7%)	35 (76.1%)	
≥ 1	35 (29.7%)	27 (32.1%)	8 (23.5%)		24 (33.3%)	11 (23.9%)	
Mechanism of Injury <sup>b,g</sup> , <i>n</i> (%)				.63			.014*
<u>Non-Sports</u>							
MVA	13 (11%)	10 (11.9%)	3 (8.8%)		12 (16.7%)	1 (2.2%)	
Fall	6 (5.1%)	6 (7.1%)	-		6 (8.3%)	-	
Non-sport collision	5 (4.2%)	3 (3.6%)	2 (5.9%)		4 (5.6%)	1 (2.2%)	
	2 (1.7%)	1 (1.2%)	1 (2.9%)		2 (2.8%)	-	
<u>Sports</u>							
Football	105 (89%)	74 (88.1%)	31 (91.2%)		60 (83.3%)	45 (97.8%)	
Soccer	56 (47.5%)	56 (66.7%)	-		25 (34.7%)	31 (67.4%)	
Basketball	20 (16.9%)	5 (6%)	15 (44.1%)		13 (18.1%)	7 (15.2%)	
Wrestling	9 (7.6%)	2 (2.4%)	7 (20.6%)		7 (9.7%)	2 (4.3%)	
Volleyball	5 (4.2%)	5 (6%)	-		5 (6.9%)	-	
Softball	5 (4.2%)	-	5 (14.7%)		3 (4.2%)	2 (4.3%)	
Lacrosse	3 (2.5%)	1 (1.2%)	2 (5.9%)		2 (2.8%)	1 (2.2%)	
Ice Skating	2 (1.7%)	2 (2.4%)	-		2 (2.8%)	-	
Cheerleading	1 (0.8%)	-	1 (2.9%)		1 (1.4%)	-	
Rugby	1 (0.8%)	-	1 (2.9%)		-	1 (2.2%)	
	3 (2.5%)	3 (3.6%)	-		2 (2.8%)	1 (2.2%)	

Days from Injury to Clinic Evaluation <sup>b</sup> , <i>n</i> (%)			.87		.76
0 to 5 days	84 (71%)	63 (75%)	26 (76.5%)	55 (76.4%)	34 (74%)
5 to 10 days	34 (29%)	21 (25%)	8 (23.5%)	17 (23.6%)	12 (26%)

*Note.* *M* (*SD*) = Mean (Standard deviation). *Mdn* = Median. ADHD = Attention Deficit Hyperactivity Disorder. MVA = Motor Vehicle Accident. Differences between groups were analyzed with <sup>a</sup>independent samples *t*-test for continuous dependent variables and <sup>b</sup> $\chi^2$  for categorical dependent variables or <sup>d</sup>Fisher's exact test (cell count <5). <sup>c</sup>Post-high school/ college (*n* = 3) or missing school type (*n* = 6) <sup>e</sup>Median income was estimated by zip code (US Census Bureau, 2006-2010). <sup>f</sup>46.2% of subjects diagnosed with ADHD were prescribed and taking ADHD medications prior to concussion (*n* = 6/13). <sup>g</sup>Differences based on mechanism of injury was calculated between overall sports and non-sports injuries.



Table 5

*Multivariate and Univariate Effects of Gender and Race on Post-Concussion ImPACT test scores (N=118)*

Source	Multivariate			ImPACT tests	Univariate		
	<i>F</i> (5, 110)	<i>p</i>	Partial $\eta^2$		<i>F</i> (1,114)	<i>p</i>	Partial $\eta^2$
Gender	1.77	.13	.07	Verbal memory	.157	.69	.001
				Visual memory	.386	.54	.003
				Visual motor	1.95	.17	.017
				Reaction time <sup>a</sup>	4.22	.04*	.036
				Symptoms <sup>b</sup>	3.60	.06	.031
Race	2.04	.08	.09	Verbal memory	1.12	.29	.010
				Visual memory	1.38	.24	.012
				Visual motor	2.29	.13	.020
				Reaction time <sup>a</sup>	.001	.98	.000
				Symptoms <sup>b</sup>	.576	.45	.005
Gender x Race	2.01	.08	.08	Verbal memory	4.92	.03*	.041
				Visual memory	.097	.76	.001
				Visual motor	.429	.51	.004
				Reaction time <sup>a</sup>	.760	.39	.007
				Symptoms <sup>b</sup>	1.03	.31	.009

*Note.* <sup>a</sup>Variable was transformed before conducting *t*-tests by using natural log to reduce skewness.

<sup>b</sup>Variable was transformed before conducting *t*-tests by using square root to reduce skewness.

Table 6

*Post-Concussion Outcome Variables Distributed by Gender and Race (N=118)*

Variable	Total Sample (n=118)	Males (n=84)	Females (n=34)	Gender difference (p value)	Whites (n=72)	Minorities (n=46)	Race difference (p value)
Resolution (days), <i>M (SD)</i>	27.55 (33.66)	27.96 (38.11)	26.53 (18.99)	.15 <sup>a</sup>	31.61 (38.62)	21.2 (22.89)	.046* <sup>a</sup>
<i>Range (days)</i>	1-201	1-201	4-71		2-201	1-109	
<i>Mdn</i>	17	16	21		18.33	13	
ImPACT Scores							
Verbal memory, <i>M (SD)</i>	77.32 (14.41)	76.73 (13.43)	78.79 (16.70)	.48	77.64 (13.87)	76.83 (15.35)	.77
<i>Range</i>	31-100	43-97	31-100		43-100	31-98	
<i>Mdn</i>	79	78.5	82.5		79.5	79	
Visual memory, <i>M (SD)</i>	66.92 (14.95)	67.61 (14.95)	65.21 (15.05)	.43	65.6 (15.05)	68.98 (14.72)	.23
<i>Range</i>	27-98	34-98	27-91		27-91	31-98	
<i>Mdn</i>	69	69.5	65.5		66	71.5	
Visual Motor, <i>M (SD)</i>	31.9 (9.18)	32.64 (9.04)	30.4 (9.47)	.23	32.88 (8.80)	30.62 (9.69)	.19
<i>Range</i>	9-51.13	13.8-51.1	9-46.65		9-51.13	13.58-49.2	
<i>Mdn</i>	33.3	33.77	32.03		33.97	31.55	
Reaction time, <i>M (SD)</i>	0.70 (0.19)	0.68 (0.18)	0.75 (0.19)	.06 <sup>a</sup>	0.70 (0.14)	0.70 (0.24)	.62 <sup>a</sup>
<i>Range</i>	0.21-1.66	0.21-1.66	0.51-1.55		0.5-1.21	0.21-1.66	
<i>Mdn</i>	0.67	0.65	0.71		0.66	0.67	

Variable	Total Sample (n=118)	Males (n=84)	Females (n=34)	Gender difference ( <i>p</i> value)	Whites (n=72)	Minorities (n=46)	Race difference ( <i>p</i> value)
Symptom score, <i>M (SD)</i>	20.2 (19.55)	18.28 (17.95)	24.94 (22.6)	.08 <sup>b</sup>	21.78 (19.45)	17.72 (19.65)	.16 <sup>b</sup>
<i>Range</i>	0-87	0-75	0-87		0-83	0-87	
<i>Mdn</i>	15	13	17.5		15	11.5	

*Note.* *M (SD)* = Mean (Standard deviation). *Mdn* = Median. Presented means, standard deviations, medians, and ranges are of untransformed raw scores. Differences between groups were analyzed with independent samples *t*-test.

<sup>a</sup>Variable was transformed before conducting *t*-tests by using natural log to reduce skewness.

<sup>b</sup>Variable was transformed before conducting *t*-tests by using square root to reduce skewness.

Table 7

*Post-Concussion Outcome variables by Race x Gender Categories (n=118)*

Variable	White Males (n=50)	Minority Males (n=34)	White Females (n=22)	Minority Females (n=12)
Resolution (days),	33.18	20.29	28.05	23.75
<i>M (SD)</i>	(44.82)	(23.85)	(18.31)	(20.71)
<i>Range</i>	2-201	1-109	4-71	6-65
<i>Mdn</i>	16.5	14	22.5	11
ImPACT Scores,				
Verbal memory,	75.52	78.50	82.45	72.08
<i>M (SD)</i>	(13.87)	(12.76)	(12.92)	(21.03)
<i>Range</i>	43-96	49-97	56-100	31-98
<i>Mdn</i>	77.5	79.5	85.5	76
Visual memory,	66.50	69.24	63.55	68.25
<i>M (SD)</i>	(15.42)	(14.23)	(14.32)	(16.5)
<i>Range</i>	35-95	34-98	27-86	31-95
<i>Mdn</i>	66	71.5	64.5	70.5
Visual Motor,	33.32	31.66	31.88	27.69
<i>M (SD)</i>	(8.73)	(9.52)	(9.08)	(9.97)
<i>Range</i>	16.52-51.13	13.83-49.2	9-46.65	13.58-40.9
<i>Mdn</i>	33.99	33.12	33.47	28.28
Reaction time,	0.69	0.68	0.73	0.78
<i>M (SD)</i>	(0.15)	(0.22)	(0.12)	(0.28)
<i>Range</i>	0.5-1.51	0.21-1.66	0.57-0.98	0.51-1.55
<i>Mdn</i>	0.65	0.67	0.71	0.71

Symptom score, <i>M (SD)</i>	20.94 (19.34)	14.36 (15.11)	23.68 (20.02)	27.25 (27.60)
<i>Range</i>	0-75	0-59	1-83	0-87
<i>Mdn</i>	15	8	17	17.5

*Note.* *M (SD)* = Mean (Standard deviation), *Mdn* = Median.

Table 8

*ImPACT Post-Concussion Neurocognitive Test Percentiles by Gender and Race (N=118)*

ImPACT Normative Percentile	Impaired $\leq 2^{nd}$ percentile	Borderline $3^{rd}$ - $9^{th}$ percentile	Low-Average $10^{th}$ - $25^{th}$ percentile	Average $26^{th}$ - $75^{th}$ percentile	Above Average $76^{th}$ - $98^{th}$ percentile	Superior $\geq 99^{th}$ percentile
Verbal memory, <i>n</i> (%)						
Males ( <i>n</i> =84)	13 (15.5%)	11 (13%)	15 (18%)	29 (34.5%)	15 (18%)	1 (1%)
Females ( <i>n</i> =34)	7 (20.5%)	1 (3%)	7 (20.5%)	13 (38%)	6 (18%)	-
Whites ( <i>n</i> =72)	12 (16.5%)	7 (10%)	12 (16.5%)	28 (39%)	13 (18%)	-
Minorities ( <i>n</i> =46)	8 (17%)	5 (11%)	10 (22%)	14 (30%)	9 (20%)	-
Visual memory, <i>n</i> (%)						
Males ( <i>n</i> =84)	10 (12%)	9 (11%)	17 (20%)	34 (40%)	13 (16%)	1 (1%)
Females ( <i>n</i> =34)	3 (9%)	3 (9%)	10 (29%)	14 (41%)	4 (12%)	-

Whites ( <i>n</i> =72)	8 (11%)	10 (14%)	19 (26%)	24 (33%)	11 (15%)	-
Minorities ( <i>n</i> =46)	5 (11%)	2 (4%)	8 (17%)	24 (52%)	6 (13%)	1 (2%)
Visual Motor, <i>n</i> (%)						
Males ( <i>n</i> =84)	22 (26%)	7 (8%)	16 (19%)	29 (35%)	10 (12%)	-
Females ( <i>n</i> =34)	14 (41%)	1 (3%)	6 (18%)	12 (35%)	1 (3%)	-
Whites ( <i>n</i> =72)	20 (28%)	4 (5.5%)	13 (18%)	27 (37.5%)	8 (11%)	-
Minorities ( <i>n</i> =46)	16 (35%)	4 (9%)	9 (19.5%)	14 (30%)	3 (6.5%)	-
Reaction time, <i>n</i> (%)						
Males ( <i>n</i> =84)	12 (14%)	12 (14%)	21 (25%)	32 (38%)	6 (7%)	1 (1%)
Females ( <i>n</i> =34)	10 (29%)	10 (29%)	6 (18%)	7 (21%)	1 (3%)	-
Whites ( <i>n</i> =72)	16 (22%)	11 (15%)	16 (22%)	26 (36%)	3 (4%)	-
Minorities ( <i>n</i> =46)	6 (13%)	11 (24%)	11 (24%)	13 (28%)	4 (9%)	1 (2%)

*Note.* Normative percentiles for cognition tests were generated by the ImPACT system.

Table 9

*Multivariate and Univariate Effects of Gender, Race, and Language on Post-Concussion ImpACT test scores (N=118)*

Source	Multivariate			ImPACT tests	Univariate		
	<i>F</i> (5, 109)	<i>p</i>	Partial $\eta^2$		<i>F</i> (1,113)	<i>p</i>	Partial $\eta^2$
Gender	1.82	.12	.08	Verbal memory	.034	.85	.000
				Visual memory	.599	.44	.005
				Visual motor	2.28	.13	.020
				Reaction time <sup>a</sup>	4.22	.04*	.036
				Symptoms <sup>b</sup>	3.01	.09	.026
Race	1.48	.30	.05	Verbal memory	.418	.52	.004
				Visual memory	.143	.71	.001
				Visual motor	3.24	.08	.028
				Reaction time <sup>a</sup>	.017	.90	.000
				Symptoms <sup>b</sup>	1.55	.22	.014
Gender x Race	1.69	.20	.06	Verbal memory	4.40	.04*	.037
				Visual memory	.023	.88	.000
				Visual motor	.600	.44	.005
				Reaction time <sup>a</sup>	.727	.37	.007
				Symptoms <sup>b</sup>	.743	.39	.007
Language	1.96	.09	.08	Verbal memory	.609	.44	.005
				Visual memory	1.48	.23	.013
				Visual motor	.948	.33	.008



	Reaction time <sup>a</sup>	.042	.84	.000
	Symptoms <sup>b</sup>	1.33	.25	.012

*Note.* LD/ADHD = Learning Disability/ Attention Deficit Hyperactivity Disorder.

<sup>a</sup>Variable was transformed before conducting *t*-tests by using natural log to reduce skewness.

<sup>b</sup>Variable was transformed before conducting *t*-tests by using square root to reduce skewness.

Table 10

*Multivariate and Univariate Effects for Gender, Race and Time on Baseline and Post-Concussion ImPACT test scores (N = 59)*

Source	Multivariate			ImPACT tests	Univariate		
	<i>F</i> (5,52)	<i>p</i>	Partial $\eta^2$		<i>F</i> (1,56)	<i>p</i>	Partial $\eta^2$
	Between Groups			Between Groups			
Gender	.861	.51	.076	Verbal memory	1.57	.22	.026
				Visual memory	.249	.62	.004
				Visual motor	.057	.81	.001
				Reaction time <sup>a</sup>	.822	.37	.016
				Symptoms <sup>b</sup>	.012	.92	.000
Race	3.20	.014*	.235	Verbal memory	.032	.86	.000
				Visual memory	.020	.89	.000
				Visual motor	11.51	<.001***	.171
				Reaction time <sup>a</sup>	.006	.94	.000
				Symptoms <sup>b</sup>	.600	.44	.011
	Within Groups			Within Groups			
Time	3.46	.009**	.249	Verbal memory	3.28	.08	.055
				Visual memory	5.61	.02*	.091
				Visual motor	2.94	.09	.050
				Reaction time <sup>a</sup>	3.16	.08	.053
				Symptoms <sup>b</sup>	17.60	<.001***	.239

Source	<i>F</i> (5,52)	<i>p</i>	Partial $\eta^2$	ImPACT tests	<i>F</i> (1,56)	<i>p</i>	Partial $\eta^2$
Time x Gender	1.51	.77	.047	Verbal memory	.576	.45	.010
				Visual memory	.398	.53	.007
				Visual motor	.280	.60	.005
				Reaction time <sup>a</sup>	.000	.99	.000
				Symptoms <sup>b</sup>	.115	.74	.002
Time x Race	.625	.68	.057	Verbal memory	.006	.94	.000
				Visual memory	.328	.57	.006
				Visual motor	.179	.67	.003
				Reaction time <sup>a</sup>	.884	.35	.016
				Symptoms <sup>b</sup>	2.49	.12	.043

*Note.* <sup>a</sup>Variable was transformed using natural log reduce skewness.

<sup>b</sup>Variable was transformed using square root to reduce skewness.

Table 11

*Mean and Standard Deviations for Outcome Variables at Baseline and Post-Concussion (N=59)*

	Baseline			Post-Concussion		Exceeds RCI
	M	SD		M	SD	80% CI <i>n</i> (%)
			Verbal Memory			
Total ( <i>n</i> =59)	84.24	8.20		78.29	12.46	28 (47.5%)
Males ( <i>n</i> = 49)	84.00	8.10		77.39	12.60	25 (51%)
Females ( <i>n</i> = 10)	85.40	9.00		82.70	11.30	3 (30%)
Whites ( <i>n</i> = 33)	84.12	7.90		77.97	12.89	15 (45.5%)
Minorities ( <i>n</i> =26)	84.38	8.70		78.69	12.14	13 (50%)
			Visual Memory			
Total ( <i>n</i> =59)	73.47	11.03		68.00	15.57	15 (25.4%)
Males ( <i>n</i> = 49)	73.53	10.73		68.61	15.98	11 (22.4%)
Females ( <i>n</i> = 10)	73.20	13.02		65.00	13.70	4 (40%)
Whites ( <i>n</i> = 33)	74.18	10.94		67.73	15.97	9 (27.3%)
Minorities ( <i>n</i> =26)	72.58	11.30		68.35	15.36	6 (23.1%)
			Visual Motor			
Total ( <i>n</i> =59)	34.54	7.19		32.52	9.32	15 (25.4%)
Males ( <i>n</i> = 49)	34.58	7.32		32.81	9.54	12 (24.5%)
Females ( <i>n</i> = 10)	34.24	6.78		31.10	8.43	3 (30%)
Whites ( <i>n</i> = 33)	37.37	5.90		34.98	8.56	9 (27.3%)

Minorities ( <i>n</i> =26)	30.94	7.13	29.40	9.47	6 (23.1%)
Reaction Time					
Total ( <i>n</i> =59)	.620	.086	.691	.195	25 (42.4%)
Males ( <i>n</i> = 49)	.614	.084	.689	.210	20 (40.8%)
Females ( <i>n</i> = 10)	.648	.096	.702	.096	5 (50%)
Whites ( <i>n</i> = 33)	.609	.062	.692	.154	15 (45.5%)
Minorities ( <i>n</i> =26)	.634	.110	.690	.239	10 (38.5%)
Symptoms Score					
Total ( <i>n</i> =59)	3.86	4.61	16.34	16.35	29 (49.2%)
Males ( <i>n</i> = 49)	3.90	4.79	16.78	17.02	24 (49%)
Females ( <i>n</i> = 10)	3.70	3.83	14.20	13.12	5 (50%)
Whites ( <i>n</i> = 33)	3.27	3.72	18.73	17.07	20 (60.6%)
Minorities ( <i>n</i> =26)	4.62	5.53	13.32	15.18	9 (34.6%)

*Note.* *M* (*SD*) = Mean (Standard deviation). CI = Confidence Interval. Days from date of concussion to first post-concussion ImPACT test (*N* = 58, *M* (*SD*) = 3.58 (2.6, *Mdn* = 3.00).

Table 12

*Change in Means from Baseline to Post-concussion on ImPACT scores (N=59)*

ImPACT tests	$\Delta$ means	<i>SD</i> of differences	95% CI	<i>t</i> (58)	<i>p</i>
Verbal Memory	5.95	14.57	[2.15, 9.75]	3.14	.003**
Visual Memory	5.48	15.56	[1.42, 9.53]	2.70	.009**
Visual Motor	2.02	8.15	[-1.09, 4.14]	1.90	.063
Reaction Time <sup>a</sup>	-1.18	.208	[-1.23, -1.12]	-43.39	<.001***
Symptoms <sup>b</sup>	-1.95	2.48	[-2.60, -1.31]	-6.05	<.001***

*Note.*  $\Delta$  means = Difference in means. *SD* = Standard deviation.

<sup>a</sup>Variable was transformed using natural log reduce skewness.

<sup>b</sup>Variable was transformed using square root to reduce skewness.

Table 13

*Percentage that Exceeded Reliable Change Index (RCI) at 80% CI Baseline to Post-concussion on ImPACT scores (N=59)*

<i>n (%)</i>	At least 1 RCI	At least 2 or more RCI	At least 3 or more RCI	At least 4 or more RCI
Total ( <i>n</i> =59)	44 (74.6%)	30 (50.8%)	19 (32.2%)	12 (20.3%)
Males ( <i>n</i> = 49)	36 (73.5%)	23 (46.9%)	16 (32.7%)	11 (22.4%)
Females ( <i>n</i> = 10)	8 (80%)	7 (70%)	3 (30%)	1 (10%)
Whites ( <i>n</i> = 33)	24 (76.9%)	17 (51.5%)	13 (39.4%)	9 (27.3%)
Minorities ( <i>n</i> =26)	20 (76.9%)	13 (50%)	6 (23.1%)	3 (11.5%)

*Note.* RCI = Reliable Change Index. The 5 RCIs were calculated on all of the ImPACT tests (verbal memory, visual memory, motor processing speed, reaction time, and symptoms score).

Table 14

*Logistic Regression Predicting Concussion Resolution Times >17 days (Sample Median) (N = 118)*

Predictor	<i>B</i>	<i>SE</i>	Wald statistic	<i>p</i>	<i>OR</i>	95% CI
Age	-	-	4.45	.11	-	-
13-14	-	-	-	-	-	-
15-16	.05	.85	.003	.95	1.05	[-.20, 5.60]
17-19	.95	.55	2.97	.08	2.59	[.88, 7.58]
Prior Concussions	.54	.50	1.15	.28	1.71	[.64, 4.56]
Mechanism of Injury	.44	.69	.40	.53	1.55	[.40, 6.02]
Headache	-	-	.91	.64	-	-
None	-	-	-	-	-	-
Migraine	-.66	.84	.61	.44	.52	[.10, 2.69]
Non-migraine	-.39	.59	.43	.51	.68	[.21, 2.18]
Learning/ Attention	-	-	6.48	.09	-	-
None	-	-	-	-	-	-
LD	.63	.66	.91	.34	1.87	[.52, 6.79]



ADHD	2.61	1.13	5.32	.02*	13.63	[1.48, 125.42]
Both	.98	1.05	.89	.35	2.67	[.35, 20.72]
Health insurance	-	-	5.07	.09	-	-
None	-	-	-	-	-	-
Private	-1.76	1.21	2.12	.15	.17	[.02, 1.85]
Public	-2.80	1.36	4.23	.04*	.06	[.004, .88]
Student	-3.02	1.42	4.51	.03*	.05	[.003, .79]
Education	.314	.66	.22	.64	1.37	[.37, 5.03]
Gender	-.74	.47	2.52	.11	.48	[.84, 5.27]
Race	-.86	.73	1.39	.11	.42	[.57, 9.96]

*Note.* CI = confidence interval for odds ratio (OR). Prior to adding gender and race, model:  $\chi^2 = 16.20$ ,  $df = 13$ ,  $N = 118$ ,  $p = .239$ . After adding gender and race, step:  $\chi^2 = 3.44$ ,  $df = 2$ ,  $N = 118$ ,  $p = .179$ , model:  $\chi^2 = 19.64$ ,  $df = 15$ ,  $N = 118$ ,  $p = .186$ .

Table 15

*Days to Resolution of Concussion: Cox Proportional Hazard Regression Results*

Predictor	<i>B</i>	<i>SE</i>	Wald statistic	<i>p</i>	<i>Exp (B)</i>	95% CI
Age	-	-	3.50	.17	-	-
13-14	-	-	-	-	-	-
15-16	-.45	.26	2.98	.08	.64	[.38, 1.06]
17-19	-.22	.43	.27	.61	.80	[.35, 1.85]
Prior Concussions	-.57	.27	4.47	.03*	.56	[.33, .96]
Mechanism of Injury	-.02	.34	.003	.96	.98	[.51, 1.90]
Headaches	-	-	.37	.83	-	-
None	-	-	-	-	-	-
Migraine	.19	.39	.25	.62	.19	[.56, 2.61]

Non-migraine	.12	.29	.19	.67	.12	[.65, 1.97]
Learning/ Attention	-	-	12.99	.005**	-	-
None	-	-	-	-	-	-
LD	-.29	.36	.64	.42	.75	[.37, 1.51]
ADHD	-1.51	.43	12.28	<.001***	.22	[.095, .51]
Both	-.67	.53	1.59	.21	.51	[.18, 1.45]
Health insurance	-	-	6.08	.11	-	-
None	-	-	-	-	-	-
Private	.71	.50	2.03	.16	2.04	[.77, 5.43]
Public	1.20	.57	4.49	.03*	3.33	[1.09, 10.15]
Student	1.38	.59	5.47	.02*	3.98	[1.25, 12.65]
Education	-.09	.32	.08	.78	.91	[.49, 1.71]
Gender	.46	.25	3.37	.07	1.59	[.97, 2.59]
Race	.23	.34	.45	.50	1.26	[.64, 2.46]

*Note.* Overall significance of the model:  $p = .018$ . Proportional hazards assumption was met. LD = Learning disability. ADHD = Attention Deficit Hyperactivity Disorder. CI = confidence interval for hazard ratio ( $Exp(B)$ ).

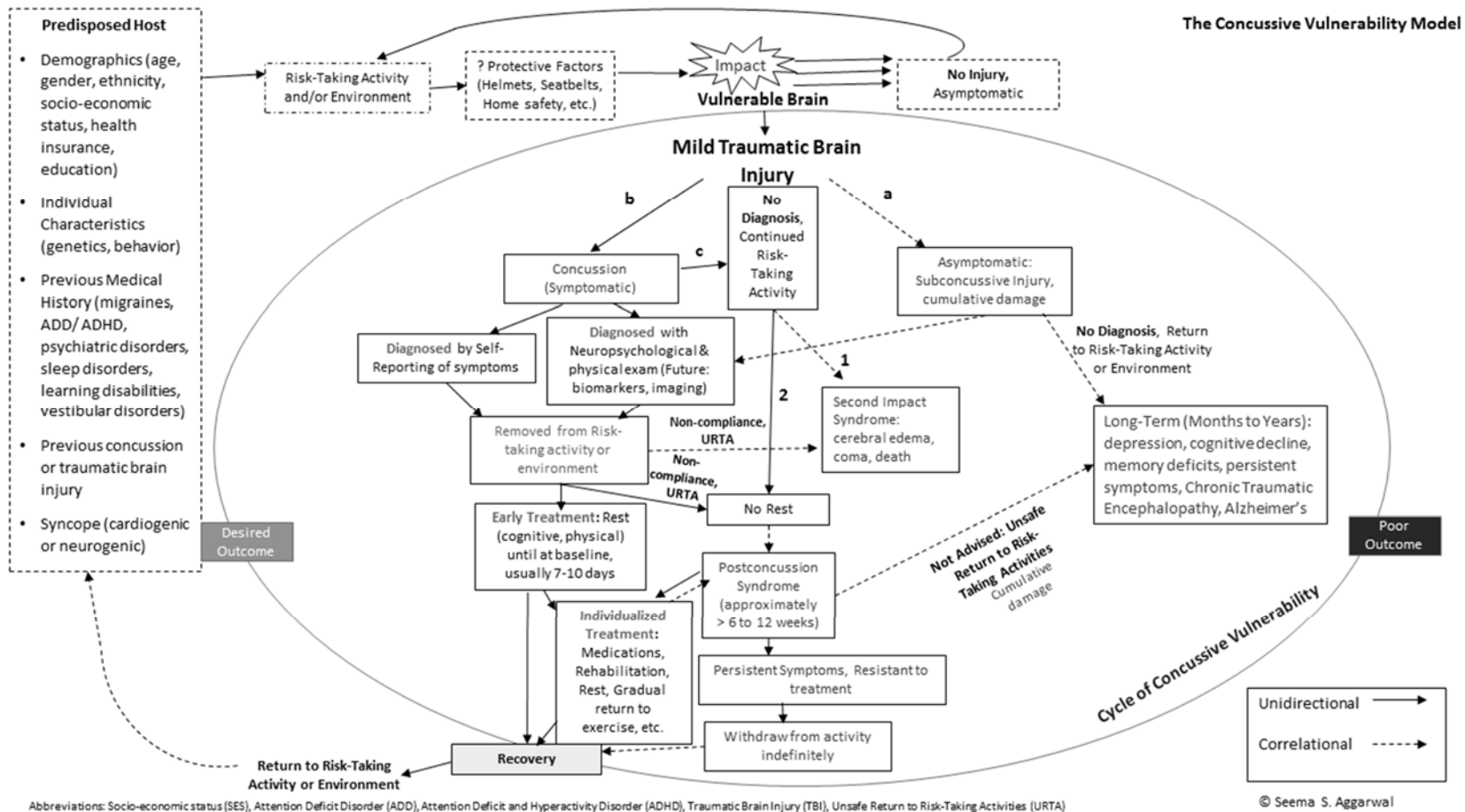


Figure 1. The Concussion Vulnerability Model

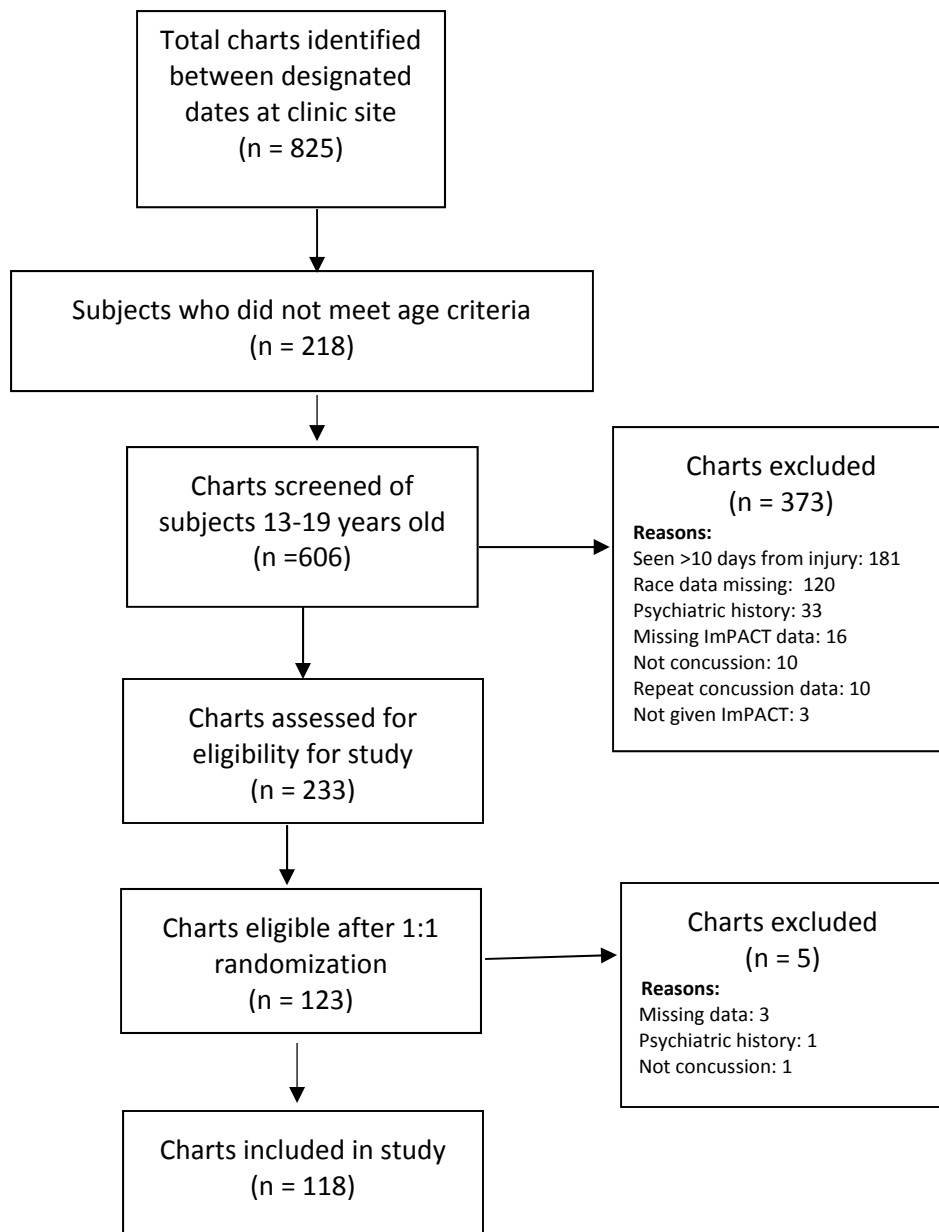
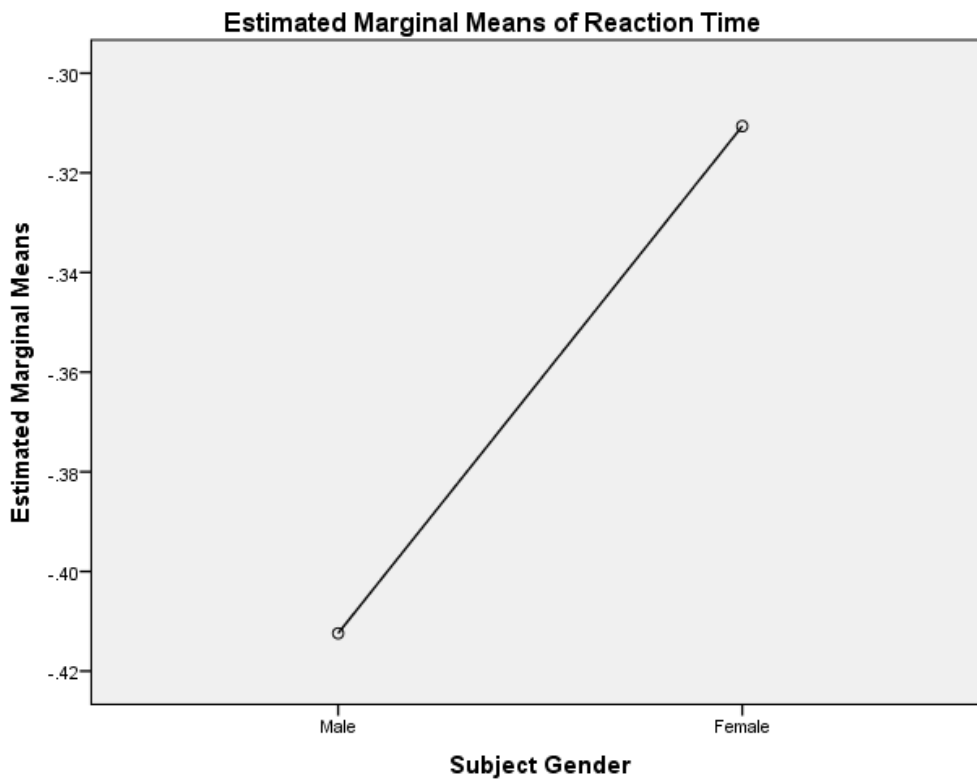
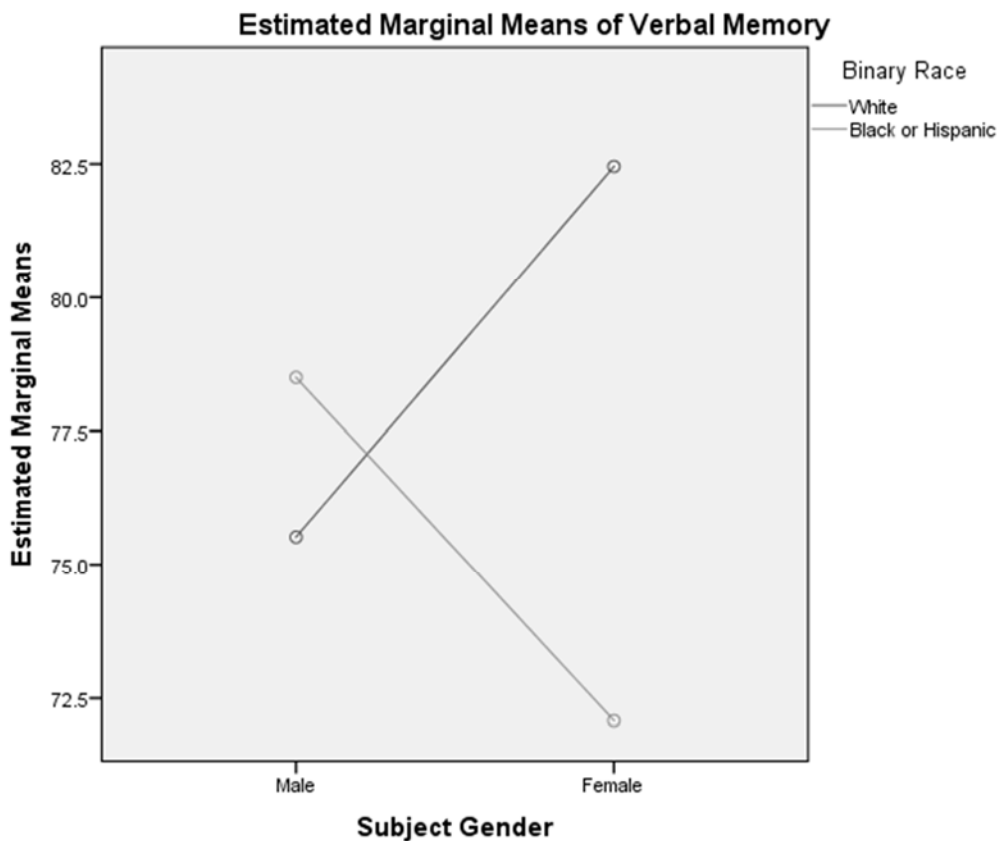


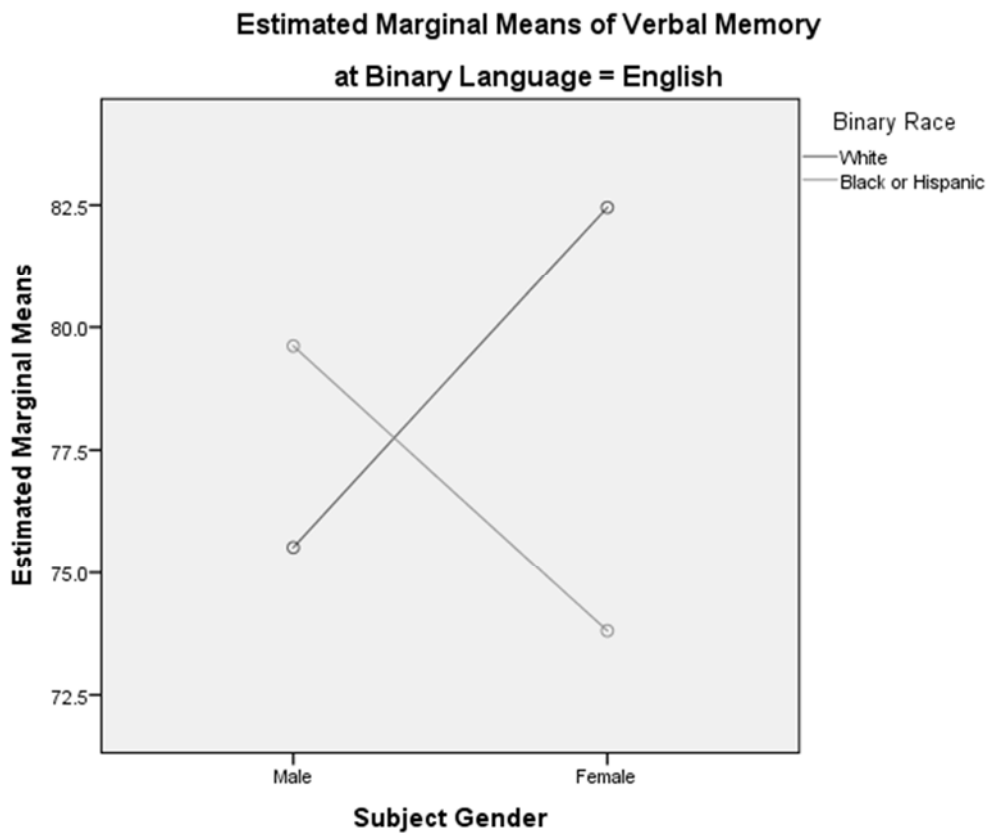
Figure 2. Flowchart of chart selection



*Figure 3.* Plot of post-concussion reaction time by gender ( $N = 118$ ,  $p = .04^*$ ). Females had slower reaction times compared with males after concussion. Reaction time was transformed using natural log to reduce skewness.

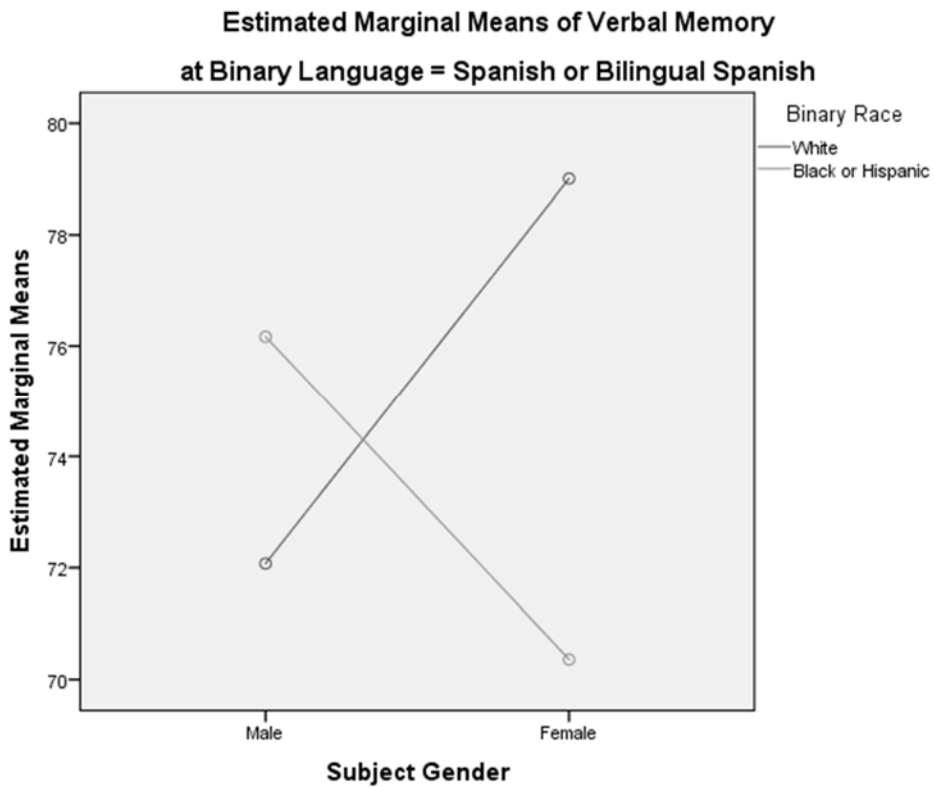


*Figure 4.* Interaction plot of post-concussion verbal memory by gender and race ( $N = 118$ ,  $p = .03^*$ ). Minority females performed worse than white females and white and minority males.



*Figure 5.* Interaction plot of post-concussion verbal memory by gender and race among subjects with primary language of English ( $N = 118, p = .04^*$ ).





*Figure 6.* Interaction plot of post-concussion verbal memory by gender and race among subjects with primary language as Spanish or Bilingual Spanish/ English ( $N = 118$ ,  $p = .04^*$ ).

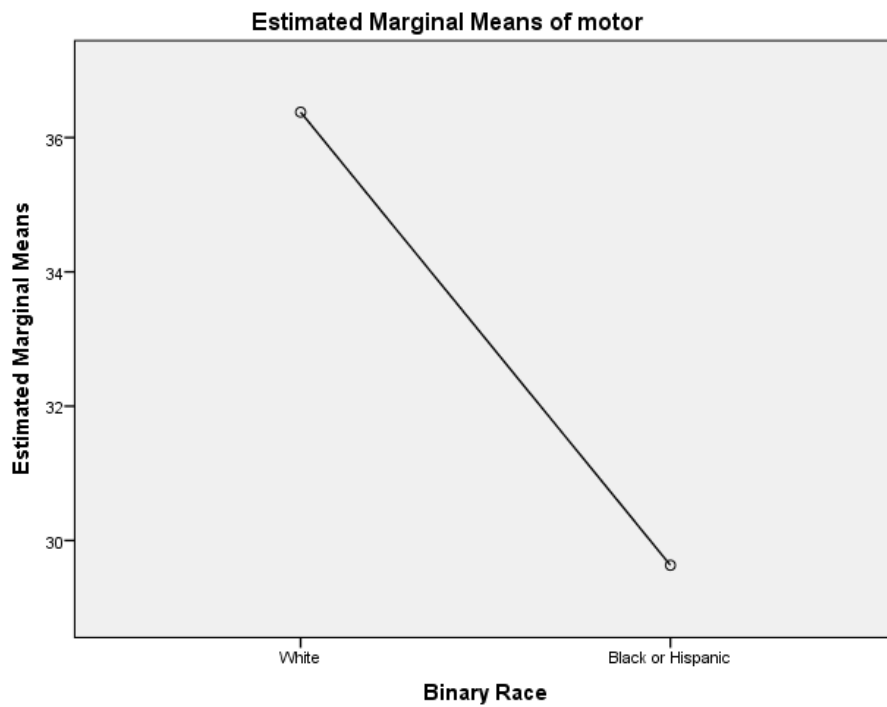


Figure 7. Plot of performance on post-concussion visual motor test by race ( $N = 59$ ,  $p = <.001^{***}$ ).

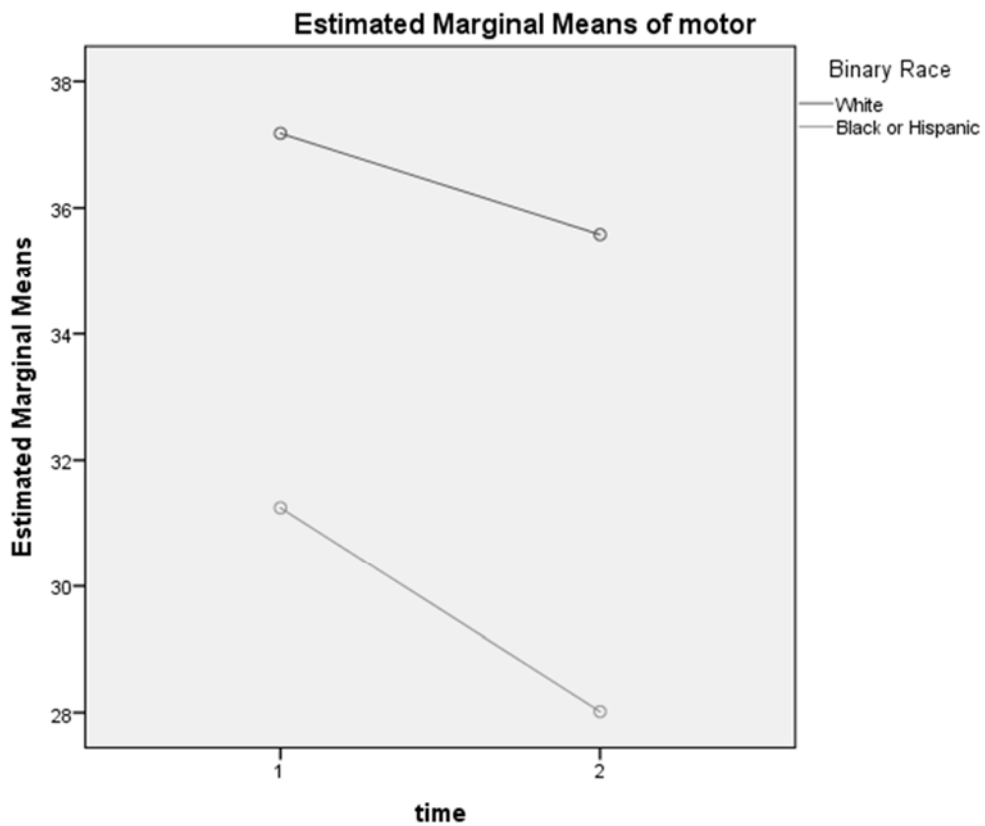
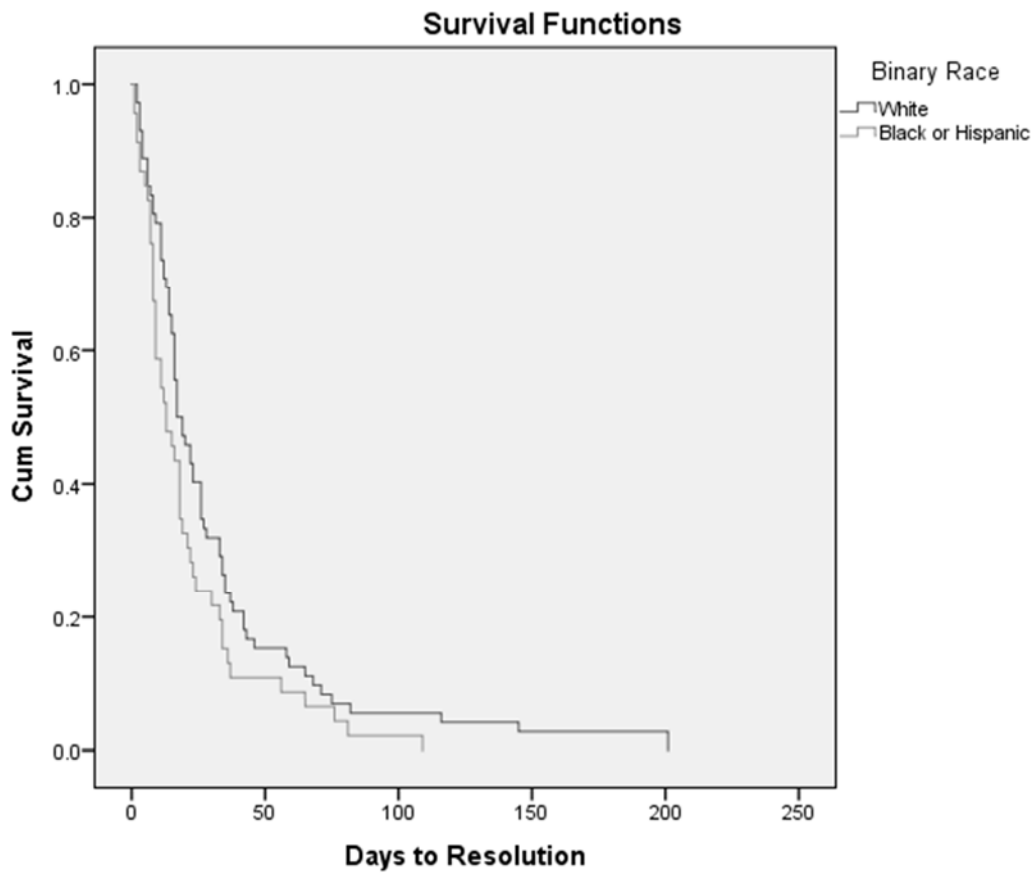


Figure 8. Interaction plot of performance on visual motor by race and time from baseline to post-concussion ( $N = 59, p = .67$ ).



*Figure 9.* Kaplan-Meier Curve of the Days to Resolution for Whites and aggregated Minorities.  $N = 118$ . Log Rank  $p = .06$ .

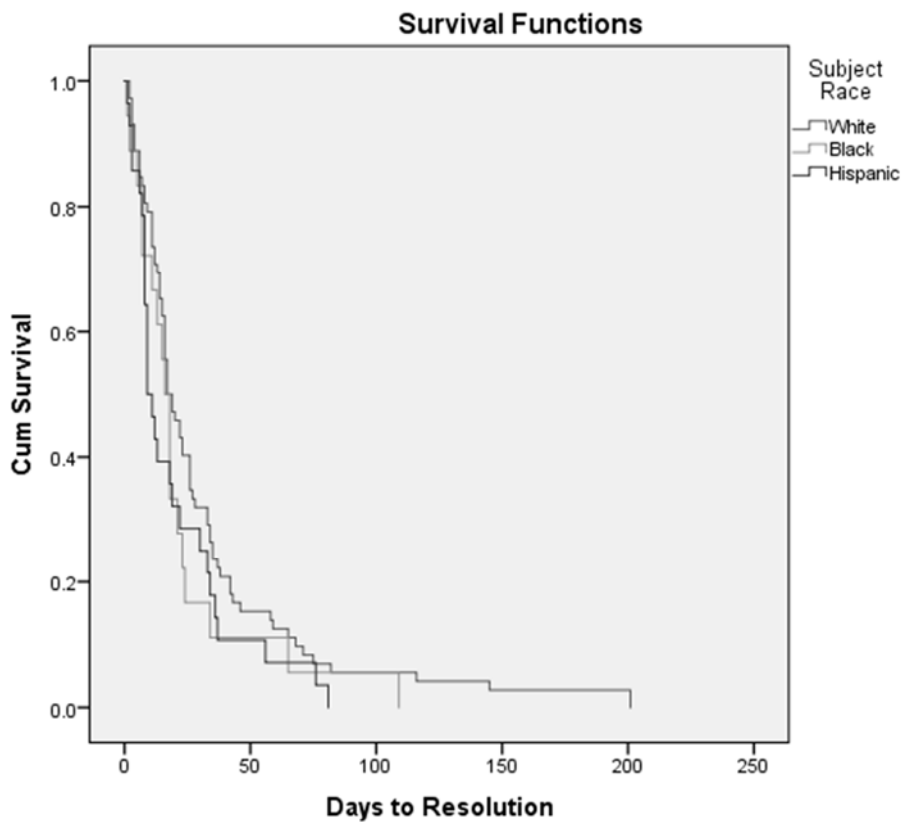


Figure 10. Kaplan-Meier Curve of the Days to Resolution for each race.  $N = 118$ . Log Rank  $p = .10$ .

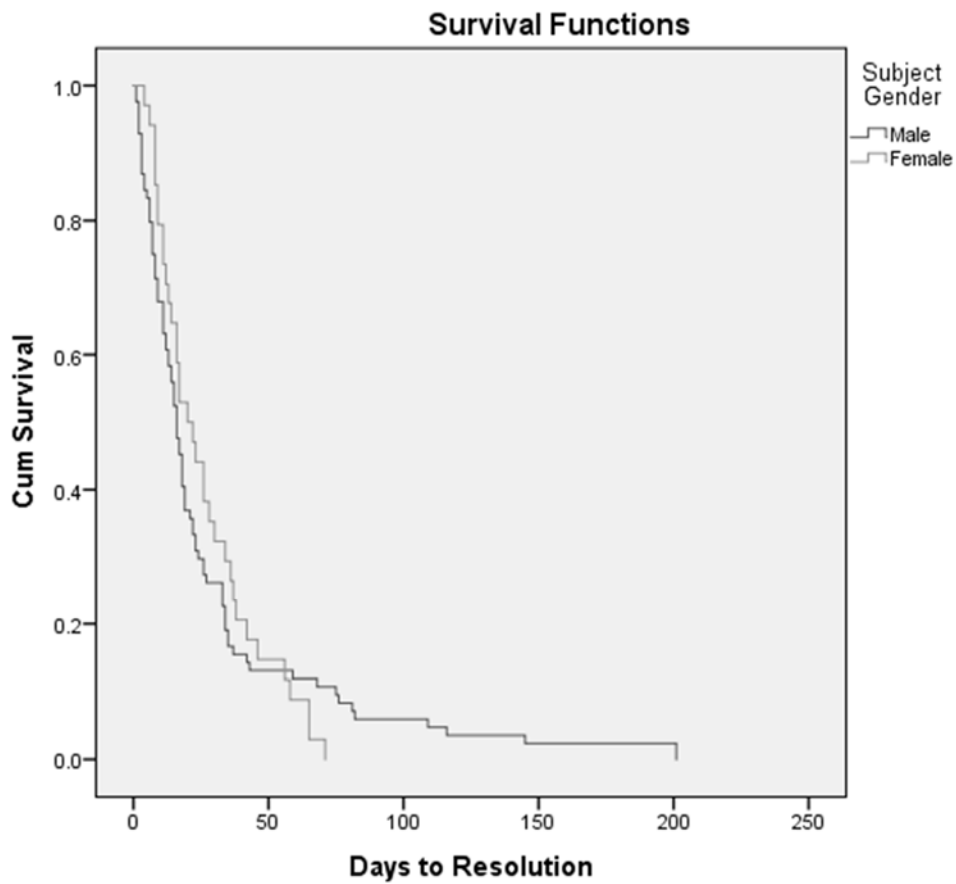


Figure 11. Kaplan-Meier Curve of the Days to Resolution for gender.  $N = 118$ . Log Rank  $p = .725$ .

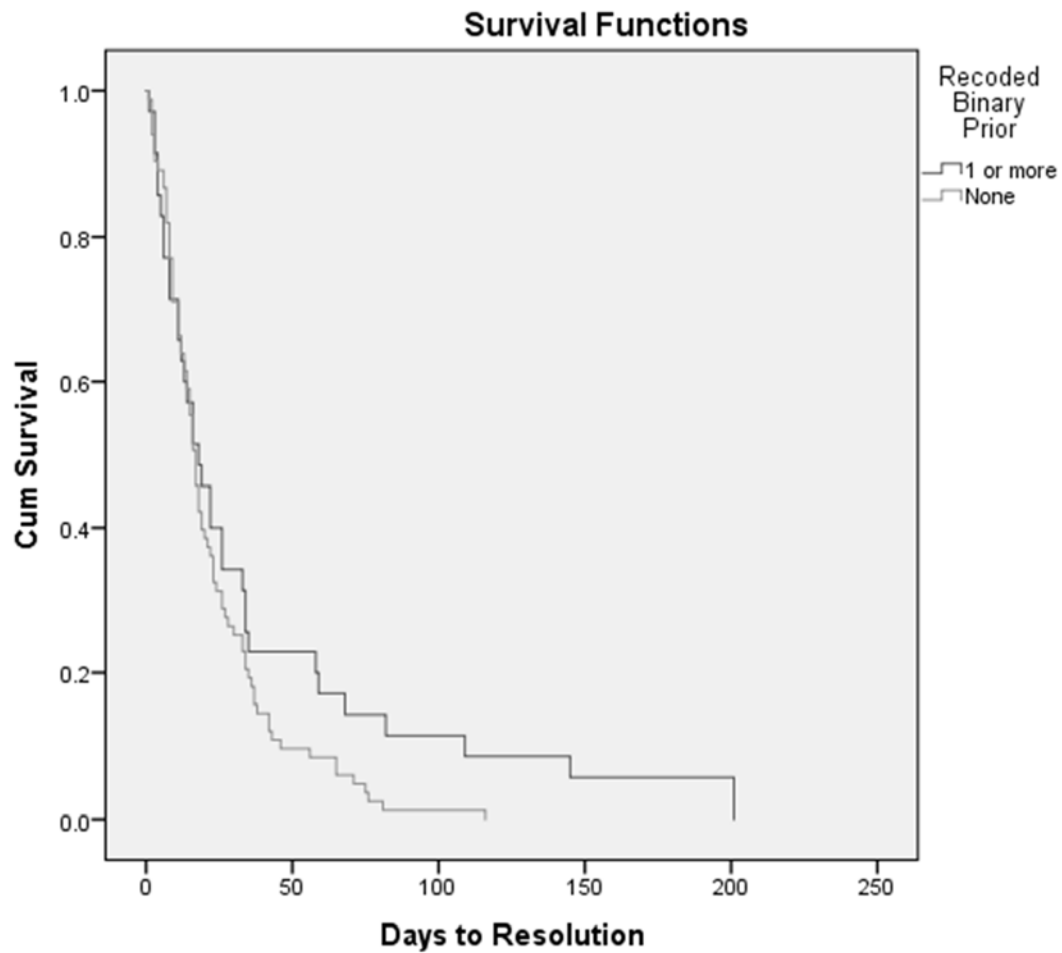
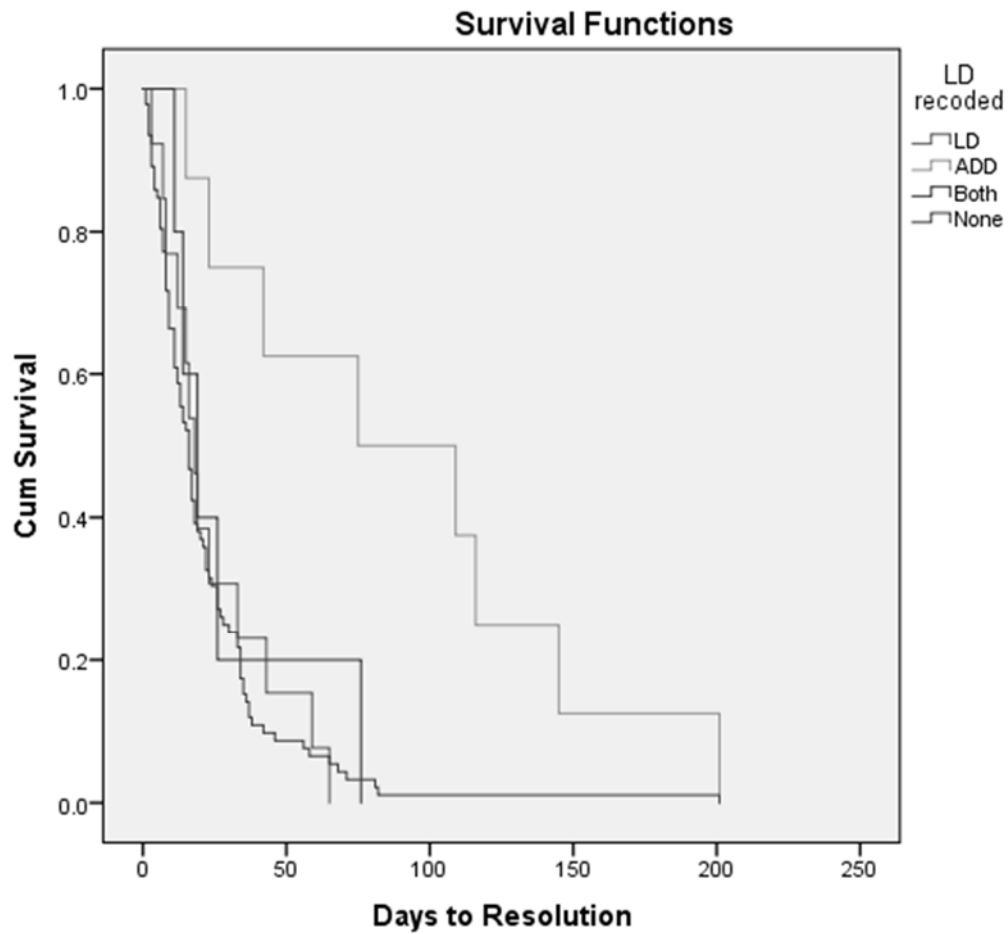


Figure 12. Kaplan-Meier Curve of the Days to Resolution for prior concussions.  $N = 118$ . Log Rank  $p = .104$ .



*Figure 13.* Kaplan-Meier Curve of the Days to Resolution for learning and attention deficit disabilities. LD = Learning Disability. ADHD = Attention Deficit Hyperactivity Disorder.  $N = 118$ . Log Rank  $p = .004^{**}$ .



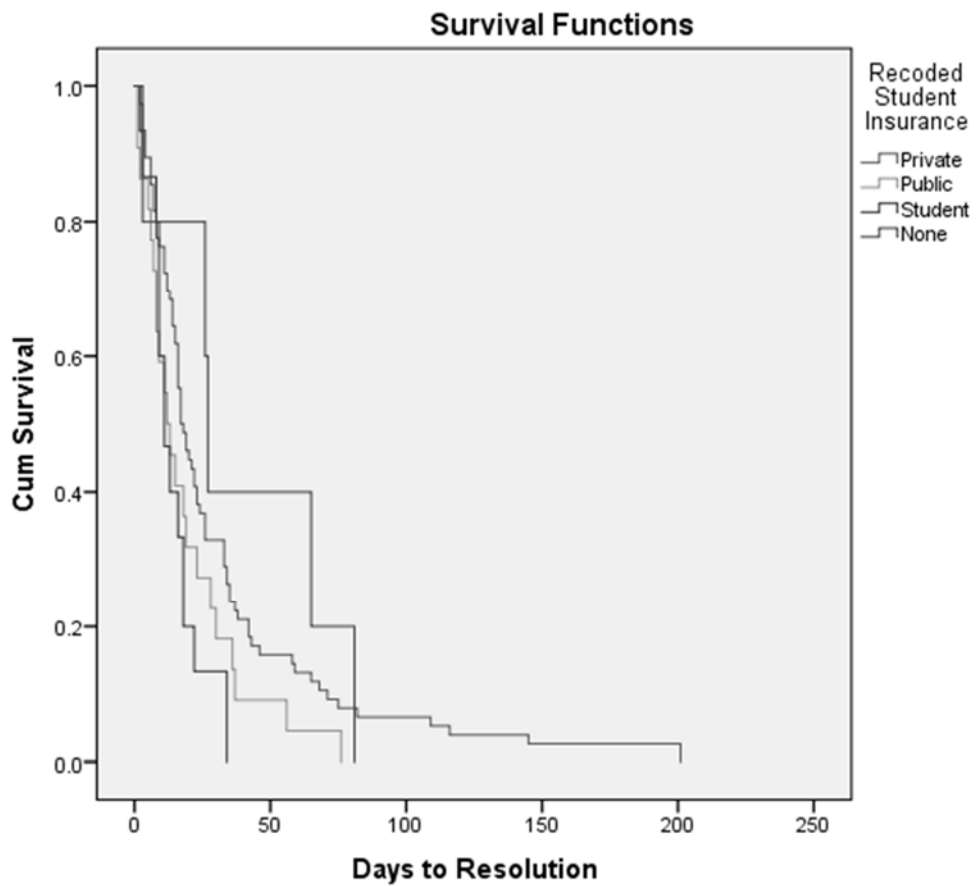


Figure 14. Kaplan-Meier Curve of the Days to Resolution for health insurance.  $N = 118$ . Log Rank  $p = .03^*$ .

March, 2016

Bernardo Innocenti  
Editor-in-Chief  
*International Journal of Sports Medicine*

Dear Dr. Innocenti:

I am writing to submit our manuscript entitled “The Impact of Gender on Concussion Presentation and Management in Adolescents and Young Adults” for consideration for publication in the *International Journal of Sports Medicine*. This manuscript is a systematic review of gender differences in sports-related concussions in adolescents and young adults ages 10-24 years old. The publication of studies on sports-related concussion has grown enormously since the adoption of a revised definition of concussion by the Concussion in Sport Group in 2001. This review indicates the need for further study of the influence of gender on concussions. Given the international relevance of this sports-related topic, we believe that this manuscript may be best suited for your journal.

We appreciate your consideration of our manuscript for review. We appreciate your time and look forward to your response. Please feel free to contact me at [Seema.S.Aggarwal@uth.tmc.edu](mailto:Seema.S.Aggarwal@uth.tmc.edu) or (832) 837-9433.

Sincerely,

Seema Aggarwal

**Manuscript B**

**The Impact of Gender on Concussion Presentation and Management in Adolescents  
and Young Adults**

The Impact of Gender on Concussion Presentation and Management in Adolescents and  
Young Adults

**Abstract**

**Purpose:** The purpose of this review is to examine what is known with respect to gender differences in the presentation and management of concussions in adolescents and young adults ages 10-24 years old.

**Methods:** A systematic quantitative review of the literature was conducted on sex/gender differences at baseline and post-concussion in adolescents and young adults. The OVID Medline, PubMed, and PsycInfo databases were reviewed.

**Results:** Thirty studies met inclusion criteria. The literature demonstrates that female athletes who play soccer, basketball, softball, and ice hockey have higher rates and/ or risk of concussion than males. Studies yielded mixed results with respect to gender differences on pre-season baseline total symptom scores and neurocognition. However, females had more sleep disturbances than males at baseline. After a concussive injury, females reported higher total symptom scores, complained of more headache symptoms, performed worse on visual memory and overall mean neurocognitive scores, and had longer recovery times, by a few days to over a month compared with males. Females required more treatment interventions including medications, vestibular rehabilitation, and physical and cognitive rest. Despite statistical significance, the effect sizes in many of the included studies were small to medium or were not reported; hence, caution should be used in the interpretation of the clinical significance.

**Conclusion:** This review demonstrated that adolescent and young adult females may take longer to recover from concussions and require more treatment interventions compared

with males. Based on this review of the literature, clinicians and researchers should be aware that concussed female adolescents and young adults may report more symptoms, have worse neurocognition, have longer recovery times, and require more therapeutic interventions than males. Future multi-disciplinary research is needed to help clinicians diagnose, treat, and predict recovery from concussions, particularly in populations at high risk for concussions and protracted recovery.

**Keywords:** Brain Concussion/\*etiology/mortality/rehabilitation, Female, Humans, Incidence, Male, Prognosis, Recovery of Function, Risk Factors, \*Sex Factors, Basketball/injuries, Hockey/injuries, Soccer/injuries, Brain/physiology

## Introduction

There are approximately 1.7 million traumatic brain injuries (TBIs) that occur in children and adults annually, of which 75% are mild TBIs (mTBIs), also termed concussions (Centers for Disease Control, 2003). Thirty percent of all concussions are sports-related concussions (SRCs) in children and adolescents ages 5 to 19 years (Harmon, et al., 2013). Other major causes of concussions include falls, motor vehicle accidents, and assaults (Faul, 2010). In 2000, the estimated direct and indirect costs of concussions in the U.S. was \$12 billion (Centers for Disease Control, n.d.). Multiple and untreated concussions may cause long-term neurologic sequelae including cognitive decline, memory loss, and depression (Hart et al., 2013; Kerr, Marshall, Harding, & Guskiewicz, 2012; Strain et al., 2015). The long-term impact of cumulative concussions in adolescents and young adults remains unknown, but the evidence suggests that there may be lasting damage with repetitive blows to the head in this age group (Bazarian et al., 2014; Breedlove et al., 2012). Therefore, future healthcare management may be necessary to treat neurological damage in these young athletes.

In 2008, there were approximately 44,000 Emergency Department (ED) visits in the U.S. that were attributed to SRCs. Of these ED visits, 58% were in adolescents ages 14 to 18 years, 17% were in 11- to 13-year olds, and 8% were in 19- to 23-year olds (Zhao L, 2011). The total incidence of concussion in U.S. high school students is almost 25 per 100,000 athletic exposures (Guerriero, Proctor, Mannix, & Meehan, 2012; Laker, 2011). Recent media attention on concussions has contributed to a sharp rise in ED visits. As an example, a recent study revealed a 92% increase in ED visits from 2002 to 2011 for evaluation of SRCs in 3,878 children ages 0 to 19 years at a U.S. level I trauma center

(Hanson, Pomerantz, & Gittelman, 2013). Physician office visits are estimated to be significantly higher than ED visits and constitute most concussion evaluations (Centers for Disease Control, n.d.). Most U.S. states have laws that require physician clearance for student athletes to return-to-play (RTP) after a suspected concussion. Therefore, cumulative health costs of SRCs are expected to grow with the increase in ED visits and requirements for physician clearance.

Concussion is defined as a functional and not structural injury after a blow to the head, neck, or body that jostles the brain (Harmon et al., 2013) and results in biochemical and neuro-metabolic changes (Giza & Difiori, 2011; Giza et al., 2013) that alter white and gray matter integrity (Committee on Sports-Related Concussions in Youth, 2014) causing physical (e.g., headache), cognitive (e.g., concentration problems), emotional (e.g., depression or anxiety), and/ or sleep disturbances (Centers for Disease Control, n.d.). Concussions cannot be identified with current standard imaging techniques (e.g., Computed Tomography (CT) or Magnetic Resonance Imaging (MRI)). Rather, concussions are usually diagnosed by symptoms reported by the patient, physical exam (e.g., balance testing for postural instability), and neurocognitive testing. The most frequently reported concussion symptoms include headache, dizziness, and fatigue (Harmon et al., 2013; Rose, Weber, Collen, & Heyer, 2015).

Concussions typically resolve within 7 to 14 days (Broglio, Collins, Williams, Mucha, & Kontos, 2015; McCrory et al., 2013). The primary treatment for concussion is physical rest (i.e., avoid physical exertion) and cognitive rest (i.e., avoid mental strain), particularly during the first 24 to 48 hours after injury. If symptoms are severe and/ or unremitting, medication for specific symptoms (e.g., headache, mood, sleep) and

rehabilitation measures (e.g., vestibular therapy, oculomotor therapy, etc.) may be prescribed (Broglio et al., 2015).

Risk factors for concussion and/ or protracted recovery may include female gender, younger age (ages 5 to 24 years), prior concussions or TBIs, migraine history, mood disorders, attention deficit disorders, learning disabilities, mechanism of injury, sport, and position of play (e.g., U.S. football quarterbacks) (Harmon et al., 2013). Studies indicate that females have higher incidence of concussions when playing similar sports with similar rules as males (e.g., soccer, basketball) (Clay, Glover, & Lowe, 2013). With respect to age, MRI studies have shown that the brain is not fully mature until approximately age 25 years (Lenroot & Giedd, 2006). Animal studies in rats have demonstrated that myelination of white matter tracts continues throughout adolescence and that unmyelinated white matter tracts are more easily disrupted compared with myelinated white matter tracts after an experimental concussion (Giza & Difiori, 2011). High school athletes may have a higher incidence of concussions compared with college athletes (Guskiewicz, Weaver, Padua, & Garrett, 2000), but more research is needed to determine whether concussion rates vary by age (Giza et al., 2013).

A major focus of Healthy People 2020 (HP 2020) is to encourage sports and exercise in adolescents and young adults ages 10-24 years in order to reduce obesity and its associated comorbidities. Another major initiative of HP 2020 is to reduce unintentional injuries (HP 2020). Concussions are a significant barrier to these initiatives and are of public concern given the growing number of young athletes. For example, in the 2003-2004 school year, there were 3.9 million US high school (HS) male athletes compared with 4.5 million HS male athletes in the 2013-2014 school year. There were



2.9 million HS female athletes in the 2003-2004 school year compared with 3.3 million HS female athletes in the 2013-2014 school year (National Federation of State High School Associations, 2014). Additionally, The National Collegiate Athletic Association (NCAA) reported that during the 2003-2004 NCAA season, there were 375,851 athletes (Johnson, 2014). By the 2013-2014 season, there was an 11% increase to 472,625 NCAA college athletes, with a nearly equal ratio of males to females (NCAA, 2011).

### **Purpose**

The data is unclear as to whether female gender and younger age are risk factors for concussion, more severe concussion symptoms, and/or delayed recovery from concussion (Giza et al., 2013; McCrory et al., 2013). The National Institutes of Health's (NIH) Vision for 2020 for Women's Health Research was developed to provide research funding to gain insights into gender differences with respect to the prevalence, development, and outcomes of several health conditions including brain disorders (National Institutes of Health, 2010). Furthermore, there has been a recent push by the Institute of Medicine (IOM) to obtain surveillance data on SRCs in individuals ages 5-21 years old due to lack of data (Committee on Sports-Related Concussions in Youth, 2014). The purpose of this systematic review is to elucidate what is known with respect to gender differences in the presentation and management of concussions in adolescents and young adults ages 10-24 years old. This age range was selected from the HP 2020 goals, as described earlier and is defined as follows: adolescents are ages 10-19 years and young adults are ages 20-24 years (Healthy People 2020, n.d.). Puberty begins around age 10 in males and females and is characterized by sex hormone changes that influence development of sex characteristics (Sizer, 2008) and brain structure (McCarthy, 2004).

This review will include individuals until age 24 years because of the cessation of brain development after this age, as described earlier. There has been a surge of concussion research in recent years that explored gender differences in adolescents and young adults. The goal of this systematic review is to examine the state of the science of gender concussion studies for researchers, clinicians, athletic trainers, and other allied health professionals who manage or study concussions in adolescents and young adults.

### **Methods**

A systematic search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Liberati et al., 2009).

#### **Search Strategy**

A systematic electronic search was conducted using OVID Medline, PubMed, and PsycInfo databases (see Appendix A) with the assistance of an academic librarian. The search was limited to peer-reviewed empirical articles written in English published between January 2002 and May 2015. The start date was restricted to 2002 based on the adoption of a revised definition of concussion by the Concussion in Sport Group (CISG) (Aubry et al., 2002). To supplement the electronic search, reference lists of the included articles and recent related systematic reviews (Brown, Elsass, Miller, Reed, & Reneker, 2015; Cancelliere, Donovan, & Cassidy, 2015; Gravel et al., 2013) were hand-searched for potential articles meeting inclusion criteria. The following key words and associated MeSH terms were used: brain concussion, mild traumatic brain injury, female, gender, and sex difference (see Appendix A).

### **Inclusion and Exclusion Criteria**

Studies were included if they met the following inclusion criteria: (a) original quantitative studies (b) the sample included adolescents and young adults ages 10-24 years old (or was designated as middle school, high school, or college-aged students) (c) concussion/ mild traumatic brain injury study (d) gender-comparative data (e) provided data with respect to symptom presentation (e.g., symptom reporting, neuropsychological data, medical exam, imaging) or management of concussion symptoms (e.g., medication, rehabilitative therapies, rest, coping strategies) pre- and/or or post-concussion. Exclusion criteria included (a) animal models, (b) moderate to severe traumatic brain injuries, (c) studies seeking to establish psychometric properties and normative scores of a concussion instrument, and (d) published abstracts only (e.g., conference proceedings).

Gender is distinguished from sex in that sex refers to the biological characteristics of an individual and gender encompasses the social constructs (e.g., masculine, feminine) of an individual (Byne, 2010). For the purposes of this review, these terms will be used interchangeably because it is difficult to discern the influence of gender and sex on symptom presentation and management.

### **Results**

The search results are presented in Figure 1. The electronic search identified eligible studies and the hand-search yielded an additional study (n=30). Extracted key data from the eligible studies are presented in tables (see Tables 1-4). Collected elements included the study purpose, design, control groups, level of evidence, age of the participants, sample size and percentages by sex, outcome measures, and key findings. The level of evidence was ranked according the Joanna Briggs Institute (JBI) (2014)

criteria from 1 (randomized controlled trials) to 5 (expert opinion). All of the studies identified in this review were JBI levels 3 (observational- analytical design) and 4 (observational- descriptive design). The quality of the evidence will be described in the review of findings.

### **Description of Evidence and Sample**

The findings of the 30 included studies addressed multiple concussion topics. The findings of the studies were organized as follows: the impact of gender on concussion risk/rates (9 studies; Tables 1-1, 1-2, 1-3, 1-4), baseline (pre-concussion) symptom presentation (11 studies; Tables 2-1, 2-2, 2-3, 2-4), post-concussion symptom presentation (13 studies; Tables 3-1, 3-2, 3-3, 3-4), and concussion management (4 studies; Table 4). The cohort samples primarily consisted of high school adolescents and college-aged young adults who were at risk for or experienced a sports-related concussion.

### **Description of Computerized Neurocognitive Instruments**

For ease of discussion and to enhance understanding, outcome measures of computerized neurocognitive screening tests used in some of the included studies will be described. The Immediate Post-Concussion Assessment and Cognitive Test (ImPACT) computerized neurocognitive battery was the most widely used battery among the studies in this review. ImPACT assesses the severity of 22 concussion symptoms (e.g., headache, sleep), verbal memory (e.g., verbal learning), visual memory (e.g., visual attention and scanning), reaction time (e.g., response time), and visual motor speed (e.g., motor speed of reaction to a visual cue) (ImPACT Applications Inc., 2007). The Concussion Resolution Index (CRI) measures similar constructs to ImPACT and provides three

summary speed composite scores including processing speed (e.g., speed of processing information) , simple reaction time (e.g., visual motor speed) and complex reaction time (e.g., decision-making speed) (Erlanger et al., 2003).

## **Findings**

The organization of the findings will be as follows: concussion risk/rates, pre-concussion baseline presentation, and post-concussion presentation and management.

### **Concussion Risk and Rates**

#### *Description of Studies*

The majority of the reviewed concussion epidemiology literature that applied to adolescents and young adults described the rates of sports-related injuries (e.g., concussion, fractures, etc.) that occurred in a particular sport and did not provide gender data that could be used to evaluate gender differences. The review of concussion epidemiology literature with sufficient gender data yielded a total of 9 different studies that assessed sport concussion rates or risk by gender. Most of the studies evaluated concussion rates/ risk in soccer (n=6; see Table 1-1) and basketball (n=6; Table 1-2). Ice hockey (n=1; see Table 1-3) and softball (n=1; see Table 1-3) concussion rates were also described. Finally, two studies (n=2; see Table 1-4) appraised gender differences with respect to concussion rates during practice or competition. The epidemiology studies primarily evaluated data extracted from databases on high school (n=7) and college (n=2) athletes. The method of reporting of sample sizes varied in that studies reported the number of total concussions, number of total injuries, and/or the number of participants (see Tables 1-1, 1-2, 1-3).

### *Sex Differences*

The review of literature suggests that females have higher rates/ risk of concussion compared with males. With respect to soccer (see Table 1-1), 5/6 studies demonstrated that females had higher rates/ risk of concussion than males (Delaney, Al-Kashmiri, Drummond, & Correa, 2008; Gessel, Fields, Collins, Dick, & Comstock, 2007; Lincoln et al., 2011; Marar, McIlvain, Fields, & Comstock, 2012; Rosenthal, Foraker, Collins, & Comstock, 2014). Three of these studies (Gessel et al., 2007; Marar et al., 2012; Rosenthal et al., 2014) retrospectively assessed concussion rates over 1 to 2 school years utilizing a national concussion reporting database for HS athletic trainers, the High school Reporting Information Online (RIO) database, and found that female soccer concussion rates was higher than males by approximately 15 athletic exposures (AEs) per 100,000 AEs. Delaney and colleagues (2008) utilized retrospective self-report concussion history surveys from 278 participants and found that female soccer players had nearly double the concussion risk ( $RR= 1.97, p <.0001$ ) of males. However, the survey instrument used in this study had no evidence of reliability or validity, and recall and/or reporting bias may have been an issue with obtaining concussion history. Lincoln and colleagues (2011) prospectively collected concussion data from 158,430 athletes from 25 schools in the same school district over 11 school years and similarly determined that female soccer players, who made up 25% of the sample population, had nearly double the risk ( $RR=1.7, 95\% CI [1.3-2.2]$ ) of concussions than males. However, Yard and colleagues (2008) found no sex differences in soccer concussion rates over 2 school years after evaluating 1,524 sports injuries in RIO, with a similar proportion of injured males and females.

In terms of basketball (see Table 1-2), 6/6 studies found that high school females had higher concussion risk/ rates than males (Borowski, Yard, Fields, & Comstock, 2008; Gessel et al., 2007; Lincoln et al., 2011; Marar et al., 2012; Rechel, Yard, & Comstock, 2008; Rosenthal et al., 2014). Borowski and colleagues (2008) and Rechel and colleagues (2008) analyzed RIO data and determined that female basketball players (106 and 395 concussions, respectively) had a significantly higher proportion of concussions (PR= 2.41, 95% CI [1.49-3.91] and 5.83 (95% CI [2.06-16.49], respectively) during competitions than males. Three studies (Gessel et al., 2007; Marar et al., 2012; Rosenthal et al., 2014) also used RIO data found that female basketball concussion rates were higher than males by approximately 5-15 AEs per 100,000 AEs. Lincoln and colleagues (2011) determined that females had twice the risk of concussions (RR= 2.1, 95% CI [1.6-2.6]) as with soccer compared with males. Marar and colleagues (2012) also found that female high school softball players had a higher concussion rate by approximately 11 AEs per 100,000 AEs than male baseball players (see Table 1-3). A retrospective review by Agel and Harvey (2010) of the NCAA Injury Surveillance System (ISS) database found that college female ice hockey players had a higher concussion rate by approximately 10 AEs per 100,000 AEs than males and this rate remained stable over 7 years (see Table 1-3). However, the number of college male ice hockey athletes (78.7%) was significantly greater than females (21.3%) in this study (Agel & Harvey, 2010).

Finally, two studies evaluated the effect of gender on the percentage of concussions that occur during practices and games in high school (Borowski et al., 2008) and college athletes (Covassin, Swanik, & Sachs, 2003) (see Table 1-4). Borowski and colleagues (2008) and Covassin and colleagues (2003) found that female athletes had a

higher percentage of concussions during games than practices (difference of 5.9% and 9%, respectively) compared with male athletes (difference of 1.2% and 3%, respectively). However, neither study reported the proportion of males to females.

A significant limitation of these epidemiology studies is that the data relies on self-reporting of concussion symptoms by the athlete to the athletic trainer. Another limitation of the epidemiology studies is the different methods of describing the sample population including the number of participants, sports injuries, and/ or concussions.

## **Pre-Concussion**

### **Baseline Symptoms**

Baseline neurocognitive data is typically collected from athletes prior to the athletic season for comparative purposes in the event of a concussive injury. When baseline data is unavailable, normative data for age, gender, and education level is utilized depending on the availability for the concussion instrument. This section of the review addresses the influence of gender on concussion total symptom scores (TSS; see Table 2-1), symptom type (see Table 2-2), and neurocognition (see Table 2-3) at baseline. The influence of prior concussions and play behavior on gender differences on baseline concussion symptoms will also be described (see Table 2-4). This knowledge is imperative for concussion specialists to more accurately interpret and possibly predict the pattern of post-concussion symptoms and neurocognition scores.

### ***Description of Studies***

There were 11 different studies that described baseline concussion symptoms. The majority (n=9) of these studies evaluated TSS, a few studies (n=3) addressed symptom type, four studies (n=4) evaluated neurocognition, and four studies (n=4) evaluated



variables that may influence concussion scores at baseline. The concussion literature refers to the variables as “concussion modifiers” (Harmon et al., 2013; McCrory et al., 2013). Outcome measures for baseline symptom presentation included self-reported symptom checklists (e.g., Graded Symptom Checklist (GSC), Sport Concussion Assessment Tool 2 (SCAT2), BDI-II, and ImPACT) and neurocognitive assessment (e.g., ImPACT). Prior concussion history was obtained from the demographic sections of the GSC, SCAT-2, and ImPACT. Most of the baseline studies (n=6) evaluated high school athletes exclusively, one study (n=1) evaluated college students exclusively, and three studies (n=3) included both high school and college athletes (see Tables 2-1 to 2-4).

### ***Baseline Sex Differences***

Several studies (n=4) found that females reported significantly ( $p \leq .05$ ) higher concussion TSS than males (Covassin, Elbin, Harris, Parker, & Kontos, 2012; Leach, Bay, & Valovich McLeod, 2013; Register-Mihalik, Mihalik, & Guskiewicz, 2009; Zuckerman et al., 2014) (see Table 2-1). Covassin, Elbin, Larson, and colleagues (2012) and Zuckerman and colleagues (2012) performed longitudinal studies, had sample sizes of 296 and 244, respectively, had a similar proportion of males to females, and excluded athletes with a history of psychiatric disorders, special education, speech therapy, or who repeated a school year. Unlike the other studies in this review, Zuckerman and colleagues (2014) matched the participants by sex, age, number of prior concussions, and date to first post-concussion test. Leach and colleagues (2013) and Register-Mihalik and colleagues (2009) performed cross-sectional studies that did not have exclusion criteria, had larger sample sizes of 3,298 and 8,930 athletes, respectively, and the proportion of

males to females was either larger than females (77.3% vs. 22.7%) or not reported. The Register-Mihalik (2009) study results had a low effect size ( $d = .07$ ).

More studies ( $n=5$ ) found no sex differences ( $p > .05$ ) on TSS at baseline (Brooks et al., 2014; Covassin, Elbin, Larson, & Kontos, 2012; Covassin, Schatz, & Swanik, 2007; Kontos, Covassin, Elbin, & Parker, 2012; Zuckerman et al., 2012). (see Table 2-1) Three of the studies were longitudinal studies with small sample sizes ranging from 75 to 80 participants (Covassin et al., 2007; Kontos et al., 2012; Zuckerman et al., 2012), and two studies were cross-sectional studies with 615 to 1,616 participants (Brooks et al., 2014; Covassin, Elbin, Larson, et al., 2012; Zuckerman et al., 2012). The majority (4/5) of the studies that found no sex differences had more exclusion criteria than the studies that identified sex differences. The exclusion criteria were as follows: prior brain injuries (Brooks et al., 2014; Covassin, Elbin, Harris, et al., 2012; Zuckerman et al., 2012), attention and learning disabilities (Brooks et al., 2014; Covassin, Elbin, Larson, et al., 2012; Kontos et al., 2012; Zuckerman et al., 2012), substance abuse and/ or psychiatric disorders (Covassin, Elbin, Larson, et al., 2012; Kontos et al., 2012; Zuckerman et al., 2012), and repeated school year (Zuckerman et al., 2012).

With respect to symptom type differences at baseline (see Table 2-2), females reported worse sleep ( $p < .01$ ) (Covassin, Elbin, Larson, et al., 2012; Leach et al., 2013; Zuckerman et al., 2014), headaches ( $p < .001$ ) (Leach et al., 2013), and emotional ( $p = .001$ ) and cognitive ( $p = .026$ ) (Covassin, Elbin, Larson, et al., 2012) symptoms. The Covassin, Elbin, Larson, et al. (2012) study also evaluated depressive symptoms on the BDI-II at baseline and individuals with history of psychiatric disorders were excluded

from the study; however, the aforementioned symptom types were unadjusted for depressive scores.

In terms of baseline neurocognition (see Table 2-3), two studies (n=2) found gender differences ( $p \leq .05$ ) (Covassin, Elbin, Kontos, & Larson, 2010; Covassin, Elbin, Larson, et al., 2012) and three studies (n=3) did not indicate a difference ( $p > .05$ ) (Brooks et al., 2014; Covassin et al., 2007; Zuckerman et al., 2012). Specifically, females had higher verbal memory scores (Covassin, Elbin, Larson, et al., 2012), better motor processing speed (Covassin et al., 2010; Covassin, Elbin, Larson, et al., 2012), and reaction times (Covassin et al., 2010) than males. Covassin, Elbin, Larson, and colleagues (2012) reported their study had low effect sizes. Three studies (n=3) found no neurocognitive gender differences at baseline (Brooks et al., 2014; Covassin et al., 2007; Zuckerman et al., 2012); however these studies had fewer total participants (n= 774) compared with the baseline studies that found neurocognitive differences (n= 1804). In addition, Brooks and colleagues (2014) adjusted scores to reflect “known” sex differences that males perform better on visual memory and females perform better on verbal memory. None of the other studies in this review adjusted for these factors. All of the baseline neurocognition studies, with the exception of Covassin and colleagues (2007), excluded participants with learning and attention disabilities.

### ***Multiple Concussions***

Leach and colleagues (2013) performed a cross-sectional study in 3,298 athletes with proportionately more males than females (3:1) and found that, at baseline, females with prior concussions reported significantly higher TSS compared with females without prior concussions and males with or without prior concussion history (see Table 2-4). In

terms of neurocognition, Covassin and colleagues (2010) performed a retrospective study in 188 athletes with a similar proportion of males and females, and discovered that males who incurred more than one prior concussion performed worse on verbal memory than females who experienced more than one prior concussion ( $p = .001$ ). Furthermore, males who experienced more than two prior concussions performed worse on visual memory than females who had more than two prior concussions at baseline ( $p = .021$ ) (Covassin et al., 2010). However, Brooks and colleagues (2014) found no sex differences ( $p = .227$ ) on baseline neurocognitive scores among hockey athletes with prior concussions. Brooks had a larger sample size with 615 participants, but there were significantly more males than females by approximately 4:1. Both, Covassin and colleagues (2010) and Brooks and colleagues (2014), excluded participants with attention and learning disabilities.

### ***Play Behavior***

Play behavior may affect baseline scores and may be influenced by gender (see Table 2-4). Kontos and colleagues (2011) determined that male soccer players headed the ball more frequently than females ( $t = 2.30, p = .03$ ) during 2 separate games, which was recorded by 2 observers. Furthermore, males performed worse on verbal memory ( $p = .04$ ), visual memory ( $p = .02$ ) and motor processing speed ( $p = .01$ ) tasks compared with females. This cross-sectional study had a small sample size of 63 participants with a proportionate ratio of males to females and excluded participants with learning disabilities, psychiatric disorders, substance abuse, prior TBIs, and history of migraines.

## **Post-Concussion**

### **Concussion Presentation**

This section will address gender differences with respect to the presentation of post-concussion symptoms including TSS (see Table 3-1), symptoms types (see Table 3-2), physical exam (e.g., postural instability) (see Table 3-2), symptom duration (see Table 3-3), and neurocognition (see Table 3-4).

### *Description of Studies*

There were 12 different studies that evaluated post-concussion symptoms. The majority (n=9) of these studies evaluated TSS, six studies (n=6) addressed symptom type, four studies (n=4) evaluated symptom duration, and five studies (n=5) evaluated neurocognition. Outcome measures for symptom presentation included self-reported symptoms (e.g., GSC, Rivermead Post Concussion Symptoms Questionnaire (RPQ), BDI-II, ImPACT, RIO, medical chart reviews), neurocognitive assessment (e.g., ImPACT, CRI), and physical exam of postural instability (e.g., Balance Error Scoring System (BESS)). Most of the baseline studies (n=5) evaluated high school athletes, two studies (n=2) evaluated college students, three studies (n=3) included both high school and college athletes, and two studies (n=2) had middle and high school students (see Tables 3-1 to 3-4).

Several studies excluded participants who had learning disabilities (Berz et al., 2013; Broshek et al., 2005; Covassin, Elbin, Bleecker, Lipchik, & Kontos, 2013; Mihalik et al., 2013; Zuckerman et al., 2014; Zuckerman et al., 2012), were in special education (Covassin, Elbin, Harris, et al., 2012; Kontos et al., 2012; Mihalik et al., 2013; Zuckerman et al., 2014; Zuckerman et al., 2012), repeated a school year (Covassin, Elbin,

Harris, et al., 2012; Kontos et al., 2012; Zuckerman et al., 2014; Zuckerman et al., 2012), had speech therapy (Covassin, Elbin, Harris, et al., 2012; Mihalik et al., 2013; Zuckerman et al., 2014; Zuckerman et al., 2012), attention deficit disorders (Broshek et al., 2005; Covassin, Elbin, Bleecker, et al., 2013; Mihalik et al., 2013; Zuckerman et al., 2014; Zuckerman et al., 2012), psychiatric disorders (Covassin, Elbin, Harris, et al., 2012; Kontos et al., 2012; Zuckerman et al., 2014; Zuckerman et al., 2012), substance abuse history (Covassin, Elbin, Harris, et al., 2012; Kontos et al., 2012; Zuckerman et al., 2014; Zuckerman et al., 2012), brain surgery (Zuckerman et al., 2014; Zuckerman et al., 2012), color-blindness, chronic migraines (Covassin, Elbin, Bleecker, et al., 2013), or had seizures (Zuckerman et al., 2014; Zuckerman et al., 2012).

Most of the longitudinal studies (7/11) used baseline scores for comparison with post-concussion scores. There were varying time-frames of post-concussion testing: 2, 7, and 14 days (Covassin, Elbin, Harris, et al., 2012; Kontos et al., 2012),  $\leq 7$  and  $> 7$  days (Berz et al., 2013), 8 days (Covassin, Elbin, Bleecker, et al., 2013), 1-2 day intervals (Broshek et al., 2005), 1,2,  $>2$  days until  $\leq 30$  days (Zuckerman et al., 2014), within 10 days (Zuckerman et al., 2012), within 3 days and 7-10 days (Covassin et al., 2007), 1, 2, 3, 5, 7, 90 days (Mihalik et al., 2013), and 90 days only (Preiss-Farzanegan, Chapman, Wong, Wu, & Bazarian, 2009).

### ***Post-Concussion Sex Differences***

Several longitudinal studies (n=5) determined that concussed females reported higher post-concussion TSS ( $p \leq .05$ ) compared with males (Berz et al., 2013; Broshek et al., 2005; Covassin, Elbin, Bleecker, et al., 2013; Covassin, Elbin, Harris, et al., 2012; Zuckerman et al., 2014) (see Table 3-1). Berz and colleagues (2013) had only 37

participants, did not specify the proportion of males to females, and did not describe instrument reliability or validity. Broshek and colleagues (2005) had a sample size of 155 and significantly more males than females by 3:1. Covassin and colleagues (2013) had a sample size of 95, a 2:3 ratio of males to females, and was the only study to adjust scores for body mass index (BMI). The authors theorized that lower BMI may contribute to weaker neck strength, which may make female athletes more susceptible to concussions than males, as described in the discussion section. Covassin, Elbin, Harris, and colleagues (2012) and Zuckerman and colleagues (2014) had a similar number of participants at 296 and 244, respectively, and nearly 1:1 ratio of males and females. Zuckerman and colleagues (2014) matched cohorts by age, sex, concussion history, and days to post-concussion testing, and had multiple exclusion criteria as described earlier; these exclusions may have contributed to selection bias.

Four studies ( $n=4$ ) found no sex differences ( $p > .05$ ) on post-concussion TSS (Frommer et al., 2011; Kontos et al., 2012; Preiss-Farzanegan et al., 2009; Zuckerman et al., 2012) (see Table 3-1). Frommer and colleagues (2011) performed a cross-sectional study obtaining concussion data from RIO. Preiss-Farzanegan and colleagues (2009) had 137 participants, more males (71%) than females (21%), and adjusted TSS for self vs. proxy report of concussion, previous loss of consciousness (LOC) or ED visit for head injury, or sport type. Kontos and colleagues (2012) had 75 participants with a male to female ratio of 2:1 and excluded participants who did not have a baseline BDI-II or who had a BDI-II score  $\geq 20$ . Zuckerman and colleagues (2012) reported that the results had low to medium effect sizes.

Concerning concussion symptom type (see Table 3-2), there was no clear pattern of sex differences with the exception of headache symptoms. Frommer and colleagues (2011) determined that concussed females reported more drowsiness and phonophobia; whereas Covassin and colleagues (2013) found that females had more migraine, cognitive, fatigue, and sleep symptoms (Covassin, Elbin, Bleecker, et al., 2013) compared with males. Concussed males reported more amnesia and confusion in the Frommer study (2011), but more frequently complained of sadness and vomiting in the Covassin study (2007) compared with females. Three studies (n=3) indicated that females complained of more PTH and/ or migraine-type headaches than males (Bramley et al., 2015; Covassin, Elbin, Bleecker, et al., 2013; Mihalik et al., 2013). The Bramley (2015) study obtained symptom data from a medical chart review and the Frommer (2011) study gathered data from RIO as mentioned earlier; hence, it is unknown whether there was missing data in these studies. Covassin and colleagues (2007) and Covassin and colleagues (2013) had low sample sizes of 79 and 95, respectively. Mihalik and colleagues (2013) had 296 participants and a larger percentage of males (81%) than females (19%). Finally, with respect to post-concussion postural instability, high school males had worse BESS scores than high school females, and college females had worse scores than college males (Covassin, Elbin, Harris, et al., 2012). The reasons for the interaction between age and sex are unclear.

In terms of concussion duration (see Table 3-3), three studies (n=3) determined that females have longer recovery times ( $p < .05$ ) from concussion than males by a few days (Zuckerman et al., 2014) to over a month (Bramley et al., 2015; Kostyun & Hafeez, 2015). The Bramley (2015) and Kostyun (2015) studies were retrospective chart reviews



and the number of missing records or data are unknown, which may contribute to information bias. Frommer and colleagues (2011) determined that symptom recovery times were similar in both genders at 3 days (HR=1.07; 95% CI [0.91-1.27]). However, this study obtained data from RIO and had more males (75%) than females (25%).

Several studies (n=4) found that females had significantly ( $p \leq .05$ ) worse neurocognition than males (Broshek et al., 2005; Covassin, Elbin, Bleecker, et al., 2013; Covassin, Elbin, Harris, et al., 2012; Covassin et al., 2007) (see Table 3-4). Specifically, females had worse mean composite neurocognitive scores (Broshek et al., 2005; Covassin, Elbin, Bleecker, et al., 2013), lower visual memory scores (Covassin, Elbin, Bleecker, et al., 2013; Covassin, Elbin, Harris, et al., 2012; Covassin et al., 2007), and lower verbal memory scores (Covassin, Elbin, Bleecker, et al., 2013) compared with concussed males. Sample sizes of these studies ranged from 79 to 296 and ratio of male to females were either not reported (Covassin et al., 2007), similar (Covassin, Elbin, Bleecker, et al., 2013; Covassin, Elbin, Harris, et al., 2012), or had more males than females by 2:1 (Broshek et al., 2005). Covassin, Elbin, Harris, and colleagues (2012) evaluated high school and college samples and found no significant interaction between age and sex ( $p > .05$ ) on neurocognition. One study (n=1) found no sex differences ( $p > .05$ ) on the neurocognitive measures of verbal or visual memory after a concussion (Zuckerman et al., 2012). This study had a small sample size of 80 with a proportionate number of males and females.

### **Concussion Management**

This section will focus on the management of concussions (see Table 4), which typically involves physical and cognitive rest, medications, and rehabilitation (e.g.,

vestibular, ocular, etc.) depending on symptoms. Concussion coping differences with respect to gender will also be addressed.

### ***Description of Studies***

There were four studies (n=4) that addressed gender differences in concussion management. Outcome measures for symptom management included medical chart notes on treatment interventions, recovery time, and symptoms, the Numeric Pain Rating Scale (NRS), and the Brief COPE Inventory (COPE). One study (n=1) evaluated the overall management of concussions, two studies (n=2) evaluated headache management, and one study (n=1) examined coping strategies among male and female adolescents (see Table 4).

### ***Concussion Management Sex Differences***

Two studies (n=2) were medical chart reviews and only included participants who had complete concussion resolution (Bramley et al., 2015; Kostyun & Hafeez, 2015). Females were prescribed significantly more rest, academic accommodations, vestibular rehabilitation (Kostyun & Hafeez, 2015), and medications (Bramley et al., 2015; Kostyun & Hafeez, 2015) after a concussion compared with males. Both studies did not indicate the number of charts that had missing data and this may contribute to information bias.

Headaches are the most commonly reported concussion symptom and are frequently treated with amitriptyline especially if the headache persists over a month (Rose et al., 2015). Bramley and colleagues (2015) determined from their retrospective chart review that compared with males, female adolescents more frequently reported PTH after a concussion and were more likely to be prescribed amitriptyline, which improved symptoms in 82% of the study sample. Another cross-sectional study examined the effect

of intravenous migraine therapy (e.g., ketorolac, prochlorperazine, metoclopramide, chlorpromazine, or ondansetron) given to adolescents within 14 days of concussion in the ED (Chan, Kurowski, Byczkowski, & Timm, 2015). Eighty-six percent of patients reported improvement in symptoms and 52% reported resolution of PTH symptoms. However, no sex differences were found with respect to PTH improvement in this study sample (Chan et al., 2015). Chan and colleagues (2015) excluded patients who had a history of neurologic impairment such as seizures, developmental delays, multi-system trauma, or inadequate NRS documentation. This study had no control or placebo group.

Finally, coping from concussions can be particularly difficult due to the need for physical rest (e.g., no sports) and cognitive rest, which requires reduced mental stimulation (e.g., computer use, reading, television) that may interfere with school activities and interactions with peers (Broglia et al., 2015). Kontos and colleagues (2013) found that concussed athletes demonstrated poorer overall coping compared with athletes who sustained orthopedic injuries. Injured females utilized more emotional coping strategies (e.g., self-distraction, humor, active coping, etc.) compared with injured males. This difference may reflect a behavioral difference between males and females and the COPE may not have captured other methods of coping that concussed males might utilize.

### **Summary of Concussion Gender Differences**

This review demonstrated that female adolescents and young adults had higher rates/ risk of concussions than their male counterparts. This review identified several gender differences with respect to concussion presentation and management. In terms of baseline TSS, 4/9 studies found that females had higher TSS than males and 5/9 studies

did not indicate a gender difference. The studies that did not indicate a difference had more exclusion criteria and smaller sample sizes. Females had worse sleep symptoms than males at baseline in 3/3 studies. With respect to baseline neurocognition, 3/5 studies indicated no sex differences, but these studies had fewer participants than the 2/5 studies that indicated that females had better neurocognition than males on motor processing speed, verbal memory, and reaction time. Males with prior concussion history performed worse on neurocognition than females in 1/2 studies and females with prior concussions had higher TSS than females in one (n=1) study. Males headed the soccer ball more than females and had worse neurocognition than females in one study (n=1).

After a concussive injury, females had higher TSS than males in 5/9 studies and 4/9 studies showed no difference. Most of the post-concussion TSS studies had multiple exclusion criteria, low sample sizes, and more males than females. In terms of symptom type differences, females reported more headache symptoms in 4/5 studies. Females had longer recovery times (e.g., few days to over a month) compared with males in 3/4 studies. Females performed worse on post-concussion visual memory and overall mean neurocognitive scores compared with males in 4/5 studies. Females required more therapeutic interventions including treatment with amitriptyline, vestibular rehabilitation, and physical and cognitive rest; however there was only one study (n=1) that evaluated multiple treatment interventions.

### **Clinical and Research Implications**

As described earlier, diagnosis of concussion relies primarily on self-report of symptoms and neurocognitive testing. Clinicians and researchers must be aware that male and female athletes may under-report their concussion symptoms out of fear from being

removed from play or pressure to continue playing by peers, coaches, parents, and others (Kroshus, Garnett, Hawrilenko, Baugh, & Calzo, 2015). Multiple concussions may lead to permanent neurologic damage, as described earlier. Therefore, currently, neurocognitive testing and balance testing are essential to aid in concussion diagnosis. However, objective diagnostic tools are needed to identify concussive damage regardless of whether the athlete reports his/ her symptoms. Future methods of diagnosis include identifying serum biomarkers (e.g., S100B) and imaging evidence (e.g., Diffusion Tensor Imaging, etc.) and may offer clues as to the reasons for concussion sex differences; more research is needed to validate the use of these diagnostic methods (Rose et al., 2015). New diagnostic methods may allow health care providers and researchers to assess concussion severity and help determine how many concussions are too many in particular populations (e.g., females) before sustaining permanent neurologic damage.

There were only four articles (n=4) that addressed treatment interventions in females. This reflects a significant gap in current evidence on gender differences in response to concussion interventions. As described previously, Kostyun and colleagues (2015) found that females were eight times as likely as males to be prescribed vestibular therapy for balance difficulties. Balance difficulties after concussion may have different underlying pathologies (e.g., benign paroxysmal positional vertigo (BPPV), vestibulo-ocular reflex (VOR) impairment, etc.) and require a trained vestibular therapist (Broglia et al., 2015). Headaches were identified as a common concussion symptom in females requiring pharmacologic therapy with amitriptyline or other migraine-specific medications. IV migraine treatment is a promising headache intervention in adolescents and young adults, but more studies are needed to substantiate its effectiveness and

evaluate the impact receiving an IV medication. Amitriptyline is an oral antidepressant that is commonly prescribed in the lower doses (10 mg) as a post-traumatic headache or migraine medication after concussions (Lee & Fine, 2010; Rose et al., 2015) and was well-tolerated in 86% of the adolescents in the Bramley (2015) study. However, 23% of the study subjects discontinued amitriptyline because of untoward side effects (e.g., somnolence, irritability, nausea). In addition, the Federal Drug Administration (FDA) warns that in clinical trials, a small number of patients up to age 24 years on a therapeutic dosage for depression became suicidal on amitriptyline and careful monitoring is needed by the prescriber and family (MedlinePlus, 2010). The therapeutic oral dose of amitriptyline in children > 12 years old with clinical depression is typically 50-100 mg daily with a maximum dosage of 200 mg (Epocrates, n.d.), which is significantly higher than the therapeutic dose for post-concussion headaches.

There is potential for the use of safe, alternative therapeutic techniques to alleviate concussion symptoms. For example, recent research on repetitive transcranial magnetic stimulation (rTMS) revealed that stimulation of the left dorsolateral prefrontal cortex (DLPFC) significantly reduced total symptom scores in concussed adult patients who had protracted recovery lasting longer than three months (Koski et al., 2015). Cognitive-behavioral therapy (CBT) should be considered as a first-line intervention in concussion patients with anxiety or depression. CBT in combination with amitriptyline was shown to be effective in a randomized clinical trial (RCT) in subjects (n=135) ages 10-17 years with migraine-type concussion headaches lasting >15 days (Powers et al., 2013); the effects by gender were not reported. A review of alternative therapies for refractory concussion symptoms found that, heart rate variability training, relaxation

training and neurofeedback training may be beneficial, but more empirical evidence is needed (Conder & Conder, 2015).

This review indicated that females may require longer physical and cognitive rest compared with males. Kostyun and colleagues (2015) noted that cognitive rest may become detrimental when adverse effects such as isolation or depression start to occur. The current recommendation for cognitive rest is that patients should gradually return to tasks requiring concentration (e.g., school work) within 24-48 hours (McCrory et al., 2013). However, this timeline may need to be adjusted if concussion symptoms are triggered by these activities (Harmon et al., 2013). A recent RCT in 89 patients ages 11-22 revealed that strict cognitive rest for 5 days (vs. usual care of 24-48 hours) was not recommended because longer cognitive rest exacerbated symptom reporting; however, results in this study were not reported by gender (Thomas, Apps, Hoffmann, McCrea, & Hammeke, 2015). More gender studies are needed to evaluate the impact of rest on concussion recovery. Finally, clinicians should follow standard return-to-play protocols, as required by state laws, in student athletes when tapering physical rest (McCrory et al., 2013). Future research on prevention and treatment interventions is needed in adolescents and females, who may be vulnerable to prolonged concussion recovery.

### **Discussion**

This review of literature indicated that females have higher rates/ risk of concussion, particularly in soccer and basketball, than males. However, more gender comparative data is needed in in other sports. In addition, there were no gender studies on concussions from other mechanisms of injury (e.g., motor vehicle accidents, etc.); hence, more studies are needed to assess rates/ risk in mechanisms of concussive injury other

than soccer and basketball. Furthermore, more prospective studies with larger sample sizes, a proportionate number of males and females, and consistent post-concussion time frames are needed to understand the effect of gender on post-concussion symptoms.

There is disagreement among experts whether the rates of concussion are truly higher in females or simply reflect gender reporting differences, in that females may be more honest with their symptoms compared with males leading to more frequent diagnosis (Dick, 2009). In general, females more frequently report more somatic pain symptoms and experience longer duration of symptoms compared with males (Barsky, Peekna, & Borus, 2001). For example, females have higher prevalence rates than males in conditions such as migraine headaches (Borsook et al., 2014), irritable bowel syndrome (Meleine & Matricon, 2014), and musculoskeletal pain disorders (LeResche, 2011). The perception of pain appears to be a complex dynamic between biologic, behavioral, and psycho-social factors. Potential reasons for gender differences with respect to pain perception may include biological differences, greater symptom awareness, social acceptability of pain expression, coping mechanisms, and clinical or research bias (Barsky et al., 2001; Racine et al., 2012a, 2012b).

There are several potential biological reasons for gender differences in symptom presentation including sex hormones, anatomy, and cerebral metabolism. Female gonadal hormones may play a significant role with concussion outcomes. Gamma-aminobutyric acid (GABA) is a pain mediator that is modulated by estrogen and progesterone. Natural fluctuations of these sex hormones during the menstrual cycle may alter the threshold of pain (Mensah-Nyagan, Meyer, Schaeffer, Kibaly, & Patte-Mensah, 2009). Concussion outcomes may be influenced by the menstrual cycle. For example, some researchers



hypothesized that concussion outcomes of symptom severity and/or protracted recovery may be worse in females when they were injured during the luteal phase (LP) of menses because of the sudden decline or withdrawal of progesterone (Mihalik, Ondrak, Guskiewicz, & McMurray, 2009; Wunderle, Hoeger, Wasserman, & Bazarian, 2013). Wunderle and colleagues found that females who had a concussion during their LP experienced more severe and prolonged somatic symptoms and reduced quality-of-life at one month post-injury compared with women who had a concussion during their FP and males (2013). Females may be more prone to other types of injury due to menstrual hormonal shifts. For example, studies have shown that females have more frequent anterior cruciate ligament injuries during the FP due to increased laxity of ligaments (Belanger, Burt, Callaghan, Clifton, & Gleberzon, 2013); it is unknown whether ligament laxity contributes to concussions in females. Another factor to consider in female athletes is that they may experience a disruption of their menstrual cycles possibly because of low body fat and energy imbalance from physical stress and caloric restriction (Nazem & Ackerman, 2012). More research is needed to determine whether females have increased risk of concussion or worse concussion outcomes if concussive injury occurs during particular phases of the menstrual cycle. However, concussion research on the menstrual cycle may have practical limitations because concussions are not predictable and menstrual cycles need to be monitored to obtain accurate hormone data in an individual, menstrual cycle duration varies by individual, female athletes may have irregular cycles as mentioned earlier, sex hormone tests are expensive, and a knowledgeable researcher on the menstrual cycle is needed to interpret the data.

The findings of this review were consistent with epidemiology studies demonstrating females have higher prevalence rates of PTH (D'Onofrio et al., 2014). PTH after concussions may encompass tension- and migraine-like symptoms. Mihalik and colleagues (2013) specifically studied post-traumatic migraine headaches, which was defined as PTH with nausea, phonophobia, or photophobia. As mentioned earlier, migraine headaches are a risk factor for prolonged concussion symptoms. Females in the general population have significantly higher rates of migraine headaches compared with males and experience a peak prevalence during their child-bearing years (Borsook et al., 2014). Females athletes have a five-fold greater risk of having a personal and/ or family history of migraine headaches compared with male athletes (Covassin, Elbin, Crutcher, & Burkhart, 2013). Some migraine headaches are hypothesized to be triggered by estrogen withdrawal during the menstrual cycle, between the end of the LP and during the first few days of the FP (Borsook et al., 2014; MacGregor, 2013). Thus, the fluctuation of sex hormones may provide a partial explanation as to the occurrence of migraine-type headaches in females after a concussion. More research is needed to elucidate the role of female hormones on pain perception, pain duration, and PTH.

In terms of neurocognition, the results of this review are consistent with previous research that determined that females consistently outperform males on verbal fluency and males outperform females on visual spatial tasks (Sundstrom Poromaa & Gingnell, 2014). There is some evidence that suggests when endogenous estrogen is high, females may perform better on verbal and visual memory tasks (Sundstrom Poromaa & Gingnell, 2014). A recent study that utilized functional Magnetic Resonance Imaging (fMRI)

demonstrated that concussed females had reduced activation of working memory brain regions compared with males (Hsu et al., 2015).

Anatomical differences may also contribute to higher risk of concussion and prolonged recovery in females. Females have comparatively a smaller head to neck ratio, weaker neck muscles, and greater angular head acceleration that may make them more vulnerable to concussions (Eckner, Oh, Joshi, Richardson, & Ashton-Miller, 2014). Additionally, one study (n=1) found that cerebral blood flow and regional brain glucose metabolism, which have been shown to be altered in rodents after a concussion (Giza & Difiori, 2011), differed in certain brain regions in healthy human adult males and females (n=400) (Hu et al., 2015). More research is needed to determine exactly whether and how these variations may explain sex differences in concussion symptom presentation.

Behavioral and psychosocial factors may also contribute to concussion gender differences. Females appraise pain differently than males and may have a heightened awareness of symptoms. In fact, research suggests that males primarily rely on internal body cues for pain perception; whereas females rely on internal and external cues (e.g., situations), which may lead to a more accurate appraisal of disease processes occurring in the body (Barsky et al., 2001). In addition, socialization may play a role in symptom expression. For example, females more readily seek health care and are generally more expressive of their symptoms compared with males, who may associate masculinity with stoicism (Barsky et al., 2001).

Male behavior may affect their concussion outcomes. Males may exhibit aggressive play behavior, which is mediated by testosterone and reinforced by social pressure. Aggressive play behavior may be associated with increased risk of concussion

(Diamond & Solomon, 2014). The Kontos (2011) study indicated that males headed the soccer ball more frequently than females and had worse baseline neurocognition. The studies on the effect of prior concussions on baseline scores indicated that male athletes who had multiple concussions were more symptomatic and had worse cognition than females with prior concussions. Covassin and colleagues (2010) suspected males in their study had significantly worse outcomes than females because they may have had more previous undiagnosed concussions than they had reported. Males may not have readily reported their concussion symptoms out of concern about the perception of their masculinity. Finally, as described earlier, females may cope better emotionally with concussive injuries compared with males; however, research is needed to determine whether better coping skills improve concussion outcomes. More concussion research is needed to evaluate gender differences with respect to play behavior, prior concussions, concussion reporting behavior, and coping styles.

Finally, on the subject of clinical and research bias, gender must be considered to ensure that appropriate, timely, efficient, and effective diagnosis and treatment is provided to concussion patients for optimal outcomes (National Institutes of Health, 2010). Studies have demonstrated that women with acute coronary syndrome (ACS) are not treated as aggressively as men (Tavris et al., 2010), perhaps, in part because women with ACS present with more vague symptoms (e.g., discomfort, back pain, fatigue, indigestion, etc.) (Canto, Canto, & Goldberg, 2014). Concussion symptoms are similarly subtle and the diagnosis of concussion can be missed depending on the presentation and reporting of symptoms. Barsky and colleagues (2001) astutely pointed out that “clinicians may be quicker to conclude that diffuse or nonspecific symptoms have no medical

explanation in women [are] more likely to ascribe such symptoms to psychosocial causes. This, in turn, could result in less vigorous attempts to ascertain a medical basis for the complaints, and less serious consideration of all possible medical etiologies” (p.270). Therefore, it is imperative to perform more gender research in concussions, particularly in light of the growing number of young female athletes at risk for concussion, to ensure that we have adequately researched all possible reasons for observed differences.

### **Limitations**

There were several limitations identified in this review. First, the initial review of abstracts for this systematic review may have eliminated some studies that may have met inclusion criteria because there was no mention of gender in the keywords or abstract. However, given the large number of publications available on brain injuries, it was not possible to review all of full-text articles (n = 1443) to examine study populations. Many studies had small sample sizes and may have lacked power to achieve statistical significance. Several studies had small effect sizes, which may suggest that while statistical significance may have been achieved, there was a lack of clinical significance. Some of the studies, particularly those evaluating prior symptoms and concussion history were subject to recall bias because clinical history was not or could not be verified. As discussed earlier, athletes may under-report their concussion symptoms, which may have led to reporting bias in some of the studies. Selection bias may have been a factor in concussion studies that had multiple exclusion criteria. Information bias may have been a problem in the studies that used retrospective medical chart reviews or databases because they may have had missing data and/ or records. In addition, some studies adjusted test scores for particular confounders (e.g., BMI) that other studies did not. Also,

computerized neurocognitive tests were utilized in most of the studies and are considered to be a screening for cognitive impairment requiring follow-up neurocognitive tests to more accurately assess neurocognitive deficiency. Hence, results from neurocognitive screening tests should be interpreted with caution. The timelines for symptoms and neurocognitive measurements after concussive injury varied or were not described in some studies, and would have been useful for the comparison of concussion recovery timelines. Finally, there were no control or placebo groups in the studies evaluating treatment of post-traumatic headaches.

### **Conclusion**

This review demonstrated that adolescent and young adult females may take longer to recover from concussions and require more treatment interventions compared with males. Based on this review of the literature, clinicians and researchers should be aware that concussed female adolescents and young adults may report more total concussion symptoms, headache complaints, worse cognition, and may require more therapeutic interventions than males. Future multi-disciplinary research is needed to help clinicians diagnose, treat, and predict recovery from concussions, particularly in populations at high risk for concussions and protracted recovery. This information will allow for an effective individualized approach to concussion management.

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Table 1-1

*Impact of Gender on Concussion Presentation: Concussion Risk/ Rates in Soccer*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Females Have Higher Concussion Risk/ Rates</b>					
Delaney et al. (2008)	To examine the effects of protective headgear on injuries in soccer athletes.	Retrospective Cohort  Headgear, no headgear  3.c	Mean Age: 15 ± 1.3  N= 133 conc soccer, 278 athletes  M: 64.7% F: 35.3%	Survey of self-reported concussion history	Female soccer players had higher conc risk (RR = 1.97, $p < .0001$ ) than males.
Gessel et al. (2007)	To examine the epidemiology of concussions in U.S. HS athletes over one school year.	Retrospective Cohort  None  3.e	Mean Age: HS  N= 396 conc all sports, 4431 injuries  M: NR F: NR	RIO	Female soccer players had higher conc rate (0.36 conc per 1000 AEs) than males (0.22 conc per 1000 AEs) (RR = 1.68, 95% CI [1.08- 2.60], $p = .03$ ).
Lincoln et al. (2011)	To examine the epidemiology of concussion in U.S. HS sports over 11 years.	Prospective Cohort  None  3.e	Mean Age: HS  N= 2651 conc all sports, 158,430 athletes  M:75% F: 25%	Injury surveillance database for a school district	Female soccer players had higher conc risk (RR=1.7, 95% CI [1.3- 2.2]) than males.
Marar et al. (2012)	To examine the epidemiology of concussion in 20 U.S.HS sports over 2 school years.	Retrospective Cohort  None  3.e	Mean Age: HS  N= 1936 conc all sports, 14,635 injuries  M: 41% F: 59%	RIO	Female soccer players had higher conc rate (3.4 per 10,000 AEs) than males (1.9) (RR = 1.8, 95% CI [1.4-2.3], $p < .001$ ).

Rosenthal et al. (2014)	To examine the epidemiology of concussion in U.S.HS sports over 2 school years.	Retrospective Cohort None 3.e	Mean Age: HS N= 4024 conc all sports M: 39% F: 61%	RIO	Female soccer players had higher conc rate (0.73 conc per 1000 AEs, 95% CI [0.60-0.89]) than males (0.41 conc per 1000 AEs, 95% CI [0.32- 0.52]).
<b>No Sex Differences in Concussion Risk/ Rates</b>					
Yard, Schroeder, Fields, Collins, and Comstock (2008)	To examine the epidemiology of soccer injuries in U.S.HS soccer over 2 school years.	Retrospective Cohort None 3.e	Mean Age: HS N= 1524 injuries M: 51% F: 49%	RIO	No sex difference in soccer conc rate (9.3% and 12.2%, respectively) (IPR = 1.31; 95% CI, 0.91-1.88).

*Note.* Abbreviations- Concussion (Conc), Male (M), Female (F), HS (High School), Not Reported (NR), Confidence Interval (CI), Athletic Exposures (AEs), Relative Risk (RR), Injury Proportion Ratio (IPR), High School Reporting Information Online (RIO); Level of Evidence- Joanna Briggs Inventory (2014)



Table 1-2

*Impact of Gender on Concussion Presentation: Concussion Risk/ Rates in Basketball*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Females Have Higher Concussion Risk/ Rates</b>					
Borowski et al. (2008)	To examine the epidemiology of injuries in U.S. HS basketball players over 2 school years.	Retrospective Cohort None 3.e	Mean Age: HS N= 106 conc M: NR F: NR	RIO	Female basketball players had higher proportion of conc (IPR= 2.41, 95% CI [1.49-3.91], $p < .01$ ) during competitions than males.
Gessel et al. (2007)	To examine the epidemiology of concussions in U.S. HS athletes over one school year.	Retrospective Cohort None 3.e	Mean Age: HS N= 396 conc all sports, 4431 injuries M: NR F: NR	RIO	Female basketball players had higher conc rate (0.21 conc per 1000 AEs) than males (0.07 conc per 1000 AEs) (RR = 2.93, 95% CI [1.64- 5.24], $p < .01$ ).
Lincoln et al. (2011)	To examine the epidemiology of concussion in U.S. HS sports over 11 years.	Prospective Cohort None 3.e	Mean Age: HS N= 2651 conc all sports, 158,430 athletes M: NR F: NR	Injury surveillance database for a school district	Female basketball players had higher conc risk (RR=2.1, 95% CI [1.6-2.6]) than males.
Marar et al. (2012)	To examine the epidemiology of concussion in 20 U.S.HS sports over 2 school years.	Retrospective Cohort None 3.e	Mean Age: HS N= 1936 conc all sports M: 41% F: 59%	RIO	Female basketball players had higher conc rate (2.1 per 10,000 AEs) than males (1.6) (RR = 1.3, 95% CI [1.03-1.8], $p < .03$ ).

Rechel et al. (2008)	To examine the epidemiology of concussion in U.S.HS sports injuries sustained in practice and competition over one school year.	Prospective Cohort None 3.e	Mean Age: HS N= 395 conc all sports M: NR F: NR	RIO	Female basketball players had a higher proportion of conc (PR = 5.83, 95% CI [2.06-16.49]) during competitions than males.
Rosenthal et al. (2014)	To examine the epidemiology of concussion in U.S.HS sports over 2 school years.	Retrospective Cohort None 3.e	Mean Age: HS N= 4024 conc all sports M: 39% F: 61%	RIO	Female basketball players had higher conc rate (0.37 conc per 1000 AEs, 95% CI [0.28- 0.47]) than males (0.24 conc per 1000 AEs, 95% CI [0.18-0.31]).

*Note.* Abbreviations- Concussion (Conc), Male (M), Female (F), HS (High School), Confidence Interval (CI), Athletic Exposures (AEs), Relative Risk (RR), Proportion Ratio (PR), Injury Proportion Ratio (IPR), High School Reporting Information Online (RIO); Level of Evidence- Joanna Briggs Inventory (2014)

Table 1-3

*Impact of Gender on Concussion Presentation: Concussion Risk/ Rates in Ice Hockey and Softball*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Females Have Higher Concussion Risk/ Rates</b>					
Agel and Harvey (2010)	To examine the epidemiology of ice hockey injuries in NCAA athletes over 7 years.	Retrospective Cohort  None  3.e	Mean Age: College  N= 454 conc, 2828 injuries  M: 78.7% F: 21.3%	NCAA ISS	Conc rate remained stable over 7 years and was higher in females (0.82/1000 AEs) than males (0.72/1000 AEs).
Marar et al. (2012)	To examine the epidemiology of concussion in 20 U.S.HS sports over 2 school years.	Retrospective Cohort  None  3.e	Mean Age: HS  N= 1936 conc all sports, 14,635 injuries  M: 41% F: 59%	RIO	Female softball players had higher conc rate (1.6 per 10,000) than male baseball players (0.5) (RR = 3.2, 95% CI [2.1-5.4], $p < .001$ ).

*Note.* Abbreviations- Concussion (Conc), Male (M), Female (F), HS (High School), Confidence Interval (CI), Athletic Exposures (AEs), Relative Risk (RR), High School Reporting Information Online (RIO), National Collegiate Athletic Association (NCAA), Injury Surveillance System (ISS); Level of Evidence- Joanna Briggs Inventory (2014)

Table 1-4

*Impact of Gender on Concussion Presentation: Concussion Risk/ Rates During Practice vs. Games*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Females Have Higher Concussion Risk/ Rates During Practice</b>					
Borowski et al. (2008)	To examine the epidemiology of injuries in U.S. HS basketball players over 2 school years.	Retrospective Cohort  None  3.e	Mean Age: HS  N= 106 conc  M: NR F: NR	RIO	Female athletes had 5% conc during practices and 14% conc during games vs. males with 3% conc during practices and 6% conc during games ( $p < .05$ ).
Covassin et al. (2003)	To examine the incidence of concussion in U.S. college athletes over 3 years.	Retrospective Cohort  None  3.e	Mean Age: College  N= 860 conc all sports  M: NR F: NR	NCAA ISS	Female athletes had 167 (3.6%) conc during practices and 304 (9.5%) conc during games vs. males with 148 (5.2%) conc during practices and 254 (6.4%) conc during games ( $p < .05$ ).

*Note.* Abbreviations- Concussion (Conc), Male (M), Female (F), Not Reported (NR), National Collegiate Athletic Association (NCAA), Injury Surveillance System (ISS); Level of Evidence- Joanna Briggs Inventory (2014)

Table 2-1

*Impact of Gender on Concussion Presentation: Baseline Total Symptom Scores (TSS)*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Females Have Higher Baseline TSS</b>					
Covassin, Elbin, Harris, et al. (2012)	To examine age and sex differences in neurocognitive performance, symptoms, and postural stability in concussed athletes	Prospective Cohort  Individual baseline scores  3.c	Mean Age HS males: 15.6 ± 1.19 Mean Age HS females: 15.43 ± 1.22 Mean Age College males: 19.52 ± 1.08 Mean Age College females: 18.94 ± 1.55  N= 296  M: 53% F: 47%	ImPACT	Females had higher baseline TSS ( $p \leq .05$ ) than males.
Leach et al. (2013)	To determine if history of prior concussion and sex influence baseline reported symptoms, headache symptoms, and quality-of-life in HS athletes	Cross-sectional  0, ≥1 prior concussions  4.b	Mean Age: 15.60 ± 1.6  N= 3298  M: 77.3% F: 22.7%	SCAT2	Females had higher baseline SCAT2 TSS scores ( $p < .001$ ) than males.

Register-Mihalik et al. (2009)	To determine the association between prior concussion history and symptoms during preseason baseline testing in male and female HS and college athletes	Cross-sectional 0, 1-2, $\geq 3$ prior concussions 4.b	Mean Age: $16.60 \pm 1.64$ N= 8930 M: NR F: NR	GSC	Females ( $p = .002$ , $d = .07$ ) had higher baseline TSS ( $2.09 \pm 2.90$ ) than males ( $1.88 \pm 2.81$ ).
Zuckerman et al. (2014)	To examine sex differences in number, severity, and resolution of symptoms in athletes with SRC	Retrospective Cohort Individual Baseline scores 3.c	Mean Age males: 16.1 Mean Age females: 16.1 N= 244 M: 50% F: 50%	ImPACT	Females had higher TSS ( $7.24 \pm 10.22$ vs. $4.10 \pm 6.52$ , $p = 0.005$ ) at baseline than males.
<b>No Sex Differences in Baseline TSS</b>					
Brooks et al. (2014)	To examine sex differences with respect to baseline symptoms and neurocognition in hockey athletes with prior concussions	Cross-sectional 0-3 prior concussions 4.b	Age range: 13-17 years old N= 615 M: 84% F: 16%	ImPACT	No sex differences on baseline TSS after adjusting for known sex differences in controls ( $F(2,230) = 0.77$ , $p = .46$ , $d = 0.01$ ).
Covassin et al. (2007)	To examine sex differences exist with respect to symptoms and neurocognitive performance in concussed college athletes.	Prospective Cohort Individual baseline scores 3.c	Mean Age: College N= 79 M: NR F: NR	ImPACT	No sex differences on baseline TSS ( $F(5,73) = 0.80$ , $p = 0.55$ ).

Covassin, Elbin, Larson, et al. (2012)	To evaluate depression and baseline neurocognitive performance and concussion symptoms in male and female HS and college athletes	Cross-sectional  Minimal, mild, moderate, severe depressive scores  4.b	Mean Age HS males: 15.9 ± 1.82 Mean Age HS females: 15.7 ± 1.1 Mean Age College males: 19.9 ± 1.7 Mean Age College females: 19.5 ± 1.6  N= 1616  M: 68% F: 32%	ImPACT  BDI-II	No sex differences on baseline TSS ( $F(1,1540) = 3.55, p = 0.06$ ) unadjusted for depression.
Kontos et al. (2012)	To examine depression, concussion symptoms, and neurocognitive performance in concussed HS and college athletes	Prospective Cohort  Individual baseline scores  3.c	Mean Age HS males: 15.9 ± 1.28 Mean Age HS females: 15.29 ± 1.2 Mean Age College males: 19.75 ± 1.05 Mean Age College females: 19.65 ± 1.65  N= 75  M: 68% F: 32%	ImPACT  BDI-II	No sex differences on baseline TSS or depression levels ( $p > .05$ ).

Zuckerman et al. (2012)	To evaluate neurocognitive and concussion symptoms in concussed male and female soccer players	Retrospective Cohort  Individual baseline scores  3.c	Mean Age males: 15.8 ± 1.88 Mean Age females: 15.9 ± 1.75  N= 80  M: 50% F: 50%	ImPACT	No sex differences on baseline TSS ( $p > .05$ ).
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*Note.* Abbreviations- Concussion (Conc), Male (M), Female (F), High School (HS), Total symptom score (TSS), Immediate Post-Concussion Assessment and Cognitive Test (IMPACT), Sport Concussion Assessment Tool 2 (SCAT2), Graded Symptom Checklist (GSC), Not Reported (NR); Level of Evidence- Joanna Briggs Inventory (2014)



Table 2-2

*Impact of Gender on Concussion Presentation: Baseline Symptom Type*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Baseline Symptom Type Differences by Gender</b>					
Covassin, Elbin, Larson, et al. (2012)	To evaluate depression and baseline neurocognitive performance and concussion symptoms in male and female HS and college athletes	Cross-sectional  Minimal, mild, moderate, severe depressive scores  4.b	Mean Age HS males: 15.9 ± 1.82 Mean Age HS females: 15.7 ± 1.1 Mean Age College males: 19.9 ± 1.7 Mean Age College females: 19.5 ± 1.6  N= 1616  M: 68% F: 32%	ImPACT  BDI-II	Females reported more cognitive ( $F(4,1544) = 4.94, p = 0.026, \eta^2 = 0.003$ ), emotional ( $F(4,1544) = 29.62, p = 0.001, \eta^2 = 0.019$ ), and sleep ( $F(4,1544) = 8.17, p = 0.004, \eta^2 = 0.005$ ) symptoms than males at baseline unadjusted for depression.
Leach et al. (2013)	To determine if history of prior concussion and sex influence baseline reported symptoms, headache symptoms, and quality-of-life in HS athletes	Cross-sectional  0, ≥1 prior concussions  4.b	Mean Age: 15.60 ± 1.6  N= 3298  M: 77.3% F: 22.7%	HIT-6	Females had higher baseline HIT-6 TSS scores than males ( $p < .001$ ).

Zuckerman et al. (2014)	To examine sex differences in number, severity, and resolution of symptoms in athletes with SRC	Retrospective Cohort Individual Baseline scores 3.c	Mean Age males: 16.1 Mean Age females: 16.1 N= 244 M: 50% F: 50%	ImPACT	Females reported having less sleep ( $0.88 \pm 1.49$ vs. $0.31 \pm 0.86$ , $p < 0.001$ ) than males at baseline.
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*Note.* Abbreviations- Concussion (Conc), Male (M), Female (F), High School (HS), Not Reported (NR), Immediate Post-Concussion Assessment and Cognitive Test (IMPACT), Headache Impact Test (HIT-6); Level of Evidence- Joanna Briggs Inventory (2014)

Table 2-3

*Impact of Gender on Concussion Presentation: Baseline Neurocognition Scores*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Sex Differences in Baseline Neurocognition</b>					
Covassin et al. (2010)	To evaluate the differences in baseline neurocognitive performance in college males and females with a history of multiple concussions	Retrospective Cohort  No, 1, 2, ≥3 prior concussions 3.c	Mean Age males: 18.35 Mean Age females: 18.29  N= 188  M: 53% F: 47%	ImPACT	Females did better on motor processing speed ( $F(1,179) = 4.85, p = .03$ ) and reaction time ( $F(1,179) = 4.26, p = .04$ ) than males at baseline.
Covassin, Elbin, Larson, et al. (2012)	To evaluate depression and baseline neurocognitive performance and concussion symptoms in male and female HS and college athletes	Cross-sectional  Minimal, mild, moderate, severe depressive scores  4.b	Mean Age HS males: $15.9 \pm 1.82$ Mean Age HS females: $15.7 \pm 1.1$ Mean Age College males: $19.9 \pm 1.7$ Mean Age College females: $19.5 \pm 1.6$  N= 1616  M: 68% F: 32%	ImPACT  BDI-II	Females did better on verbal memory ( $F(1,1544) = 12.16, p = 0.001, \eta^2 = 0.008$ ) and motor processing speed ( $F(1,1544) = 5.98, p = 0.015, \eta^2 = 0.004$ ) than males at baseline unadjusted for depression.

<b>No Sex Differences in Baseline Neurocognition</b>					
Brooks et al. (2014)	To examine sex differences with respect to baseline symptoms and neurocognition in hockey athletes with prior concussions	Cross-sectional 0-3 prior concussions 4.b	Age range: 13-17 years old N= 615 M: 84% F: 16%	ImPACT	No sex differences in baseline neurocognition ( $F(5,376) = 1.33, p=0.252$ ) in those without prior conc history.
Covassin et al. (2007)	To examine sex differences exist with respect to symptoms and neurocognitive performance in concussed college athletes.	Prospective Cohort Individual baseline scores 3.c	Mean Age: College N= 79 M: NR F: NR	ImPACT	No sex differences in baseline neurocognition ( $F(5,73) = 0.80, p = 0.55$ ).
Zuckerman et al. (2012)	To evaluate neurocognitive and concussion symptoms in concussed male and female soccer players	Retrospective Cohort Individual baseline scores 3.c	Mean Age males: $15.8 \pm 1.88$ Mean Age females: $15.9 \pm 1.75$ N= 80 M: 50% F: 50%	ImPACT	No sex differences in baseline verbal memory ( $t(78) = 1.02, p = 0.312$ ) and visual memory ( $t(78) = -1.71, p = 0.091$ ).

*Note.* Abbreviations- Concussion (Conc), Male (M), Female (F), High School (HS), Not Reported (NR), Immediate Post-Concussion Assessment and Cognitive Test (IMPACT); Level of Evidence- Joanna Briggs Inventory (2014)

Table 2-4

*Impact of Gender on Concussion Presentation: Baseline Modifiers*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Possible Modifier of Baseline Scores: Previous Concussions</b>					
Brooks et al. (2014)	To examine sex differences with respect to baseline symptoms and neurocognition in hockey athletes with prior concussions	Cross-sectional 0-3 prior concussions 4.b	Age range: 13-17 years old N= 615 M: 84% F: 16%	ImPACT	No sex differences in baseline neurocognition with prior conc history ( $F(5,227) = 1.40$ , $p = .227$ ).
Covassin et al. (2010)	To evaluate the differences in baseline neurocognitive performance in college males and females with a history of multiple concussions	Retrospective Cohort 0, 1, 2, $\geq 3$ prior concussions 3.c	Mean Age males: 18.35 Mean Age females: 18.29 N= 188 M: 53% F: 47%	ImPACT	Males with >1 conc did worse than females with >1 conc ( $t(3,46) = 4.59$ , $p = .001$ ) on verbal memory.  Males with >2 conc did worse than females with >2 conc on visual memory ( $p = .021$ ).
Leach et al. (2013)	To determine if history of prior concussion and sex influence baseline reported symptoms, headache symptoms, and quality-of-life in HS athletes	Cross-sectional 0, $\geq 1$ prior concussions 4.b	Mean Age: $15.60 \pm 1.6$ N= 3298 M: 77.3% F: 22.7%	SCAT2	Females with a prior concussion history reported higher TSS ( $18.3 \pm 18.5$ ) than ( $11.8 \pm 13.7$ ) females without prior concussions ( $10.2 \pm 13.5$ ) and males with ( $11.8 \pm 13.7$ ) or without ( $6.6 \pm 9.9$ ) prior concussion history ( $p = .014$ ).

<b>Possible Modifier of Baseline Scores: Play Behavior</b>					
Kontos, Dolese, Elbin, Covassin, and Warren (2011)	To examine the relationship between soccer heading and computerized neurocognitive performance and symptoms in non-concussed soccer players.	Cross-sectional  Low, moderate, high heading groups  4.b	Age range: 13-18 years old Mean Age: 15.89 ± 1.17  N= 63  M: 57% F: 43%	ImPACT	Males ( $M = 8.81$ , $SD = 7.42$ ) headed the ball more ( $t = 2.30$ , $p = 0.03$ ) than females ( $M = 3.83$ , $SD = 2.15$ ) and had lower verbal memory ( $p = 0.04$ ), visual memory ( $p = 0.02$ ), and motor processing speed ( $p = 0.01$ ) than females.

*Note.* Abbreviations- Concussion (Conc), Male (M), Female (F), High School (HS), Not Reported (NR), Immediate Post-Concussion Assessment and Cognitive Test (IMPACT); Level of Evidence- Joanna Briggs Inventory (2014)

Table 3-1

*Impact of Gender on Concussion Presentation: Post-Concussion Total Symptom Scores (TSS)*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Females Have Higher Post-Concussion TSS</b>					
Berz et al. (2013)	To examine sex differences with respect to symptoms and symptom recovery rate in athletes presenting to clinic at $\leq 7$ and $>7$ days from SRC	Retrospective Cohort  None  3.e	Age range: 11-17 years old Mean Age: $15 \pm 1.9$  N= 37  M: NR F: NR	Symptom severity scores rated 0 to 6 on 22-item self-report scale	Females had higher TSS at the initial evaluation whether at $\leq 7$ or $>7$ days post-conc than males ( $p < .05$ ).
Broshek et al. (2005)	To examine sex differences with respect to symptoms and neurocognition in HS and college athletes after SRC	Prospective Cohort  Individual baseline scores  3.c	Mean Age: $18.72 \pm 2.1$  N= 155  M: 75.5% F: 24.5%	CRI	Females had higher TSS than males ( $p < 05$ ) post-conc.

Covassin, Elbin, Harris, et al. (2012)	To examine age and sex differences in neurocognitive performance, symptoms, and postural stability in concussed athletes	Prospective Cohort  Individual baseline scores  3.c	Mean Age HS males: 15.6 ± 1.19 Mean Age HS females: 15.43 ± 1.22 Mean Age College males: 19.52 ± 1.08 Mean Age College females: 18.94 ± 1.55  N= 296  M: 53% F: 47%	ImPACT	Females had higher TSS after a conc than males ( $F(1,118) = 4.525, p = .035, \eta^2 = .037$ ).
Covassin, Elbin, Bleecker, et al. (2013)	To evaluate the differences in neurocognitive performance and symptoms in concussed male and female soccer players	Prospective Cohort  Individual baseline scores  3.c	Mean Age males: 17.69 ± 2.1 Mean Age females: 17.78 ± 2.3  N= 95  M: 41% F: 59%	ImPACT	Females had higher TSS ( $F(1,82) = 9.12, p = .003$ ) than males 8 days post-conc after adjusting for BMI.
Zuckerman et al. (2014)	To examine sex differences in number, severity, and resolution of symptoms in athletes with SRC	Retrospective Cohort  Individual Baseline scores  3.c	Mean Age males: 16.1 Mean Age females: 16.1  N= 244  M: 50% F: 50%	ImPACT	Females had higher TSS scores (21.38 ± 19.02 vs 16.80 ± 17.07, $p = 0.049$ ) post-conc.



<b>No Sex Differences in Post-Concussion TSS</b>					
Frommer et al. (2011)	To compare symptoms type and resolution time between males and females with SRC over 2 school years.	Cross-sectional  None  4.b	Mean Age males: 16 ± 1.2 Mean Age females: 15.8 ± 1.2  N= 812  M: 75% F: 25%	RIO	No sex differences on TSS ( $p = .49$ ) post-conc.
Preiss-Farzanegan et al. (2009)	To evaluate the relationship between gender, age and concussion symptoms at 3 months after SRC	Prospective Nested Cohort  None  3.e	Mean Age males: 13.1 ± 2.7 Mean Age females: 13.1 ± 3.0  N= 137  M: 71% F: 21%	RPQ	No sex differences on TSS ( $OR = 0.87$ , 95% CI [0.45-1.71], $p = .695$ ) post-conc, even after adjustment for confounders of self vs. proxy report, previous LOC or ED visit for head injury, or sport type
Kontos et al. (2012)	To examine depression, conc symptoms, and neurocognitive performance in concussed HS and college athletes	Prospective Cohort  Individual baseline scores  3.c	Mean Age HS males: 15.9 ± 1.28 Mean Age HS females: 15.29 ± 1.2 Mean Age College males: 19.75 ± 1.05 Mean Age College females: 19.65 ± 1.65  N= 75  M: 68% F: 32%	ImPACT  BDI-II	No sex differences on TSS or depression levels ( $p > .05$ ) post-conc.

Zuckerman et al. (2012)	To evaluate neurocognitive and concussion symptoms in concussed male and female soccer players	Retrospective Cohort  Individual baseline scores  3.c	Mean Age males: 15.8 ± 1.88 Mean Age females: 15.9 ± 1.75  N= 80  M: 50% F: 50%	ImPACT	No sex differences on TSS ( $p > .05$ ) post-conc.
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*Note.* Abbreviations- Concussion (Conc), Sport-related concussion (SRC), Male (M), Female (F), High School (HS), Not Reported (NR), Total Symptom Scores (TSS), Immediate Post-Concussion Assessment and Cognitive Test (IMPACT), Rivermead Post Concussion Symptoms Questionnaire (RPQ), Reporting Information Online (RIO) database, Emergency Department (ED), Loss of Consciousness (LOC); Level of Evidence- Joanna Briggs Inventory (2014)

Table 3-2

*Impact of Gender on Concussion Presentation: Post-Concussion Symptom Type*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Post-Concussion Symptom Type Differences by Gender</b>					
Bramley et al. (2015)	To evaluate treatment effectiveness of amitriptyline for PTH in concussion patients	Retrospective Cohort  None  3.e	Age range: 13-18 years old  N= 400  M: 62% F: 38%	Medical chart review	Females were more likely to report PTH (90% vs.79%, $p = 0.004$ ) than males.
Covassin et al. (2007)	To examine sex differences exist with respect to symptoms and neurocognitive performance in concussed college athletes.	Prospective Cohort  Individual baseline scores  3.c	Mean Age: College  N= 79  M: NR F: NR	ImPACT	Males reported higher scores on vomiting ( $F(1,77) = 5.95, p = 0.017$ ) and sadness ( $F(1,77) = 13.05, p = 0.001$ ) than females after conc.
Covassin, Elbin, Bleecker, et al. (2013)	To evaluate the differences in neurocognitive performance and symptoms in concussed male and female soccer players	Prospective Cohort  Individual baseline scores  3.c	Mean Age males: $17.69 \pm 2.1$ Mean Age females: $17.78 \pm 2.3$  N= 95  M: 41% F: 59%	ImPACT	Females had worse migraine, cognitive, fatigue symptoms ( $F(1,82) = 10.8, p = .001$ ) and sleep symptoms ( $F(1,82) = 9.2, p = .003$ ) than males 8 days post-conc after adjusting for BMI.

Frommer et al. (2011)	To compare symptoms type and resolution time between males and females with SRC over 2 school years.	Cross-sectional None 4.b	Mean Age males: 16 ± 1.2 Mean Age females: 15.8 ± 1.2  N= 812  M: 75% F: 25%	RIO	<p>Headache was most common symptom (40% [n = 113] in males, 44% [n = 48] in females); no sex difference (<math>p = 5.49</math>).</p> <p>In years 1 and 2, males reported amnesia (<math>p = .03</math> and <math>p = .001</math>, respectively) and confusion/disorientation (<math>p = .04</math> and <math>p = .002</math>, respectively) more than females.</p> <p>In year 2, females reported drowsiness (<math>p = .02</math> and <math>p = .001</math>, respectively) and sensitivity to noise (<math>p = .03</math> and <math>p = .002</math>, respectively) more than males.</p>
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Mihalik et al. (2013)	To compare postural stability, neurocognitive performance, and symptom recovery in concussed athletes with PTH, PTM, and no headache following SRC	Prospective Cohort  Individual baseline scores; No headache, PTH, PTM  3.c	Mean Age: 16.7 ± 1.9  N= 296  M: 81% F: 19%	GSC	Concussed females were 2.13 times more likely than males to report PTM symptoms by day 7 (95% CI [1.29-3.51]) despite similar reporting of headache at baseline.
<b>Post-Concussion Symptom Type Differences by Gender: Postural Instability</b>					
Covassin, Elbin, Harris, et al. (2012)	To examine age and sex differences in neurocognitive performance, symptoms, and postural stability in concussed athletes	Prospective Cohort  None  3.c	Mean Age HS males: 15.6 ± 1.19 Mean Age HS females: 15.43 ± 1.22 Mean Age College males: 19.52 ± 1.08 Mean Age College females: 18.94 ± 1.55  N= 296  M: 53% F: 47%	BESS	HS males performed slightly worse than HS females on the BESS (mean, 18.8 and 13.0, respectively, $p = .001$ ) after conc.  College females performed worse on the BESS than college males (mean, 21.1 and 16.9, respectively, $p = .001$ ) after conc.

*Note.* Abbreviations- Concussion (Conc), Sport-related concussion (SRC), Male (M), Female (F), Not Reported (NR), High School (HS), Immediate Post-Concussion Assessment and Cognitive Test (IMPACT), Graded Symptom Checklist (GSC), Balance Error Scoring System (BESS), Post-traumatic headache (PTH), Post-traumatic migraine (PTM), Confidence Interval (CI); Level of Evidence: Joanna Briggs Inventory (2014)

Table 3-3

*Impact of Gender on Concussion Presentation: Post-Concussion Symptom Duration*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Females Have Longer Duration of Post-Concussion Symptoms</b>					
Bramley et al. (2015)	To evaluate treatment effectiveness of amitriptyline for PTH in concussion patients	Retrospective Cohort  None  3.e	Age range: 13-18 years old  N= 400  M: 62% F: 38%	Medical chart review	Females had a longer recovery time (median 80 days vs. 34 days, $p < .001$ ) than males.
Kostyun and Hafeez (2015)	To determine recovery time and treatment interventions in concussed athletes treated at a concussion clinic	Retrospective Cohort  None  3.e	Mean Age males: 14.9 $\pm$ 3.4 Mean Age females: 14.3 $\pm$ 2.3  N= 266  M: 62% F: 38%	Medical chart review	Females had longer conc recovery times than males (75.6 $\pm$ 73.0 and 49.7 $\pm$ 62.0 days, respectively, $p = 0.002$ ); 41.2% of females vs. 20.7% of males took >60 days to recover.
Zuckerman et al. (2014)	To examine sex differences in number, severity, and resolution of symptoms in athletes with SRC	Retrospective Cohort  Individual Baseline scores  3.c	Mean Age males: 16.1 Mean Age females: 16.1  N= 244  M: 50% F: 50%	ImPACT	Females took slightly longer than males (9.1 $\pm$ 7.1 days vs 7.0 $\pm$ 5.1 days, $p = 0.013$ ) to return to baseline symptom levels.

<b>No Sex Differences in Duration of Post-Concussion Symptoms</b>					
Frommer et al. (2011)	To compare symptoms type and resolution time between males and females with SRC over 2 school years.	Cross-sectional None 4.b	Mean Age males: 16 ± 1.2 Mean Age females: 15.8 ± 1.2 N= 812 M: 75% F: 25%	RIO	Symptom resolution time and return-to-play time was similar in both sexes of up to 3 days (HR = 1.07; 95% CI (0.91-1.27)).

*Note.* Abbreviations- Concussion (Conc), Sports-related concussion (SRC), Male (M), Post-traumatic headache (PTH), Female (F), Not Reported (NR), Immediate Post-Concussion Assessment and Cognitive Test (IMPACT), Reporting Information Online (RIO) database; Level of Evidence- Joanna Briggs Inventory (2014)

Table 3-4

*Impact of Gender on Concussion Presentation: Post-Concussion Neurocognition Scores*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Sex Differences in Post-Concussion Neurocognition</b>					
Broshek et al. (2005)	To examine sex differences with respect to symptoms and neurocognition in HS and college athletes after SRC	Prospective Cohort  Individual baseline scores  3.c	Mean Age: 18.72 ± 2.1  N= 155  M: 75.5% F: 24.5%	CRI	Females were 1.7 times more likely to have worse neurocognition than males even after adjusting for the use of helmets ( $p < .05$ ) post-conc.  Females had worse declines in simple (visual cue) and complex (decision-making) reaction times than their preseason baseline levels ( $p < .05$ ).



Covassin, Elbin, Bleecker, et al. (2013)	To evaluate the differences in neurocognitive performance and symptoms in concussed male and female soccer players	Prospective Cohort  Individual baseline scores  3.c	Mean Age males: 17.69 ± 2.1 Mean Age females: 17.78 ± 2.3  N= 95  M: 41% F: 59%	ImPACT	Females had worse mean neurocognitive, verbal memory ( $F(1,82) = 5.98; p = .017$ ) and visual memory ( $F(1,82) = 4.65; p = .034$ ) scores than males at baseline and 8 days post-conc after adjusting for BMI.
Covassin et al. (2007)	To examine sex differences exist with respect to symptoms and neurocognitive performance in concussed college athletes.	Prospective Cohort  Individual baseline scores  3.c	Mean Age: College  N= 79  M: NR F: NR	ImPACT	Females performed worse than males on visual memory ( $F(1,77) = 11.26; p = 0.001$ ) 3 days after conc.
Covassin, Elbin, Harris, et al. (2012)	To examine age and sex differences in neurocognitive performance, symptoms, and postural stability in concussed athletes	Prospective Cohort  Individual baseline scores  3.c	Mean Age HS males: 15.6 ± 1.19 Mean Age HS females: 15.43 ± 1.22 Mean Age College males: 19.52 ± 1.08 Mean Age College females: 18.94 ± 1.55  N= 296  M: 53% F: 47%	ImPACT	Females performed worse than males on visual memory ( $F(1,118) = 3.95, p = .049, \eta^2 = .032$ ).

<b>No Sex Differences in Post-Concussion Neurocognition</b>					
Kontos et al. (2012)	To examine depression, conc symptoms, and neurocognitive performance in concussed HS and college athletes	Prospective Cohort  Individual baseline scores  3.c	Mean Age HS males: 15.9 ± 1.28 Mean Age HS females: 15.29 ± 1.2 Mean Age College males: 19.75 ± 1.05 Mean Age College females: 19.65 ± 1.65  N= 75  M: 68% F: 32%	ImPACT  BDI-II	No sex differences on neurocognition ( $p > .05$ ) post-conc.
Zuckerman et al. (2012)	To evaluate neurocognitive and concussion symptoms in concussed male and female soccer players	Retrospective Cohort  Individual baseline scores  3.c	Mean Age males: 15.8 ± 1.88 Mean Age females: 15.9 ± 1.75  N= 80  M: 50% F: 50%	ImPACT	No sex differences on verbal memory ( $t(78) = -0.46, p = 0.671$ ) or visual memory ( $t(78) = -0.50, p = 0.619$ ) after conc.

*Note.* Abbreviations- Concussion (Conc), Sport-related concussion (SRC), Male (M), Female (F), Not Reported (NR), High School (HS), Immediate Post-Concussion Assessment and Cognitive Test (IMPACT), The Concussion Resolution Index (CRI); Level of Evidence: Joanna Briggs Inventory (2014)

Table 4

*Impact of Gender on Concussion Management*

Reference	Study Purpose	Design, Controls, Level of Evidence	Sample	Outcome measures	Key Findings
<b>Overall Management</b>					
Kostyun and Hafeez (2015)	To determine recovery time and treatment interventions in concussed athletes treated at a concussion clinic	Retrospective Cohort None 3.e	Mean Age males: 14.9 ± 3.4 Mean Age females: 14.3 ± 2.3  N= 266  M: 62% F: 38%	Medical chart review	Females were 7 times more likely to be prescribed rest ( <i>OR</i> = 7.11, 95% CI [2.13, 6.21, <i>p</i> < .001), 3 times more likely to be prescribed academic accommodations ( <i>OR</i> = 3.63, 95% CI [2.71, 18.6, <i>p</i> < .001), 8 times more likely to be prescribed vestibular therapy ( <i>OR</i> = 8.23, 95% CI [3.7, 18.1, <i>p</i> < .001), and 4 times more likely to be prescribed medication ( <i>OR</i> = 4.23, 95% CI [1.91, 9.37, <i>p</i> < .001) than males after conc.

<b>Headache Management</b>					
Bramley et al. (2015)	To evaluate treatment effectiveness of amitriptyline for PTH in concussion patients	Retrospective Cohort  None  3.e	Age range: 13-18 years old  N= 400  M: 62% F: 38%	Medical chart review	Females were more likely to be prescribed amitriptyline (10-100mg) PTH (24% vs.13%, $p = 0.004$ ) than males.
Chan et al. (2015)	To evaluate IV migraine treatment for PTH in the ED in concussion patients	Cross-sectional  None  4.b	Mean Age: 13.8 years old  N= 254  M: 49% F: 51%	NRS	Similar improvements in PTH by sex.
<b>Coping Strategies</b>					
Kontos, Elbin, Newcomer Appaneal, Covassin, and Collins (2013)	To compare the coping responses between males and females with concussion, orthopedic injuries and controls	Cross-sectional  Orthopedic injury and Healthy controls  4.b	Mean Age: 19.51 ± 2.35  N= 123  M: 60% F: 40%	COPE	Injured females used multiple coping mechanisms including self-distraction ( $F \{1, 1 = 4.26, p = .04, \eta^2 = .04$ ), active coping ( $F (1, 121) = 4.46, p = .04, \eta^2 = .04$ ), instrumental support ( $F (1, 121) = 6.11, p = .02, \eta^2 = .05$ ), humor ( $F (1,121) = 3.82, p = .05, \eta^2 = .03$ ), and self-blame ( $F (1, 121) = 4.99, p = .03, \eta^2 = .04$ ) than males.

*Note.* Abbreviations- Concussion (Conc), Male (M), Female (F), Post-traumatic headache (PTH), Intravenous (IV), Emergency Department (ED), Numeric Pain Rating Scale (NRS), Brief COPE Inventory (COPE), Odds Ratio (OR), Confidence Interval (CI) ; Level of Evidence: Joanna Briggs Inventory (2014)

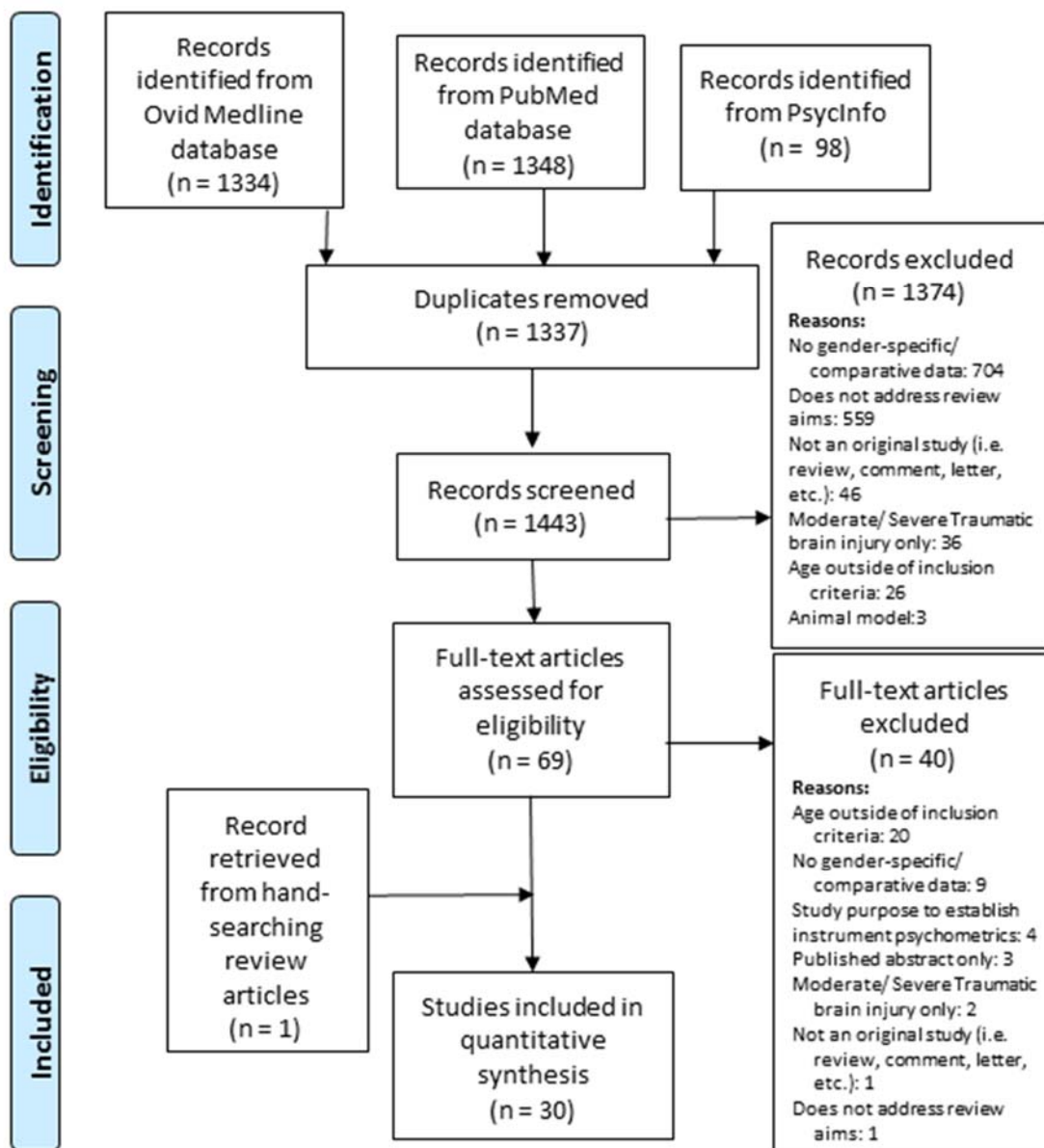


Figure 1. Flowchart of article selection

Appendix A  
Search Strategies and Result

## Ovid Medline search strategy

1	brain concussion/ or post-concussion syndrome/
2	(concussion* or concussive or concussed or mild traumatic brain injur* or mild tbi or mtbi).ti,ab,kw.
3	1 or 2
4	Women/
5	females/
6	(women or girls or female*).ti,ab,kw.
7	sex characteristics/
8	(sex differences or gender differences or sex characteristics or gender characteristics).ti,ab,kw.
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
12	Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
13	Cross-Sectional Studies/ or cross-sectional.ti,ab. or ("prevalence study" or "incidence study" or "prevalence studies" or "incidence studies" or "transversal studies" or "transversal study").ti,ab.
14	odds ratio/ or logistic models/ or regression analysis/
15	Epidemiologic Studies/
16	(ANOVA or epidemiolog* or meta-regression or odds ratio or regression analysis).ti,ab,kw. or ((objective* adj3 study) or (current study)).ab.
17	11 or 12 or 13 or 14 or 15 or 16
18	10 and 17
19	limit 18 to english language
20	limit 19 to yr="2002 - 2015"

## PubMed search strategy

1	brain concussion[mesh:noexp] OR post-concussion syndrome[mesh:noexp]
2	(concussion*[tiab] OR concussive[tiab] OR concussed[tiab] OR mild traumatic brain injur*[tiab] OR mild tbi[tiab] OR mtbi[tiab])
3	#1 OR #2
4	Women[mesh:noexp]
5	females[mesh:noexp]
6	(women[tiab] OR girls[tiab] OR female*[tiab])
7	sex characteristics[mesh:noexp]
8	(sex differences[tiab] OR gender differences[tiab] OR sex characteristics[tiab] OR gender characteristics[tiab])
9	#4 OR #5 OR #6 OR #7 OR #8
10	#3 AND #9
11	cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]
12	"Case-Control Studies"[Mesh:noexp] OR "retrospective studies"[mesh:noexp] OR "Control Groups"[Mesh:noexp] OR (case[TIAB] AND control[TIAB]) OR (cases[TIAB] AND controls[TIAB]) OR (cases[TIAB] AND controlled[TIAB]) OR (case[TIAB] AND comparison*[TIAB]) OR (cases[TIAB] AND comparison*[TIAB]) OR "control group"[TIAB] OR "control groups"[TIAB]
13	Cross-Sectional Studies[Mesh:noexp] OR "cross-sectional"[TIAB] OR "prevalence study"[tiab] OR "prevalence studies"[tiab] OR "incidence study"[TIAB] OR "incidence studies"[TIAB] OR "transversal study"[tiab] OR "transversal studies"[tiab]
14	odds ratio[mesh:noexp] OR logistic models[mesh:noexp] OR regression analysis[mesh:noexp]
15	Epidemiologic Studies[mesh:noexp]
16	(ANOVA[tiab] OR epidemiolog*[tiab] OR meta-regression[tiab] OR odds ratio[tiab] OR regression analysis[tiab] OR (objective[tiab] AND study[tiab]) OR (objectives[tiab] AND study[tiab]) OR "current study"[tiab])
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16
18	#10 AND #17
19	#18 AND english[la]
20	#19 AND 2002:2015[dp]



## PsycINFO search strategy

1	brain concussion/
2	(concussion* or concussive or concussed or mild traumatic brain injur* or mild tbi or mtbi).ti,ab,id.
3	1 or 2
4	human females/
5	(women or girls or female*).ti,ab,id.
6	(sex differences or gender differences or sex characteristics or gender characteristics).ti,ab,id.
7	Human Sex Differences/
8	4 or 5 or 6 or 7
9	3 and 8
10	(9 and human.po.) or (9 not animal.po.)
11	limit 10 to (all journals and yr="2002 - 2015")

March, 2016

Jeffrey S. Kreutzer and Nathan D. Zasler  
Editors-in-Chief  
*Brain Injury*

Dear Drs. Kreutzer and Zasler:

I am writing to submit our manuscript entitled “Framework of Concussive Vulnerability” for consideration for publication in *Brain Injury*. This manuscript represents the formation of a concept related to the occurrence and potential short-term and long-term neurologic effects of concussion. There is no current concussion model that comprehensively examines the concept of concussion with respect to post-concussive vulnerability and cumulative neurologic damage. The Concussive Vulnerability model can be used as an algorithm for concussions by clinicians. We believe that this manuscript is appropriate for publication in your journal because it comprehensively describes mild traumatic brain injuries in the adolescent and adult populations.

We appreciate your consideration of our manuscript for review. We look forward to your response. Please feel free to contact me at [Seema.S.Aggarwal@uth.tmc.edu](mailto:Seema.S.Aggarwal@uth.tmc.edu).

Sincerely,

Seema Aggarwal, PhD(c), RN, NP-C

**Manuscript C**

**Framework of Concussive Vulnerability**

## Framework of Concussive Vulnerability

### **Abstract**

**PURPOSE:** To describe a conceptual model that will guide studies on mild traumatic brain injuries (mTBIs) or concussions. **ORGANIZING FRAMEWORK:** The conceptual framework of concussive vulnerability is based on theoretical and empirical literature about (a) the pathophysiology of concussion (b) current concussion guidelines, and (c) methods of prevention, early diagnosis, and primary treatment modalities for concussion. Key concepts of this framework are: concussive vulnerability, protection, symptom reporting, biomarkers/ imaging methods, and rest as a primary treatment method. The main outcome of concussions is short and long-term neurologic deficits which influence loss of functional status and quality of life. **CONCLUSIONS:** The conceptual model described in this paper is a framework for understanding the mechanism of concussion injury, diagnosis, and treatment. The model may be useful to provide a more comprehensive foundation for concussion research.

**Key words:** concussion, sports, head injury, head trauma, traumatic brain injury, mild traumatic brain injury, concept, model, framework, algorithm, return-to-play, athletes, second impact syndrome, post-concussion syndrome, post-concussive vulnerability

**Clinical Relevance:** The Concussive Vulnerability Framework offers an organizational model for the pathophysiology, prevention, diagnosis, and treatment of concussions

## **Background and Purpose**

There are an estimated 1.4 to 3.8 million Traumatic Brain Injuries (TBIs) that occur in children and adults annually, of which 75 to 90% are concussions or mild Traumatic Brain Injuries (mTBIs) (Centers for Disease Control, n.d.). U.S. and global mild traumatic brain injury (mTBI) incidence rates are estimated at 600 per 100,000 individuals (Cancelliere et al., 2012). Sports-related concussions (SRCs) among high-school, college, and professional athletes have gained recent national and international attention due to concerns over potential long-term detrimental neurologic effects. Thirty percent of all concussions that occur in U.S. children and adolescents ages 5 to 19 years are classified as SRCs (Harmon et al., 2013). These estimates include under-reported and unrecognized concussions (Langlois, Rutland-Brown, & Wald, 2006). Other common causes of mTBI include falls, motor vehicle accidents, and traumatic blows (Centers for Disease Control, n.d.).

Studies have shown undiagnosed or untreated concussions can lead to Post-Concussion Syndrome (PCS), a syndrome of prolonged concussive symptoms, or rarely Second-Impact Syndrome (SIS), severe or fatal brain damage incurred from a second impact immediately after sustaining an initial concussion (Blume & Hawash, 2012; Weinstein, Turner, Kuzma, & Feuer, 2013). Athletes who sustain multiple concussions may develop long-term brain damage including cognitive decline, depression, and associated white matter abnormalities (Guskiewicz et al., 2005; Hart et al., 2013). Repetitive brain trauma may be associated with Chronic Traumatic Encephalopathy (CTE), a rare neuro-degenerative brain condition that was discovered in the post-mortem

brains of athletes who played certain sports such as American football, ice hockey, and boxing (Yi, Padalino, Chin, Montenegro, & Cantu, 2013). However, it remains unknown whether neuro-degenerative diseases such as CTE or Alzheimer disease (AD) are linked to multiple concussions (Guskiewicz et al., 2005).

### **Definition of Concussive Vulnerability**

Concussion is defined as a functional and not structural injury to the brain caused by a traumatic blow, jolt, or transmitted force to the brain resulting in a set of symptoms including physical effects (i.e. persistent headaches), cognitive changes, emotional difficulties, and sleep pattern alterations (Centers for Disease Control, n.d.; McCrory et al., 2013). The notion of vulnerability as it applies to the risk and potential consequences of concussive injury is prevalent in concussion literature. There are four different ways vulnerability is referred to in the literature: the easy disruption of the neuroplasticity of the pediatric brain (Choe, Babikian, DiFiori, Hovda, & Giza, 2012), the vulnerability of the postconcussive brain to additional insult and damage (Borich et al., 2013; Giza & DiFiori, 2011), the vulnerability of particular regions of the brain to injury (Umile, Sandel, Alavi, Terry, & Plotkin, 2002; Zhang, Red, Lin, Patel, & Sereno, 2013), and the vulnerability caused by multiple concussions to long-term neurologic damage (i.e. depression and decreased cognition) (Didehbani, Munro Cullum, Mansinghani, Conover, & Hart, 2013; Kerr, Marshall, Harding, & Guskiewicz, 2012).

To date, concussion damage cannot be detected by standard imaging evidence such as Computed Tomography (CT) scans or Magnetic Resonance Imaging (MRI). Therefore, concussions were not thought to cause actual brain damage or have any neurological sequelae. However, there is mounting evidence utilizing protein biomarkers

and new imaging techniques that demonstrate concussive injury at the cellular and micro-structural levels (Jeter et al., 2013).

Based on these definitions of concussion and vulnerability in literature, the concept of *concussive vulnerability* was generated. Hence, a comprehensive definition of concussive vulnerability that reflects this new evidence of brain damage from concussions is *the propensity of an individual to sustain a brain injury caused by biomechanical forces that culminates in a pattern of symptoms due to microstructural and cellular damage that may result in long-term neurologic impairment* (Prins, Alexander, Giza, & Hovda, 2013; Shenton et al., 2012; Umile et al., 2002).

### **Key Concepts of Concussive Vulnerability**

Within the framework of concussive vulnerability, there are four key sets of relationships. The relationships that will be described are between concussive vulnerability and protection, symptom reporting, biomarkers/ imaging methods, and treatment. The term, vulnerability, is not explicitly stated in these relationships, but is an implicit component of concussions in the current literature for reasons described earlier. The concept of protection will be evaluated in terms of the prevention of concussion utilizing protective equipment. The concepts of symptom reporting and biomarkers/ imaging methods will be discussed as methods of concussion diagnosis. Finally, the notion of rest will be addressed as the cornerstone treatment for concussion. The majority of evidence provided in this paper are related to SRCs due to the limited availability of data with respect to other forms of concussive injury.

## Relationship of Concepts

### Concussive Vulnerability and Protection

It is hypothesized that protection in the form of protective equipment may reduce concussive vulnerability. However, there is mixed evidence with regard to their effectiveness against concussion. Personal protective equipment (PPE) such as head protection (i.e. helmets and headgear) (Athiviraham et al., 2012; Duhaime et al., 2012; Forbes, Awad, Zuckerman, Carr, & Cheng, 2012; McIntosh et al., 2011), mouth guards (Trojian & Mohamed, 2012), and eye guards (Kriz et al., 2012) have not been shown to prevent concussions. Present-day helmets do not prevent rotational injury to the brain which is thought to cause shear injury to the axons resulting in a concussion (Cantu, 1996). However, helmets have been shown to reduce the incidence of more severe head injuries including intracranial hemorrhage and skull fractures (Bambach, Mitchell, Grzebieta, & Olivier, 2013). Helmet Impact Telemetry System (HITS) technology is currently being utilized in studies to ascertain magnitude, direction, and head impact location associated with concussion and may yield potential forms of effective PPE against concussions. (Duhaime et al., 2012; Forbes et al., 2012).

Environmental hazard protection measures such as natural and synthetic playing surfaces are inconclusive in regards to concussion protection (Wright & Webner, 2010). More studies are needed to determine if altering flooring or play surfaces can reduce the risk concussions. Future studies should evaluate other forms of environmental protection (i.e. grab bars or lighting) to reduce the risk of concussions from other common mechanisms of injury including falls, particularly among the elderly (Papa, Mendes, & Braga, 2012).



### **Concussive Vulnerability and Symptom Reporting**

Early diagnosis and treatment reduce concussive vulnerability and associated sequelae. When concussed individuals do not report their symptoms, it delays timely diagnosis and treatment which are crucial for concussion recovery and prevention of long-term sequelae such as PCS, SIS, cognitive and behavioral changes (Guskiewicz et al., 2003; Hart et al., 2013; Kerr et al., 2012). Approximately half of all SRCs are under-reported by athletes (Harmon et al., 2013). Several studies have evaluated reasons for athletes not reporting their concussive symptoms. These studies have found that athletes under-report concussions most commonly for reasons such as fear of being removed from play (Chrisman, Quitiquit, & Rivara, 2013; Llewellyn, Burdette, Joyner, & Buckley, 2013; McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004), not recognizing concussion symptoms (Fraas, Coughlan, Hart, & McCarthy, 2013; McCrea et al., 2004), not letting down team-mates (McCrea et al., 2004; Register-Mihalik et al., 2013) or coaches (Chrisman et al., 2013; Register-Mihalik et al., 2013), and minimizing the gravity of having concussion symptoms (Llewellyn et al., 2013) despite sustaining previous concussions (McCrea et al., 2004).

Based on this evidence, current research is being conducted on the effectiveness of concussion education on self-reporting behaviors (Bramley, Patrick, Lehman, & Silvis, 2012). The potential consequences of concussive vulnerability have resulted in SRC laws and sporting guidelines to protect players by requiring diagnostic evaluation by a medical professional if a concussion is suspected (Adler & Herring, 2011). More research is necessary to ascertain the impact of SRC regulations on concussion-reporting behaviors.

## **Concussive Vulnerability and Biomarkers/ Imaging Methods**

Potential methods of concussion diagnosis that may reduce concussive vulnerability in the near future include the detection of neural biomarkers and novel imaging techniques. Several recent studies have focused on the protein biomarker, S100 $\beta$ , which may be specific for concussion injuries particularly if extracted from cerebral spinal fluid (Jeter et al., 2013). Serum biomarkers ubiquitin C-terminal hydrolase-L1, glial fibrillary acidic protein, were shown to correlate with worse cognitive performance in concussed military personnel during a blast training exercise (Tate et al., 2013). Diffusion Tensor Imaging (DTI) is a highly researched imaging technology that has revealed white matter changes in both concussions and asymptomatic subconcussive brain injuries (Bazarian, Zhu, Blyth, Borrino, & Zhong, 2012; Gardner et al., 2012; Shenton et al., 2012). The use of Proton Magnetic Resonance Spectroscopy (MRS) has demonstrated that subconcussive abnormalities may last for months after a concussion (Gardner, Iverson, & Stanwell, 2013). Functional MRI (fMRI) studies have shown an overall loss of brain connectivity particularly in patients who have experienced multiple concussions or subconcussive injuries (Johnson et al., 2012). Finally, Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) imaging evidence has demonstrated post-concussive anomalies in the temporal or frontal lobes (Umile et al., 2002). More high quality research is needed to determine the diagnostic and prognostic capabilities of these biomarkers and imaging methods. Larger sample sizes, randomized control trials, blinding, and standardized techniques will enhance generalizability of these studies. These biomarkers and imaging methods may prove to be useful diagnostic tools for the early detection of concussions.

## **Concussive Vulnerability and Treatment**

As stated earlier, rest is paramount to reducing concussive vulnerability and neurologic sequelae. Mental and physical exertion aggravates concussion symptoms (Majerske et al., 2008; McGrath et al., 2013; Silverberg & Iverson, 2013). Cognitive and physical rest are beneficial for concussive recovery, particularly during the acute, symptomatic phase which usually lasts between 7 and 10 days (Grady et al., 2012; Leddy et al., 2012; Moser et al., 2012). Cognitive rest requires avoiding activities that require concentration or are mentally stimulating (i.e. reading, use of electronic devices, etc.). Physical rest entails avoiding physical exercise or physical exertion (Leddy, Sandhu, Sodhi, Baker, & Willer, 2012). However, recently there has been mounting evidence that low-intensity physical exercise performed after the acute phase of concussion, which does not aggravate symptoms, may promote concussion recovery and prevent deconditioning, fatigue, and reactive depression (Grady et al., 2012; Leddy et al., 2012; Schneider, et al., 2013). If symptoms are present despite rest or beyond six weeks, then other interventions including medications and rehabilitative measures may be necessary. Rehabilitation may be required to treat persistent concussive symptoms such as dizziness, cognitive difficulties, hearing problems, or neuro-ocular disturbances (Harmon et al., 2013). However, there are many concussed patients who are not diagnosed by a medical professional, not instructed to rest, or find it difficult to adhere to physician recommendations for rest due to loss of work time, income, or boredom from inactivity (Arbogast et al., 2013). Unfortunately, without physical and cognitive rest, these patients are at risk for short and long-term neurological consequences (Blume & Hawash, 2012). Therefore, rest remains the primary treatment measure to reduce concussive vulnerability.

### **Components of the Concussive Vulnerability Model**

The Concussive Vulnerability Model (CVM) was developed to synthesize current literature for the purpose of guiding future studies and interpreting the relationship of new studies to reduce concussive vulnerability (see Figure 1). The CVM builds upon the Dynamic Recursive Model for Sports Injury (Meeuwisse, Tyreman, Hagel, & Emery, 2007). Conceptual elements utilized from this model include the predisposed individual, external risk factors, the inciting event, possible injury, repeat participation, and removal from activity (Meeuwisse et al., 2007). There are two major components of the CVM: the process of concussion development and the cycle of concussive vulnerability.

#### **The Process of Concussion Development**

There is a sequence of events that must take place for a concussion to occur, as depicted by the dashed boxes in the CVM (see Figure 1). A predisposed host may have one or multiple antecedents which may make him/ her susceptible to concussions. For example, females may have more frequent and severe concussion symptoms as compared to males (Harmon et al., 2013). Individual characteristics such as aggressive play behavior or genetics may also have a role in the occurrence of concussions (Harmon et al., 2013). Previous medical history including migraine headaches, depression, and Attention Deficit Disorder (ADD) are key factors for assessing the potential of a concussed patient to experience prolonged symptoms. In addition, previous concussions or TBIs may lower the threshold for an individual to develop a concussion (McCrory et al., 2013). Finally, a significant cause of concussions in the elderly is falls which are often attributed to cardiogenic or neurogenic syncope (Papa et al., 2012; Rubenstein & Josephson, 2002).

When the susceptible individual participates in a risk-taking activity (i.e. contact sports) or is in an environment with potentially dangerous conditions (i.e. wet, slippery environment), he/ she may be injured. A potential modifier for this risk might be protective equipment as noted earlier. A brain injury is typically caused by a forceful collision between the vulnerable brain of a predisposed host and an object or person. Fortunately, a physical impact to the head or body does not usually result in a concussion as depicted in the CVM.

### **The Cycle of Concussive Vulnerability**

A collision may result in a mTBI, thereby making the host's brain vulnerable to further insult. Thus, he may enter "cycle of concussive vulnerability" as shown in the CVM (see Figure 1). There are three major mTBI injury pathways the host may follow: (a) he/ she may be asymptomatic and continue risk-taking activity, (b) he/ she may be symptomatic, diagnosed with a concussion, and removed from the risk-taking activity, or (c) he/ she may be symptomatic, not diagnosed with a concussion, and continues the risk-taking activity.

In the first pathway, depicted as "a" in the CVM, the host experienced a subconcussive injury (see Figure 1). Multiple subconcussive injuries may result in cumulative damage and long-term neurologic consequences. As discussed earlier, to date, concussive symptoms must be reported by the patient in order to be diagnosed. Subconcussive injuries do not usually result in symptoms and therefore cannot currently be diagnosed. However, as mentioned earlier, imaging methods such as DTI, fMRI, MRS, have the potential to be utilized for diagnosing concussive and subconcussive injuries in the future (Bazarian et al., 2012; Gardner et al., 2013; Johnson et al., 2012). At

present, these imaging tests are expensive and an algorithm needs to be developed in order to determine which patients would benefit from these imaging methods.

The second pathway, shown as “b” in the CVM, is ideal because the patient’s concussive injury is diagnosed, treated, and monitored. As mentioned earlier, most concussions resolve within 7 to 10 days with cognitive and physical rest (McCrorry et al., 2013). When the patient becomes asymptomatic, he/ she can follow a gradual step-wise protocol to return to his/ her risk-taking activity or environment (Makdissi, Cantu, Johnston, McCrorry, & Meeuwisse, 2013). However, some patients may take longer to recover from a concussion and may require an individualized treatment approach (i.e. medications) (McCrorry et al., 2013).

The third pathway, labeled as “c” in the CVM, is the least desirable path due to potential for poor outcomes. There are two potential outcomes when a concussed individual continues the risk-taking activity. As described previously, he or she may rarely experience SIS which is depicted as “1” in the CVM. The second outcome is that he or she may develop PCS, labeled as “2” in the CVM, which occurs in approximately 10 to 15% of all concussed persons a (McCrorry et al., 2013). SIS or PCS can occur when the individual has a concussion antecedent, does not rest due to lack of awareness of having a concussion or non-compliance to treatment recommendations, and/or prematurely resumes risk-taking activities. PCS can lead to persistent symptoms and require an indefinite withdrawal from activity. However, some patients may make a full recovery over time after a long-period of avoiding the inciting activity or environment. Unfortunately, some patients with PCS may be resistant to treatment, particularly with repetitive brain trauma. If an individual with PCS prematurely returns to risk-taking

activities, he or she may experience cumulative neurologic damage and suffer from long-term neurologic impairments. More evidence is needed to ascertain how much cumulative damage can be sustained from concussive or subconcussive injuries before resulting in permanent neurologic consequences such as decreased cognition, depression, persistent symptoms, CTE, or AD.

Concussion outcomes depend on antecedents, diagnosis, and treatment. Presently, there is insufficient proof that concussions can be prevented. Therefore, the CVM illustrates the importance of early diagnosis with reporting behavior and development of technology to detect concussive injury. The CVM also illustrates the significance of rest as the cornerstone treatment of concussions.

### **Conclusion**

The Concussive Vulnerability Model presents a comprehensive framework illustrating the dynamic nature of concussive vulnerability. This framework can be used to guide future research, provide a context within which to interpret new concussion knowledge, and draw clinical implications and practice recommendations. This model can be utilized by concussion specialists, primary care providers, neuropsychologists, nurses, athletic trainers, and coaches. Concussion researchers can use the model as a framework to understand the relationship between the vulnerability of the host to his environment and the treatment and recovery after occurrence.

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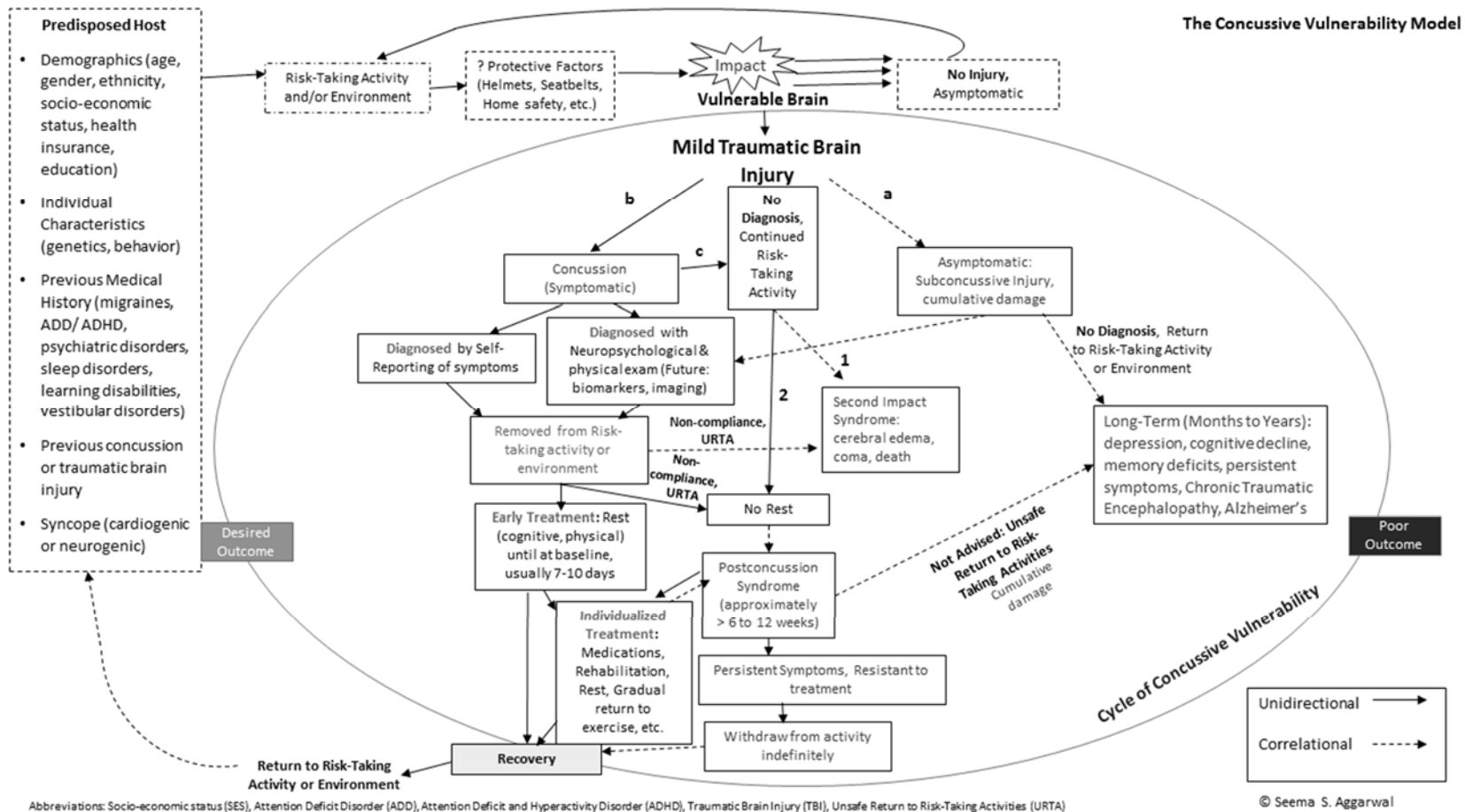


Figure 1. The Concussive Vulnerability Model



**Appendix A**

**University of Texas Health Science Center Houston**

**CPHS Approval**



Committee for the Protection of Human Subjects

8100 Fannin Street, Suite 1100  
Houston, Texas 77030

**Dr. Seema Aggarwal**  
UT-H - SN - Department of Family Health

**NOTICE OF APPROVAL TO BEGIN RESEARCH**

**July 31, 2015**

**HSC-SN-15-0599** - Clinical and demographic variables that are associated with cognitive deficits, concussion symptom severity, and duration in adolescents: A retrospective study

**PROVISIONS:** This approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered by the Committee for the Protection of Human Subjects, e.g. study documents, informed consent, etc.

**APPROVED:** By Expedited Review and Approval

**REVIEW DATE:** 07/30/2015

**APPROVAL DATE:** 07/31/2015

**EXPIRATION DATE:** 06/30/2016

**CHAIRPERSON:** John C. Ribble, MD

Subject to any provisions noted above, you may now begin this research.

**CHANGES:** The principal investigator (PI) must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. **ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.**

**INFORMED CONSENT DETERMINATION:**

Waiver of Consent Granted

**HEALTH INSURANCE PORTABILITY and ACCOUNTABILITY ACT (HIPAA):**

**Waiver for Retrospective Chart Review granted:**

Information to be accessed:

Medical record number, treatment dates

Information to be retained:

Medical record number, Treatment dates

**UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS:** The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

**RECORDS:** The PI will maintain adequate records, including signed consent and HIPAA documents if required, in a manner that ensures subject confidentiality.



Committee for the Protection of Human Subjects

6410 Fannin Street, Suite 1100  
Houston, Texas 77030

**NOTICE OF APPROVAL TO IMPLEMENT REQUESTED CHANGES**

November 20, 2015

**HSC-SN-15-0599** - Clinical and demographic variables that are associated with cognitive deficits, concussion symptom severity, and duration in adolescents: A retrospective study  
PI: Dr. Seema Aggarwal

Reference Number: 129481

**PROVISIONS;** Unless otherwise noted, this approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consent, etc.

**APPROVED:** By Expedited Review and Approval

**CHANGE APPROVED:** Revised Protocol Version 2.0 (dated 10/23/2015)  
Revised Data Collection Form Version 2.0 (dated 10/23/2015)  
Waiver for Retrospective Chart Review –Modified

**REVIEW DATE:** November 11, 2015

**APPROVAL DATE:** November 20, 2015

**CHAIRPERSON:** L. Maximilian, MD *L. Maximilian Buja*

Upon receipt of this letter, and subject to any provisions noted above, you may now implement the changes approved.

**CHANGES:** The principal investigator (PI) must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. **ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.**

**HEALTH INSURANCE PORTABILITY and ACCOUNTABILITY ACT (HIPAA):**

**Waiver for Retrospective Chart Review granted:**

Information to be accessed: Medical record number, treatment dates, zip code, date of birth

Information to be retained: Medical record number, Treatment dates, zip code

**UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS:** The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

**RECORDS:** The PI will maintain adequate records, including signed consent documents if required, in a manner that ensures subject confidentiality.

**Appendix B**  
**Study Operations Procedure**

## Study Operations Protocol

Clinical and demographic variables associated with cognitive deficits, symptom severity, and duration after concussive injury in adolescents: A retrospective study

### Data Collection

#### ROOM FOR DATA COLLECTION

1. Setup private room or area for patient data collection

#### SUPPLIES

- Computer with Windows 7, 8, or 8.1 and internet access
- Login Information (computer, Aventail VPN, Citrix/ Allscripts, ImPACT)
- Mobile phone with DuoMobile App

#### EQUIPMENT PREPARATION

1. Boot up computer
2. Log into computer with password
3. Connect to Aventail VPN with login and password (to get into central server- “U” drive)
4. Connect to Citrix Allscripts: <http://citrix.uth.tmc.edu/> , login with username/ password, enter passcode “push”, click “Approve” on DuoMobile, click on Allscripts application, click on “Permit use”, login to Allscripts and click “New session”
5. On computer, login to central server and click on “Seema Aggarwal” to access data files
6. Connect to ImPACT applications: <https://www.impacttestonline.com/customercenter/> and login

#### DATA COLLECTION PROCEDURE

##### A. Collection of data for Inclusion/ Exclusion Criteria

1. Open “InclusionExclusionWorkst\_1.xls” from central server (“U” drive)
2. Login to Citrix/ Allscripts and ImPACT
3. Select Provider “Summer Ott”
4. Select “Surgical Patient View”
5. Allscripts- Select date of appointment and new patient evaluations only- noted as “NCC” or “E60” or “E90” under Type of visit and/ or “New Eval” under Comments on the “Daily Schedule” page under “Daily” tab
6. Double click on selected new patient to go to “Clinical Desktop” tab
7. In “InclusionExclusionWorkst\_1.xls”, type in Date of appointment, MRN, DOB (used to automatically calculate age under “Age” column), and Gender from patient demographic data displayed on the top of page

8. Click on the letter/ symbol “i” located under patient demographic data displayed on the top of page to open the pop-up “Patient Profile Dialog” box. Click on “Demographics” and scroll down to note “Language”, “Race”, and “Ethnicity”. type into spreadsheet. For language, only type in if there is a language other than English.
9. Under “Chart Viewer” tab on right side, double click to open “Questionnaire/ Consents” form to view “Patient History” form. Look at “Date problem began” for date of injury/ DOI. Scroll down to “Current Medications” and “Health” section and look for evidence of psychiatric history. Open “Chart Note” by appropriate provider and scan to confirm or determine DOI, psychiatric history, and number of prior concussions. Go back to spreadsheet and type “D” for depression, “A” for anxiety, or “O” for other psychiatric history. Do not complete the rest of the worksheet fields if the patient has a positive psychiatric history (exclusion criteria). If patient has 1 concussion or more, then note 1, 2, or  $\geq 3$ . If patient has no concussions, leave cell blank.
10. Go to ImPACT website, type in patient name (last name first) and look at post-injury ImPACT test dates. Type in the patient’s “Post-Injury 1” date in worksheet under “1<sup>st</sup> ImPACT date” and last post-injury date available under “last ImPACT date”. Type in “Y” or “N” under “ImPACT #2 score available?” In worksheet, under “ImPACT #1  $\geq 10$  days?”, days from DOI to 1<sup>st</sup> ImPACT date will automatically be calculated. Under “Days from DOI to ImPACT #2”, days will automatically be calculated. Note- if ImPACT scores are missing, go back to “Chart Viewer” and click through provider notes to see if scanned into Allscripts.
11. Under “Other” in worksheet, type in additional notes if needed.
12. If patient met the inclusion criteria, then in 1<sup>st</sup> column on spreadsheet, type in count number and highlight row yellow.
13. Double check data after each entry to ensure it is complete and accurate.
14. After every 5 entries, scan them and make sure data entry is complete and accurate.
15. When done with worksheet, save in central server and disconnect from Avenail, (to disconnect from central server). Log out of ImPACT and Allscripts. Do not forget to enter action items completed in dissertation research log.

## **B. Linking Log**

1. Copy MRNs into “LinkingLog.xls” under column “MRNs”
2. Under “Unique Subject Code” column, number starting with 1 (type “1” in cell 2, “2” in cell 3 and double click on “+” sign in lower right corner and all of the unique subject codes will be populated.
3. Copy and paste the unique subject codes into a column labeled “Unique Subject Codes” from linking log into spreadsheet and delete column with MRNs. Now the working spreadsheet is completely de-identified.

4. Password protect (with a strong password) the linking log (located on the central server only) by going to File -> ProtectWorkbook -> Encrypt with Password. (If you ever need to remove the password follow same procedure, but erase the password in the password box).

### C. Randomization of Subjects Procedure

1. Randomize using R Console
2. For 1: 1 acceptance ratio, R Console code is as follows:
 

```
## create randomization variable
z1 = runif(233, 0, 1)
z2 = z1 > 0.5
## view and check
cbind(1:233, z2)
sum(z2)
## save file
concussion.rand = data.frame(Subj=1:233,
Rand_Select=as.numeric(z2))
write.csv(concussion.rand, "concussion.rand.csv", row.names=F)
```
3. Saved automatically as concussion.rand.csv → “1” identifies the randomly selected subjects and “0” represents subjects who were not selected
4. Copy and paste the “Random” column in the working spreadsheet, “InclusionExclusionWorksht\_5\_ToBeRandomized.xls”
5. Select the rows that will be selected (Cntrl Shift down and right arrows). Re-sort the data by clicking on Sort&Filter -> Custom Sort -> Sort by “Random” column, Sort on “Values”, Order “Largest to Smallest”. The “Random” column will be re-sorted with “1s” on top. Delete the rows with the “0s”. Save file with the randomly selected subjects with the “1s” as “InclusionExclusionWorksht\_Final.xls”. The clinical data of these randomly selected subjects will be used in the dissertation study.

### D. Data Collection on Randomized Subjects

1. Open SPSS version 23. Create SPSS file (DissertationDataCollection.spv) for data collection of the randomly selected subjects. Import subject data from InclusionExclusionWorksht\_Final, xls.
2. In the SPSS variable view of DissertationDataCollection.spv, list the demographic and outcome variables by Name, Type (numeric, string, etc.), and label per IRB approved protocol. Add type of measure (nominal, ordinal, scale) under “Measure” column. Reduce number of decimals as needed under “Decimals” column. Choose “center” under Align column to align values to the center of the cells.
3. To add options for each variable (e.g., Male, Female), click on the Variable View tab (bottom). Go to the Values column and click on the

desired cell. Type in numeric value under Value and type in appropriate Label, and click “Add” and click “Ok”.

4. Double-check spreadsheet to ensure all columns and fields are ready for data collection.
5. Open LinkingLog.xls to look up MRN numbers.
6. Open Allscripts and use MRN to view patient chart.
7. Open ImpACT website and search by patient name (last, first and check date of birth). Select first and last ImpACT data and click “View with Norms”.
8. To find data for each variable:
  - a. Date of Initial Appointment: Allscripts general data
  - b. Subject Number: See LinkingLog.xls for MRN
  - c. Subject Age: Allscripts Demographics profile
  - d. Subject Gender: Allscripts Demographics profile
  - e. Subject Race: Allscripts Demographics profile
  - f. Primary language: Allscripts Demographics profile, chart note, ImpACT report
  - g. Date of Injury: Allscripts chart note, patient questionnaire
  - h. 1st ImpACT date: Allscripts chart note, ImpACT report
  - i. Days from DOI to 1st ImpACT: calculate
  - j. Last ImpACT available? Check “yes” if available on ImpACT website
  - k. Last ImpACT date: ImpACT report
  - l. Days from DOI to last ImpACT: calculate
  - m. Number Prior Concussions: Allscripts chart note, patient questionnaire, ImpACT report
  - n. Repeat Concussion data? Check “yes” if have 2 or more records in Allscripts
  - o. Repeat Concussion Visit Date: Allscripts chart note
  - p. Mechanism of Injury: Allscripts chart note
  - q. Sport Position: Allscripts chart note, ImpACT report
  - r. Migraine History: Allscripts chart note, questionnaire
  - s. LD/ AD(H)D History: Allscripts chart note
  - t. Health Insurance Status: Allscripts Demographic profile or scanned images under health care provider
  - u. Zip Code: Allscripts Demographic profile
  - v. Education Years: ImpACT report
  - w. Verbal Memory and percentile: ImpACT report
  - x. Visual Memory and percentile: ImpACT report
  - y. Visual Motor and percentile: ImpACT report
  - z. Reaction Time and percentile: ImpACT report
  - aa. Symptoms score: ImpACT report
  - bb. Baseline or Normative Data: Allscripts chart note



- cc. Baseline/ Normative Verbal Memory and percentile: ImPACT report/ ImPACT manual
  - dd. Baseline/ Normative Visual Memory and percentile: ImPACT report/ ImPACT manual
  - ee. Baseline/ Normative Visual Motor and percentile: ImPACT report/ ImPACT manual
  - ff. Baseline/ Normative Reaction Time and percentile: ImPACT report/ ImPACT manual
  - gg. Baseline Symptoms score: ImPACT report
  - hh. Premorbid Cognition for Normative Data selection: Allscripts Chart note
9. Type in data (above) into each row and appropriate column in DissertationDataCollection.spv
  10. Check data for missing or inaccurate data every 5 subject entries.
  11. Save to central server.
  12. At the end of data collection, review for missing and accurate data.

#### **Data Analysis (to be refined with statistician)**

Open SPSS version 23.

- A. Aim 1: Descriptive statistics (IBM SPSS book, p18) (Leech, Barrett, & Morgan, 2011)
  1. Generate Codebook (can only be done in SPSS version 23): Analyze-> Codebook-> Choose desired variables-> Save
  2. Sort data: Date-> Sort Cases-> Select Age, Gender Race-> Ok
  3. For continuous/ scale dependent variable: Analyze-> Descriptive Statistics-> Explore -> Choose desired variable-> Plots: Normality plots with tests-> Shapiro Wilk (if  $p < .05$ , non-normal distrib)-> Ok
  4. If distribution is normal: Compare Means -> Options: move desired statistics to box on the right, check ANOVA and eta and Test for Linearity; If not normal distribution, can perform t-test: Analyze-> Independent Samples T-Test-> Choose multiple Dependent variable and the move one Independent variable into Grouping variable-> Ok
  5. To get Descriptive Stats for 2 nominal variables: Analyze-> DS-> CrossTabs-> Ok, Check  $\chi^2$
  6. To get means: Analyze-> Compare Means -> Means-> Add DV, Add IV in box, click next and add other IV-> Ok
- B. Aim 2: Generalized Linear Models (GLM)- (IBM SPSS book Ch.8) (Leech et al., 2011)
  1. Analyze-> General Linear Models-> Univariate-> fill in Dependent variable (e.g., verbal memory, visual memory, motor processing, reaction time, symptoms), fixed factors (e.g., gender, race)-> Profile Plots: race to horizontal axis and gender to separate lines-> Add-> Options: DS,

Estimates of Effect size, observed power, parameter estimates, and tests of homogeneity-> Continue-> Ok

2. If have baseline data: Analyze-> General Linear Models-> Repeated Measures-> fill in number of levels (2)-> Define-> Ok
  3. To recode a variable: Transform-> Recode into Different Variables-> Select Variable1 (e.g., Race or Language) and click on Old/ New Variables-> "0-> 0, 1-> 1, 2->1, click on System: Missing-> code Output Variable2
- C. Aim 3: Hierarchical logistic regression- (IBM SPSS book Ch.7) (Leech et al., 2011)
1. Analyze-> Regression-> Binary Logistic-> move variables to Dependent box-> move variables to Covariate box-> Save-> select Probabilities, Cooks, Leverage, Studentized -> Options-> Select CI Exp(B)-> Continue-> Ok
  2. If have complete data for resolution time, then do Survival Analysis.
    - i. Analyze-> Survival-> Kaplan-Meier-> DaystoResolution-> Status: Event (Resolution) Define Event: Single value: 1-> Options: Survival tables, mean/ median survival, Plots: Survival; Factor: Gender (Race also)- Compare Factor, Log Rank-> Ok
    - ii. Analyze-> Survival-> Cox Regression-> Time: DaystoResolution, Status: event (resolution); Define: Single value: 1 -> Covariates: age, prior conc, migraine, LD/Attention, Insurance, Education, Mech of Injury; Next: Gender, Race -> Plots: Survival, LML, Separate Lines for a categorical variable (gender or race)-> Options: CI for expB-> Ok

### **Troubleshooting**

#### **A. Citrix, Allscripts, VPN**

1. If have difficulty with connecting to Aventail VPN, Allscripts application or logging on to Citrix, call UT Help Desk (713) 486-4848
2. If need assistance with Allscripts features, email [UTPAllscriptsSupport@uth.tmc.edu](mailto:UTPAllscriptsSupport@uth.tmc.edu) or email [Richard.A.Raymundo@uth.tmc.edu](mailto:Richard.A.Raymundo@uth.tmc.edu)
3. If Allscripts does not show up on Citrix (and there are no known outages), create HEAT Ticket <https://msitapps.uth.tmc.edu/mshelpdesk/login.jsp> or email [Marceli.Palak@uth.tmc.edu](mailto:Marceli.Palak@uth.tmc.edu) (phone: (713) 500-2181)
4. If have difficulty with authorization to review charts for UT Physicians-Department of Orthopedics, email department manager [Lenice.Socha@uth.tmc.edu](mailto:Lenice.Socha@uth.tmc.edu)
5. If need additional Allscripts training, email [Erwin.A.Raymundo@uth.tmc.edu](mailto:Erwin.A.Raymundo@uth.tmc.edu)

## B. IBM SPSS difficulties

1. Go to SPSS Manual:  
[ftp://public.dhe.ibm.com/software/analytics/spss/documentation/statistics/23.0/en/client/Manuals/IBM\\_SPSS\\_Statistics\\_Core\\_System\\_User\\_Guide.pdf](ftp://public.dhe.ibm.com/software/analytics/spss/documentation/statistics/23.0/en/client/Manuals/IBM_SPSS_Statistics_Core_System_User_Guide.pdf)
2. IBM SPSS for Intermediate Statistics: Use and Interpretation (4<sup>th</sup> edition) (Leech et al., 2011)
3. Discovering statistics using IBM SPSS statistics (Field, 2012)
4. SPSS Survival Manual (Pallant, 2005)
5. If these resources are insufficient, contact Dr. Padhye  
[Nikhil.S.Padhye@uth.tmc.edu](mailto:Nikhil.S.Padhye@uth.tmc.edu)

## C. ImPACT Test difficulties

1. Email Dr. Ott if have login issues: [Summer.D.Ott@uth.tmc.edu](mailto:Summer.D.Ott@uth.tmc.edu) or email [support@impacttest.com](mailto:support@impacttest.com)
2. If need assistance with interpretation or other information, see ImPACT User Manual: <https://www.impacttest.com/pdf/ImPACTTechnicalManual.pdf> (ImPACT Applications Inc., 2007)
3. See ImPACT website for other issues: <https://www.impacttest.com/> Contacts for ImPACT: Melinda Dietz [mdietz@impacttest.com](mailto:mdietz@impacttest.com), Hannah Eichelberger [heichelberger@impacttest.com](mailto:heichelberger@impacttest.com), or Labiba Russo [lrusso@impacttest.com](mailto:lrusso@impacttest.com)

## References

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**Appendix C**  
**Code Book**

## SPSS Codebook

**ageOrdinal**

		Value	Count	Percent
Standard Attributes	Position	6		
	Label	OrdinalAge		
	Type	Numeric		
	Format	F8		
	Measurement	Ordinal		
	Role	Input		
Valid Values	0	13-14	27	22.9%
	1	15-16	51	43.2%
	2	17-19	40	33.9%

**gender**

		Value	Count	Percent
Standard Attributes	Position	7		
	Label	Subject Gender		
	Type	Numeric		
	Format	F1		
	Measurement	Nominal		
	Role	Input		
Valid Values	0	Male	84	71.2%
	1	Female	34	28.8%

**race**

		Value	Count	Percent
Standard Attributes	Position	8		
	Label	Subject Race		
	Type	Numeric		
	Format	F1		
	Measurement	Nominal		
	Role	Input		
Valid Values	0	White	72	61.0%
	1	Black	18	15.3%
	2	Hispanic	28	23.7%

**race2**

		Value	Count	Percent
Standard Attributes	Position	9		
	Label	Binary Race		
	Type	Numeric		
	Format	F8		
	Measurement	Nominal		
	Role	Input		
Valid Values	0	White	72	61.0%
	1	Black or Hispanic	46	39.0%

**language**

		Value	Count	Percent
Standard Attributes	Position	10		
	Label	Primary language		
	Type	Numeric		
	Format	F7		
	Measurement	Nominal		
	Role	Input		
Valid Values	0	English	101	85.6%
	1	Spanish	7	5.9%
	2	Bilingual- Eng and Span	10	8.5%

**language2**

		Value	Count	Percent
Standard Attributes	Position	11		
	Label	Binary Language		
	Type	Numeric		
	Format	F8		
	Measurement	Nominal		
	Role	Input		
Valid Values	0	English	101	85.6%
	1	Spanish or Bilingual Spanish	17	14.4%

**prolonged**

		Value	Count	Percent
Standard Attributes	Position	19		
	Label	ProlongedRecov		
	Type	Numeric		
	Format	F8		
	Measurement	Ordinal		
	Role	Input		
Valid Values	0	Up to 14 days	49	41.5%
	1	Over 14 days	69	58.5%

**prolonged2**

		Value	Count	Percent
Standard Attributes	Position	20		
	Label	Prolonged Median		
	Type	Numeric		
	Format	F8		
	Measurement	Ordinal		
	Role	Input		
Valid Values	0	Up to 17 days	62	52.5%
	1	Greater than 17 days	56	47.5%



**prior**

		Value	Count	Percent
Standard Attributes	Position	22		
	Label	Number Prior Concussions		
	Type	Numeric		
	Format	F4		
	Measurement	Ordinal		
	Role	Input		
	Valid Values	0	No Concussions	83
1		1 Concussion	29	24.6%
2		2 Concussions	3	2.5%
3		3 Concussions	3	2.5%
		or more		

**prior3**

		Value	Count	Percent
Standard Attributes	Position	24		
	Label	Recoded Binary Prior		
	Type	Numeric		
	Format	F8		
	Measurement	Ordinal		
	Role	Input		
	Valid Values	0	1 or more	35
1		None	83	70.3%

## moi

		Value	Count	Percent
Standard Attributes	Position	27		
	Label	Mechanism of Injury		
	Type	Numeric		
	Format	F12		
	Measurement	Nominal		
	Role	Input		
Valid Values	0	Fall	5	4.2%
	1	MVA	6	5.1%
	2	Sport: Football	56	47.5%
	3	Sport: Soccer	20	16.9%
	4	Sport: Basketball	9	7.6%
	5	Sport: Lacrosse	2	1.7%
	6	Sport: Volleyball	5	4.2%
	7	Sport: Ice Skating	1	0.8%
	8	Non-sport Collision	2	1.7%
	9	Sport: Softball	3	2.5%
	10	Cheerleading	1	0.8%
	11	Wrestling	5	4.2%
	12	Rugby	3	2.5%

## moi3

		Value	Count	Percent
Standard Attributes	Position	29		
	Label	Recoded MOI binary		
	Type	Numeric		
	Format	F8		
	Measurement	Nominal		
	Role	Input		
Valid Values	0	Non-Sports	13	11.0%
	1	Sports	105	89.0%

## position

		Value	Count	Percent
Standard Attributes	Position	30		
	Label	Sport Position		
	Type	Numeric		
	Format	F12		
	Measurement	Nominal		
	Role	Input		
Valid Values	0	Not applicable	22	18.6%
	1	Football: Defensive Line	4	3.4%
	2	Football: Running Back	6	5.1%
	3	Football: Right or Left Tackle	5	4.2%
	4	Football: Wide Receiver	6	5.1%
	5	Football: Linebacker	6	5.1%
	6	Not specified	36	30.5%
	7	Football: Quarterback	6	5.1%
	8	Football: Offensive Line	3	2.5%
	9	Football: Right/ Left Guard	3	2.5%
	10	Basketball: Forward	1	0.8%
	11	Basketball: Post	3	2.5%
	12	Basketball: Point Guard, Shooting Guard	1	0.8%
	13	Football: Safety	1	0.8%
	14	Football: Tight End	1	0.8%

15	Softball/ Baseball: Pitcher	1	0.8%
20	Volleyball: Middle	1	0.8%
21	Volleyball: Server	1	0.8%
30	Soccer: Sweeper	1	0.8%
31	Soccer: Goalie	6	5.1%
32	Soccer: Midfield	3	2.5%
33	Soccer: Forward	1	0.8%
40	Cheerleading:Base	0	0.0%

## migraine3

		Value	Count	Percent
Standard Attributes	Position	33		
	Label	Recoded migraine		
	Type	Numeric		
	Format	F8		
	Measurement	Nominal		
	Role	Input		
	Valid Values	0	Migraine incl family hx	9
1		Non-migraine headaches	20	16.9%
2		None	89	75.4%

## learnattn3

		Value	Count	Percent
Standard Attributes	Position	37		
	Label	LD recoded		
	Type	Numeric		
	Format	F8		
	Measurement	Nominal		
	Role	Input		
	Valid Values	0	LD	13
1		ADD	8	6.8%
2		Both	5	4.2%
3		None	92	78.0%

learnattn4

		Value	Count	Percent
Standard Attributes	Position	38		
	Label	LD/ ADD Combo Recoded		
	Type	Numeric		
	Format	F8		
	Measurement	Nominal		
	Role	Input		
	Valid Values	0	ADD, LD, or both	25
	1	None	93	78.8%

insurance2

		Value	Count	Percent
Standard Attributes	Position	40		
	Label	Insurance Recoded		
	Type	Numeric		
	Format	F8		
	Measurement	Nominal		
	Role	Input		
	Valid Values	0	None	5
	1	Private, Private and Student	76	64.4%
	2	Public, Student, Both	37	31.4%

insurance4

		Value	Count	Percent
Standard Attributes	Position	42		
	Label	Recoded Student Insurance		
	Type	Numeric		
	Format	F8		
	Measurement	Nominal		
	Role	Input		
	Valid Values	1	Private	76
	2	Public	22	18.6%
	3	Student	15	12.7%
	4	None	5	4.2%

incomeQuart

		Value	Count	Percent
Standard Attributes	Position	46		
	Label	Income Quartiles		
	Type	Numeric		
	Format	F8		
	Measurement	Ordinal		
	Role	Input		
Valid Values	0	1st Quartile	33	28.0%
	1	2nd Quartile	26	22.0%
	2	3rd Quartile	34	28.8%
	3	4th Quartile	25	21.2%



**yearsedu2**

		Value	Count	Percent
Standard Attributes	Position	48		
	Label	Recoded Education Yrs		
	Type	Numeric		
	Format	F8		
	Measurement	Ordinal		
	Role	Input		
Valid Values	0	Middle School	40	33.9%
	1	High School	78	66.1%

**premorcogn**

		Value	Count	Percent
Standard Attributes	Position	69		
	Label	Premorbid Cognition for Normative data		
	Type	Numeric		
	Format	F8		
	Measurement	Ordinal		
	Role	Input		
Valid Values	0	impaired	0	0.0%
	1	low-average	6	5.1%
	2	average	70	59.3%
	3	above average	42	35.6%

**Appendix D**

**Collaborative Institutional Training Initiative Certificate**

**COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)  
COURSEWORK REQUIREMENTS REPORT\***

\* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Seema Aggarwal (ID: 4600740)
- **Email:** seema.s.aggarwal@uth.tmc.edu
- **Institution Affiliation:** University of Texas Health Science Center at Houston (ID: 661)
- **Phone:** 8328379433
  
- **Curriculum Group:** CITI Good Clinical Practice Gradebook
- **Course Learner Group:** GCP
- **Stage:** Stage 1 - Basic Course
  
- **Report ID:** 15006912
- **Completion Date:** 01/22/2015
- **Expiration Date:** 01/21/2017
- **Minimum Passing:** 80
- **Reported Score\*:** 98

**REQUIRED AND ELECTIVE MODULES ONLY**

	<b>DATE COMPLETED</b>
The CITI Good Clinical Practice Course for Clinical Trials Involving Drugs and Devices	01/17/15
Overview of New Drug Development	01/17/15
Overview of ICH GCP	01/22/15
ICH - Comparison Between ICH GCP E6 and U.S. FDA Regulations	01/22/15
Conducting Investigator-Initiated Studies According to FDA Regulations and GCP	01/22/15
Investigator Obligations In FDA-Regulated Clinical Research	01/22/15
Managing Investigational Agents According to GCP Requirements	01/22/15
Overview of U.S. FDA Regulations for Medical Devices	01/22/15
Informed Consent In Clinical Trials of Drugs, Biologics, and Devices	01/22/15
Detecting and Evaluating Adverse Events	01/22/15
Reporting Serious Adverse Events	01/22/15
Audits and Inspections of Clinical Trials	01/22/15
Monitoring of Clinical Trials by Industry Sponsors	01/22/15
Completing the CITI GCP Course	01/22/15

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing institution identified above or have been a paid independent Learner.

**CITI Program**  
 Email: [citisupport@miami.edu](mailto:citisupport@miami.edu)  
 Phone: 305-243-7970  
 Web: <https://www.citi-program.org>

**COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI PROGRAM)  
COURSEWORK REQUIREMENTS REPORT\***

\* NOTE: Scores on this Requirements Report reflect quiz completions at the time all requirements for the course were met. See list below for details. See separate Transcript Report for more recent quiz scores, including those on optional (supplemental) course elements.

- **Name:** Seema Aggarwal (ID: 4600740)
- **Email:** seema.s.aggarwal@uth.tmc.edu
- **Institution Affiliation:** University of Texas Health Science Center at Houston (ID: 661)
- **Phone:** 8328379433
  
- **Curriculum Group:** Human Research
- **Course Learner Group:** Group 1 Biomedical Researcher and Key Personnel
- **Stage:** Stage 1 - Basic Course
  
- **Report ID:** 15006911
- **Completion Date:** 01/22/2015
- **Expiration Date:** 01/21/2018
- **Minimum Passing:** 80
- **Reported Score\*:** 96

**REQUIRED AND ELECTIVE MODULES ONLY**

	<b>DATE COMPLETED</b>
Avoiding Group Harms - U.S. Research Perspectives	01/22/15
Belmont Report and CITI Course Introduction	01/22/15
History and Ethics of Human Subjects Research	01/22/15
Basic Institutional Review Board (IRB) Regulations and Review Process	01/22/15
Informed Consent	01/22/15
Records-Based Research	01/22/15
Genetic Research In Human Populations	01/22/15
Vulnerable Subjects - Research Involving Children	01/22/15
Vulnerable Subjects - Research Involving Pregnant Women, Human Fetuses, and Neonates	01/22/15
FDA-Regulated Research	01/22/15
Research and HIPAA Privacy Protections	01/22/15
Conflicts of Interest in Research Involving Human Subjects	01/22/15
University of Texas Health Science Center at Houston	01/22/15

For this Report to be valid, the learner identified above must have had a valid affiliation with the CITI Program subscribing Institution identified above or have been a paid Independent Learner.

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## CURRICULUM VITAE

Seema S. Aggarwal, PhD(c), RN, NP-C

The University of Texas School of Nursing  
 6901 Bertner Avenue  
 Houston, TX 77030-3901  
Seema. S. Aggarwal@uth.tmc.edu

**Education**

Doctor of Philosophy, Nursing Candidate	The University of Texas Health Science Center at Houston	Expected 05/2016
Master of Science, Nursing, Adult-Gerontology Nurse Practitioner	The University of Texas Health Science Center at Houston	12/2012
Bachelor of Science, Nursing, <i>Cum Laude</i>	Texas Woman's University (Houston, TX)	05/2007
Bachelor of Science, Biology, <i>Cum Laude</i>	Monmouth University (West Long Branch, NJ)	05/1998
High School Diploma, International Baccalaureate	Bellaire High School (Bellaire, TX)	05/1991

**Licensures and Certifications**

Advanced Practice Registered Nurse - Texas	Active – AP123515, Rx 13955	04/2013- Present
Registered Nurse- Texas	Active- 741271	06/2007- Present
BLS for Healthcare Provider	American Heart Association	01/2016- 01/2018

**Professional Positions**

UT Physicians, Department of Orthopedic Surgery	Nurse Practitioner (Volunteer)	2013-2015
Houston Independent School District	Registered Nurse –School Nurse	2008-2011
St. Luke's Episcopal Hospital	Registered Nurse- Staff Nurse	2007-2008

MD Anderson Hospital	Student Nurse Externship	2006
JAMM Consulting, Inc.	Computer Programmer (Sun JAVA® language)	1998-2005

### **Awards and Recognitions**

PhD Accelerated Scholar	Houston Rodeo & Livestock Scholar	2013- 2016
Outstanding Nurse Practitioner Award	University of Texas Houston Health Science Center	2012
MSN Faculty Award of Excellence Award	University of Texas Houston Health Science Center	2012
Redbud Award Outstanding Mentor Award	Texas Woman's University	2007
Houston's Top 5 Nursing Students by the <i>Houston Chronicle</i>	Texas Woman's University	2007
Outstanding Student Scholarship	Texas Woman's University	2006
Sigma Theta Tau Nursing Honor Society	Texas Woman's University	2007
Beta Beta Beta Biology Honor Society	Monmouth University	1998
Biology Research Intern Service Award	Monmouth University	1998

### **Professional Memberships**

Sigma Theta Tau International	Member	2007-Present
Houston Area Nurse Practitioners (HANP)	Member	2013-Present
American Academy of Nurse Practitioners (AANP)	Member	2013-Present

American Academy of Neuroscience Nurses (AANN)	Member	2013-Present
American Academy of Neurology (AAN)	Member	2014-Present
American College of Sports Medicine (ACSM)	Member	2014-Present
Southern Nursing Research Society (SNRS)	Member	2013-Present
National Association of School Nurses (NASN)	Member	2008-Present

### Institutional Service

*Institution: The University of Texas Health Science Center at Houston*

PhD Council	Student Representative	2015-2016
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### Presentations

Aggarwal, S. (2016, April). *Clinical and Demographic Predictors of Concussion Recovery in Adolescents: A Retrospective Study*. Poster session presented at the meeting of the Sport Neuropsychology Society's 4th annual Sport Concussion Symposium, Houston, TX.

Aggarwal, S. (2015, February). *Framework of Concussive Vulnerability*. Poster session presented at the annual meeting of the Southern Nursing Research Society, Tampa, FL.

Aggarwal, S., Gomez, M., & Reynolds, R.B. (2014, April). *Glioblastoma Multiforme Survival Analysis*, Poster session presented at The University of Texas Houston Health Science Center School of Nursing, Houston, TX.

Seema Aggarwal, Kerri Sherman, Owen Carolan, Robert Hutchins, and Dennis E. Rhoads. (1998, May). *Glutathione-Binding Proteins and Chemoreception in Cnidarians*. Paper presented at the meeting of the New Jersey Academy of Science.