HHS Public Access

Author manuscript

J Neuroimaging. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

J Neuroimaging. 2020 July ; 30(4): 387–409. doi:10.1111/jon.12726.

Sex-Related Differences in the Effects of Sports-Related Concussion: A Review

Inga K. Koerte, **Vivian Schultz**, **Valerie J. Sydnor**, **David R. Howell**, **Jeffrey P. Guenette**, **Emily Dennis**, **Janna Kochsiek**, **David Kaufmann**, **Nico Sollmann**, **Stefania Mondello**, **Martha E. Shenton**, **Alexander P. Lin**

Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (IKK, VS, VJS, JPG, ED, JK, DK, NS, MES, APL); cBRAIN, Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, Ludwig-Maximilian-University, Munich, Germany (IKK, VS, JK, DK, NS); Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA (IKK); Sports Medicine Center, Children's Hospital Colorado, Aurora, CO (DH); Department of Orthopedics, University of Colorado School of Medicine, Aurora, CO (DH); Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (JPG, MES, APL); Department of Neurology, University of Utah, Salt Lake City, UT (ED); Department of Radiology, Charité Universitätsmedizin, Berlin, Germany (DK); Department of Diagnostic and Interventional Neuroradiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany (NS); TUM-Neuroimaging Center, Klinikum rechts der Isar, Technische Universität München, Munich, Germany (NS); Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy (SM); Oasi Research Institute-IRCCS, Troina, Italy (SM); VA Boston Healthcare System, Boston, MA (MES); and Center for Clinical Spectroscopy, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (APL).

Abstract

Sports-related concussion is a serious health challenge, and females are at higher risk of sustaining a sports-related concussion compared to males. Although there are many studies that investigate outcomes following concussion, females remain an understudied population, despite representing a large proportion of the organized sports community. In this review, we provide a summary of studies that investigate sex-related differences in outcome following sports-related concussion. Moreover, we provide an introduction to the methods used to study sex-related differences after sports-related concussion, including common clinical and cognitive measures, neuroimaging techniques, as well as biomarkers. A literature search inclusive of articles published to March 2020 was performed using PubMed. The studies were reviewed and discussed with regard to the methods used. Findings from these studies remain mixed with regard to the effect of sex on

Correspondence: Address correspondence to Inga Katharina Koerte, M.D., Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, 1249 Boylston Street, Boston, MA 02215. ikoerte@bwh.harvard.edu.

clinical symptoms, concussion-related alterations in brain structure and function, and recovery trajectories. Nonetheless, there is initial evidence to suggest that sex-related differences following concussion are important to consider in efforts to develop objective biomarkers for the diagnosis and prognosis of concussion. Additional studies on this topic are, however, clearly needed to improve our understanding of sex-related differences following concussion, as well as to understand their neurobiological underpinnings. Such studies will help pave the way toward more personalized clinical management and treatment of sports-related concussion.

Keywords

Concussion; neuroimaging; sex differences

Introduction

Sports-related concussion is common, with a 20% risk each year for an individual contact-sport athlete.[1] Common symptoms associated with sports-related concussion include transient impairments in cognition, behavior, and neurological function.[2,3] The pathophysiology that gives rise to symptoms following a concussion is not fully understood, although there is evidence that brain tissue shearing leads to alterations in membrane permeability, metabolism, neurotransmitter levels, and blood flow.[4]

Females are at higher risk of sustaining a sports-related concussion.[5] Coincidently, girls and women are involved in the National Collegiate Athletic Association more than ever before. Currently, approximately 43% (~210,000) of all collegiate level-athletes are female.[6] However, notwithstanding this large number of female athletes, they remain understudied in sports-related concussion.[7] Moreover, despite the higher risk of females of sustaining a concussion in comparison to males,[8–10] studies including both female and male athletes to examine sex-related differences following concussion are sparse.[8,11–36]

Findings from the available literature indicate that females have prolonged recovery trajectories and worse outcomes following concussion compared to males.[12,14–18,21,24–30,36–45] This evidence comes primarily from studies that have utilized subjective symptom reporting, neurological evaluations, and/or computerized neurocognitive test performance, i.e., approaches that offer indirect insight into the brain (see Table 1 for a description of commonly used assessment tools). The availability of modern neuroimaging techniques, such as diffusion magnetic resonance imaging (dMRI) and magnetic resonance spectroscopy (MRS), however, now makes it possible to detect and measure objectively even subtle brain alterations following concussion (for a review, see Ref. 46; see also Fig 1 and Table 2 for more information regarding advanced neuroimaging techniques used in the study of sex-specific differences following concussion).

The purpose of this review is to provide an overview of findings from studies that focus on sex-related differences following concussion in athletes, and to elucidate possible risk factors for prolonged trajectories of recovery and worse outcome.

In what follows, we first provide a brief description of the clinical presentation of sports-related concussion. This is then followed by a review of articles that examine sex-related differences following sports-related concussion where we first summarize studies that did not find any sex-related differences (Table 3), followed by a summary of studies that report sex-related differences (Table 4). We then give an overview of the few studies that used neuroimaging (Table 5) or fluid biomarkers in the study of the effect of sex following sports-related concussion.

Description of Sports-Related Concussion

The definition of concussion varies (e.g., see discussions in Sharp and Jenkins[47] and Quarrie and Murphy[48]). Concussion is a clinical diagnosis assigned to “a transient syndrome that is characterized by an alteration in brain function occurring immediately following an impact to the head.”[49] Altered brain function may include a period of decreased or lost consciousness, or a loss of memory related to the trauma, known as post-traumatic amnesia. The symptoms of concussion can also vary and include headache, nausea, vomiting, impaired balance, muscle weakness, vision changes, and aphasia, as well as alterations in mental state and mood, such as confusion, disorientation, slowed thinking, decreased attention, memory problems, anxiety, irritability, and depression (e.g., Refs. 50, 51–53). Most of these symptoms resolve within a short period of time (days to weeks), but some sequelae of brain injury—typically a symptom-complex, including affective, cognitive, sleep, and somatic features—may persist for months or even years.[54–59] This complex of symptoms is referred to as postconcussion syndrome (PCS), which occurs in approximately 15–30% of individuals who sustain a concussion.[58,60]

Biological Sex- and Gender-Related Differences

The terms “sex” and “gender” are used inconsistently in research studies on sports-related concussion.[61] These two terms are not, however, synonymous. “Sex” is determined by an individual’s biology, based on chromosomes, gonads, and sex hormone levels.[62,63] Biological sex can be categorized into female, male, and intersex.[62] The term gender, on the other hand, refers to socially assigned behaviors, roles, attributes, and identities of men and women and boys and girls.[62,63] Given these definitions, the term “biological sex-related differences” should be used when describing biological differences between females and males, while the term “gender-related differences” should be used to emphasize behavioral or social differences between men and women.

In this review article, we provide an overview of the existing literature on biological sex- and gender-related differences after sports-related concussion. Wherever possible, we aim to use the terms “biological sex” and “gender” appropriately according to the definitions provided. However, it is important to note that most studies published to date did not explicitly distinguish between differences related to biological sex versus differences related to gender. Further, not all studies reported how information on participant sex and/or gender was obtained. Thus, most of the sex-related differences reported in the studies summarized below likely represent a combination of differences due to biological sex and gender. In this review, we refer to biological sex- and gender-related differences as sex-related differences.

Studies Investigating Differences Between Female and Male Athletes Following Sports-Related Concussion

In this section, we present: (1) clinical and cognitive studies with no findings of sex-related differences (Table 3), (2) clinical and cognitive studies with findings of sex-related differences (Table 4), and (3) neuroimaging and fluid biomarker studies investigating sex-related differences following concussion (Table 5).

We used PUBMED with the following keywords to identify relevant articles: concussion or mild traumatic brain injury (TBI), sports, gender difference or sex difference, and assessment. The following script was used: (assessment) AND (((concussion) OR mild traumatic brain injury)) AND sports AND ((sex difference) OR gender difference). The dates for the articles selected were inclusive to March 2020. Studies were selected if: (a) it was clear that the majority of subjects had sustained at least one sports-related concussion; (b) both females and males were included; and (c) sex-related outcome measures were evaluated. We did not include case studies, review articles, articles that focused on animal models, or articles that focused on repetitive head trauma resulting from head banging, epilepsy, or physical abuse.

Studies Reporting No Sex-Related Differences

Table 3 lists the six studies that did not find a significant difference in clinical or cognitive outcome measures between females and males postconcussion. We summarize these studies below.

Studies Using ImPACT Testing Battery

A study by Brooks et al[31] examined a cohort of 615 youth ice hockey players between the ages of 13 and 18 years with and without a history of a concussion. Participants completed the ImPACT testing battery and a graded symptom checklist to investigate the effect of concussion history and sex. The authors reported no significant differences in ImPACT composite scores between females and males with a history of concussion, indicating that in this cohort of adolescent athletes, concussion did not differentially affect neurocognitive abilities between the sexes. The authors furthermore reported no significant difference in total symptom ratings between males and females, noting, however, that females had higher ratings on average, and that their analyses may have been statistically underpowered to detect this difference.

In a more recent study, Brooks et al[64] used the ImPACT battery to examine cognitive function and symptom burden in 9,314 youth soccer players; players were divided into four groups based on having a history of no prior concussion, one prior concussion, two prior concussions, or three plus prior concussions. The authors found no sex by number of concussion interactions when examining ImPACT cognitive scores or total symptom ratings, indicating that the effects of concussion history on cognitive test performance and symptom severity did not significantly differ between females and males.

Finally, a study by Zuckerman and colleagues investigated sex-related differences in neurocognitive functioning before and after concussion.[35] Eighty high school athletes (40 females and 40 males) completed the ImPACT battery before the start of the season, as well as approximately 1 week postconcussion (7.2 days postconcussion on average for females and 5.4 days postconcussion on average for males). No sex-related differences in baseline or postconcussion cognitive scores were reported.

Studies Using Other Outcome Measures

Kontos and colleagues[32] prospectively investigated the relationship between depression (using the Beck Depression Inventory-II), neurocognitive performance, and symptoms among 75 athletes who sustained a concussion. They reported that recovery patterns for symptoms and neurocognitive performance were similar between the sexes. Males and females reported similar levels of depression-specific symptoms after concussion. These findings seem to suggest that postinjury recovery trajectories are similar among females and males.

Black et al[8] investigated the incidence of concussion, symptom resolution, and neurocognitive function resolution among 791 athletes with a mean age of 19.3 years. A higher prevalence of concussions was found among females (n = 42/75 concussed athletes in the study), but no sex-related differences in neurocognitive deficits or symptom resolution were reported following concussion. Consistent with a prior research,[65] neurocognitive recovery took longer than symptom resolution (median = 11 days) among all participants, but the time required for recovery was not different between females and males.

Finally, another study by Zuckerman and colleagues[66] assessed 1,507 concussed collegiate athletes and identified 70 males and 42 females with persistent postconcussive symptoms (defined as symptoms lasting longer than 4 weeks). Recurrent concussion and the emergence of specific symptoms following concussion (retrograde amnesia, difficulty concentrating, insomnia, and sensitivity to light) were associated with the development of persistent PCS. Sex, however, was not associated with the incidence of persistent PCS.

In summary, studies examining athletes across diverse age ranges did not identify significant differences between females and males following concussion with respect to ImPACT test performance, total symptom scores, time to neurocognitive recovery or symptom resolution, or incidence of persistent PCS. Females did, however, tend to endorse greater overall symptoms and depression symptoms, and tend to exhibit an increased time to general symptom resolution, compared to males, though these trends were not statistically significant.

Studies Reporting Sex-Related Differences

While the studies reviewed above failed to identify sex-related differences in symptom presentation or recovery postconcussion, the majority of studies (n = 25) have indeed found that sex and gender influence diverse outcome measures following a sports-related concussion. Table 4 provides an overview of these studies, which are summarized below.

Symptom Burden

Berz and colleagues[13] examined 37 athletes aged 9–17 years who completed the PCSS during both initial and follow-up assessments. Females showed higher symptom scores at the time of initial assessment compared with males. A study by Merritt and Arnett[25] investigated collegiate athletes who were tested preinjury and within days after concussion. Subjects completed the PCSS and ImPACT along with a set of several neuropsychological tests. Female athletes reported more symptoms than males. Specifically, sex predicted postconcussion symptom scores, while other demographic characteristics did not. Ono et al[28] investigated elementary, middle, and high school athletes who were tested at baseline and within 1 week of injury. Similarly to the previous study, females showed a higher number of symptoms at baseline and throughout the recovery process, particularly emotional and somatic symptoms. Further, in a study by Preiss-Farzanegan et al[29] females demonstrated higher risk for certain symptoms, including headache, dizziness, fatigue, irritability, and concentration problems, compared with males. Interestingly, adult (but not minor) female athletes were at increased risk for postconcussive symptoms (more than 3 months) compared to males. Importantly, the increased risk could not be explained by characteristics of the sports or other confounders suggesting an age by sex interaction in the risk of developing PCS. Frommer et al[22] examined symptom reports collected from high school athletes' coaches and clinicians over a 2-year period. While no sex-related differences were found in the number of postconcussive symptoms reported, symptom clusters differed, with males reporting more cognitive symptoms than females, and females reporting more somatic and neurobehavioral symptoms than males. Mihalik et al[26] evaluated 296 young athletes (mean age 16.7 years) following a concussion, with a specific focus on postconcussion migraine. Subjects were divided into three groups based on symptom report on the first day postinjury. Subjects in the migraine group ($n = 52$) reported headache, nausea, and either phonophobia or photophobia. Athletes in the headache group ($n = 176$) reported headache but no migraine-like symptoms, and the remaining subjects reported no headache ($n = 68$). Athletes suffering from migraine-like symptoms following concussion took longer to recover than those with post-traumatic headache and those not reporting headache following injury. Female athletes were 2.13 times more likely to report posttraumatic migraine compared with males. Of note, the prevalence of migraine in the general population is known to be higher in women (9.7%) compared to men (6%).[67] A similar difference in prevalence has also been observed in a large cohort of children and adolescents (girls: 10.5%, boys: 7.6%).[68] Nonetheless, the reported difference in prevalence following concussion is larger than that observed in the general population, suggesting an increased vulnerability for migraine development following concussion in girls and women.

In summary, studies reported higher symptom scores acutely and an increased risk for postconcussive symptoms 3 months postinjury in female athletes following sports-related concussion. Further, females endorsed different symptom patterns compared to males. Females seem to be particularly vulnerable to the development of postconcussion migraine.

Cognitive Function

Sandel et al[69] extracted data from the medical records of 224 soccer and lacrosse players from the ImPACT Applications Inc. database, and examined metrics from baseline (i.e., preinjury) and within 3 days postinjury testing. At baseline, there were no differences between males and females. However, following concussion, females performed worse on all ImPACT composite scores and reported more symptoms compared with males. Also using the ImPACT battery, Covassin et al[20] found that males reported significantly higher vomiting and sadness symptom scores, while females performed worse on visual memory tasks following concussion. In another study by Covassin et al,[18] 150 high school and 72 collegiate athletes completed the ImPACT testing preinjury as well as on day 2, 7, and 14 following concussion. Females reported more symptoms and performed worse on visual memory following concussion as compared to males. A more recent study by Covassin et al[17] replicated this visual memory finding. In this study of high school and collegiate soccer players, females reported a significantly higher number of postconcussive symptoms and exhibited worse visual memory performance compared to males 8 days after concussion. Analyzing 2,140 male and 856 female collegiate athletes enrolled in the CARE study (Concussion Assessment, Research, and Education), O'Connor et al[70] reported small but significant sex-related differences on the visual memory task scale from ImPACT, with males performing better, echoing results from Brooks et al and Covassin et al reported above. Males were significantly more likely to report zero symptoms on the SCAT or BSI-18. A study by Colvin et al[15] evaluated 141 female and 93 male soccer athletes at a median of 9 days postconcussion. Female athletes reported a significantly higher number of symptoms than male athletes following concussion. Moreover, females exhibited significantly slower composite reaction times on neurocognitive tests compared to males. Finally, Broshek et al[14] examined a cohort of 94 male and 37 female high school and collegiate athletes. The computer-based Concussion Resolution Index (CRI) was administered at baseline and during multiple postinjury evaluations. Females reported a significantly higher number of concussion symptoms than males. In addition, females showed significantly greater deviations from baseline cognitive performance, although they were evaluated a mean of 24 hours later than males, which would have given them more time to recover. Furthermore, compared to males, females were 1.5 times more likely to be cognitively impaired following concussion; after adjusting for wearing protective headgear, females were more than twice as likely to be cognitively impaired following concussion. A study by Léveillé et al[71] included a small sample size and found that male concussed athletes performed more poorly when identifying negative emotions in an emotion recognition task compared to male controls and female concussed athletes, while female concussed athletes and female controls did not perform significantly differently. Sicard et al[72] focused on potential long-term effects of concussion, examining 98 male and 98 female asymptomatic athletes who were at least 6 months postinjury. Female athletes responded significantly more slowly on a 2-back task than male athletes. They did not report any sex-related differences in accuracy on the 2-back task, or on tests of processing speed or attention.

In summary, in addition to underscoring findings of greater symptom burden, studies found worse cognitive functioning (i.e., visual memory, reaction time, and emotion cognition) in females compared to males following sports-related concussion.

Trajectory of Recovery

A study by Zuckerman et al[30] examined 122 male and 122 female athletes at middle school, high school, and collegiate levels using the ImPACT battery at baseline and postconcussion. Female athletes reported more postconcussion symptoms compared with males. Moreover, it took female athletes an average of 2.1 days longer to return to their individual baseline than males. A study by Baker et al[12] investigated 110 male and 37 female athletes (aged 13–19 years) in a longitudinal study design. Females not only reported a greater number of symptoms and increased symptom severity compared with males (as assessed using SCAT2 and either ImPACT or ANAM), but they also took almost twice as long to recover (as tested using BCTT). Gallagher et al[73] examined symptom severity using the SCAT2 or SCAT3 in a sample of 40 male and 50 female collegiate athletes, with the measure collected every 24 hours after injury until return to play. Interestingly, they also examined the impact of hormonal birth control in female athletes, reporting greater symptom burden in female athletes not taking hormonal birth control, suggesting that hormonal profiles may play a role. Female athletes had a longer length of recovery despite similar peak symptom severity. Miller and colleagues (2016)[27] also identified an association between prolonged recovery and sex. A total of 294 young athletes were included. Medical history, SCAT2, symptom severity at presentation, injury characteristics, and balance were assessed. Female sex was the strongest risk factor among all multivariate models associated with prolonged recovery from concussion (>28 days). More recently, Desai et al (2019)[95] analyzed data from 192 patients (75 females and 117 males). On average, females presented to the clinic later postinjury than males (15 vs. 9 days), and they presented with significantly greater symptom scores. Females additionally took longer to return to preinjury functioning compared to males across all recovery measures examined, including time to return to school without accommodations, time to return to noncontact exercise, time to return to full sport, time to return to baseline neurocognitive functioning, and time to vision and vestibular examination normalization. Finally, a recent study by Chandran et al[74] assessed concussion diagnosis frequency following head and neck injuries in high school soccer players. The odds of sustaining a concussion following an injury to the head or neck were 84% higher in female athletes than in male athletes, and females additionally had significantly higher odds of experiencing symptoms of light sensitivity and drowsiness.

The above-mentioned studies indicate that female sex is a risk factor not only for increased symptom severity but also for prolonged recovery following sports-related concussion. Moreover, female sex may also be a risk factor for sustaining future concussions.

Vestibular-Oculomotor Function

Henry et al[24] assessed the recovery trajectories of athletes after sports-related concussion using ImPACT and a Dizziness Handicap Inventory-adapted interview in addition to assessing vestibular-oculomotor function. While there was no effect of sex on neurocognitive recovery, females recovered more slowly in both dizziness and vestibular-oculomotor function than males. A study by Sufrinko and colleagues[75] included 36 male and 28 female athletes (aged 9–18 years) who presented at a clinic within 21 days of injury. Sex-related differences were evaluated using the Vestibular/Ocular Motor Screen, BESS, ImPACT, and PCSS. Females reported more postconcussive symptoms and showed higher vestibular ocular reflex scores than males, while no saccadic movement, near point of convergence, neurocognitive test, or balance differences were identified. The authors concluded that among a diverse set of clinical outcomes, only vestibular-ocular reflex tests were able to discriminate between sexes.

Gait Performance

Howell and colleagues[36] investigated gait characteristics (i.e., walking speed, stride length, and step rate) of female and male youth athletes within 14 days of concussion and uninjured controls in single-task (walking down a hallway) and dual-task (walking down a hallway while concurrently completing a cognitive task) conditions. Concussed females demonstrated a greater change between single-task and dual-task conditions for the step rate variable. Female and male controls did not, however, exhibit a significant difference. The authors suggest that executive functioning may be differentially affected by concussion between sexes, resulting in a greater change between single-task and dual-task conditions for concussed females compared to concussed males. The authors suggest that objective measures, such as instrumented gait measurements, may be able to characterize better between sex-related differences following concussion than self-report measures (e.g., symptom inventories).

Heart Rate Variability

Hutchison and colleagues[76] examined 16 male and 10 female student athletes who had sustained a concussion, as well as 16 male and 10 female age-matched healthy controls. Heart rate variability and cortisol levels were measured. Acutely postconcussion (i.e., within 1 week postinjury), all concussed subjects reported greater symptom severity, worse emotional disturbance, and worse sleep quality than controls, but no differences between females and males were observed. However, heart-rate variability response among female athletes was more sensitive to concussion than males. The authors suggested that decreased parasympathetic activity without a corresponding sympathetic activity increase could underlie the altered heart-rate variability observed in females.

These studies provide evidence that sex may influence how the brain responds to concussion. Convergent evidence from over 10 available studies demonstrates that females report more severe postconcussion symptoms compared to males, making this the most common finding among the studies reviewed in Table 4. While this sex-related disparity in symptom endorsement may affect all symptom categories, females are more likely to experience somatic, neurobehavioral, emotional, and vestibular-oculomotor symptoms than males. A number of studies additionally reported greater decrements in neurocognitive functioning following concussion in females, with decrements in visual memory and reaction time being the most prominent. Further, the few studies that examined recovery reported that females take longer to return to baseline following a sports concussion, i.e., females appear to have an increased risk for experiencing a protracted illness course and for enduring persistent PCS at 3 months postinjury. Finally, few studies investigating neurological and physiological function indicate sex-specific differences in vestibular-oculomotor function and gait performance and heart rate variability. Differences in clinical and cognitive symptoms between the sexes following concussion may be related to differences in heart rate variability, neuroinflammatory markers, or hormonal profiles.

Imaging Studies

Very few studies ($n = 4$) have investigated sex-related differences following sports-related concussion using imaging techniques, despite the potential that these methods offer for elucidating neurological underpinnings of sex-differences in clinical and cognitive outcomes (Table 5). Chamard et al[77] followed a cohort of 25 male and 20 female ice hockey players over one play season. All participants received baseline and end of season MRI and MRS. Five males and six females who sustained a concussion were additionally scanned 72 hours, 2 weeks, and 2 months after injury. The ratios of the following metabolites in the corpus callosum were analyzed: Glu/Cr-phosphocreatine, mI/Cr, and NAA/Cr. No differences were found between athletes who sustained a concussion during the season and those who did not. However, the group of female athletes who were not diagnosed with a concussion showed a significant decrease in their NAA/Cr ratios over time, whereas all metaboliteratios remained stable in male athletes who were not diagnosed with a concussion. It is possible that the decrease in NAA is reflective of neuronal injury due to exposure to subconcussive injury during the season, and that females may be more sensitive to these injuries compared to males.

Helmer and colleagues[23] investigated the same cohort using SWI. There were sex-related differences at baseline in the control group with higher hypointensity burden in males compared to females. Following concussion, there was a statistically significant increase in the hypointensity burden in male athletes compared to baseline. The same trend was also observed among female athletes who sustained a concussion, although the increase was smaller and not statistically significant. No differences in the hypointensity burden were found among the nonconcussed athletes between baseline and end of season scans. These results highlight the importance of appreciating sex-related differences at baseline. Future studies are needed that investigate the relationship between frequency and force of head impact and hypointensity burden.

A study by Fakhran et al[78] collected DTI data within 3 days of initial clinical evaluation of 47 males and 22 females who sustained a concussion, as well as 10 male and 11 female healthy controls. A voxel-based group comparison of fractional anisotropy (FA) values was performed with TBSS. White matter tracts corresponding to the significant clusters found in TBSS were identified using standardized atlases. Males with concussion showed significantly lower FA values in the uncinate fasciculus bilaterally compared to females with concussion and both male and female controls. Moreover, males experienced a significantly longer time to symptom resolution. This result is interesting in the light of previous studies mentioned above that reported longer recovery time in females. Of note, the control group in this study is very small. Future studies using DTI in larger cohorts are clearly needed to better understand microstructural differences between females and males following concussion.

Hsu et al[42] included 15 males and 15 females who sustained a concussion, as well as 15 male and 15 female controls. The primary mechanism of injury was fall for both males and females; however, three subjects (two males and one female) sustained a sports-related concussion. All subjects underwent fMRI and neuropsychological testing, and working memory was assessed during an fMRI task. Additionally, digit span and continuous performance testing were conducted before the scan. Subjects were scanned twice, 1 month following concussion and 6 weeks thereafter. Lower digit span scores were found in females with concussion compared with female controls. In the initial working memory scan, hyperactivation was found in the group of males who sustained a concussion but hypoactivation was found in the group of females who sustained a concussion in bilateral frontal and parietal regions, compared with controls. In the second scan, females who sustained a concussion still showed hypoactivation, whereas the hyperactivation among males who sustained a concussion resolved. In the healthy, previous fMRI studies have shown an association between increased activation in frontal and parietal areas and working memory loads.[42] The hypoactivation in females could reflect more severe injury in females. However, it is unclear if hypoactivation patterns are reflective of worse injury given other studies that have shown hyperactivation following injury.[79]

Interestingly, despite the relatively limited number of studies and some mixed results, these studies collectively reveal differences in imaging measures following concussion in males and females. For example, the MRS study showed a lower concentration of NAA, which can be interpreted as a marker of heightened neuronal injury in females compared to males. The SWI study revealed sex-related differences in hypointensity burden at baseline, highlighting that differences in imaging measures may exist even preinjury and need to be taken into account when assessing sex-specific differences following concussion. Further, one DTI study showed lower FA in males in the uncinate fasciculus; however, the sample size of the male control group was small. Conclusions as to whether females are more or less vulnerable to injury than males following concussion are difficult to make based on neuroimaging findings alone. Moreover, it remains unclear whether the differences reported might also be related to differences in the severity of injury between the two sexes. Nonetheless, these studies demonstrate how neuroimaging can be harnessed to provide valuable quantitative and objective measures of injury that provide insight into different underlying pathological pathways of injury. Future studies are clearly needed to investigate further the underlying neural pathomechanisms involved in concussion, and to understand the clinical implications of sex-specific differences following concussion.

Fluid Biomarker Studies

The past two decades have witnessed an increased interest in the potential utility of fluid biomarkers as promising objective measure in the diagnosis and prognosis of sports-related concussion.[80,81] Candidate fluid biomarkers that have been explored include axonal (tau and neurofilament light (NFL)), glial (S100B and glial fibrillary acidic protein (GFAP)), and neuronal (neuron-specific enolase (NSE) and UCH-L1) injury markers.[82] Nonetheless, this area of research is in its infancy. Most importantly, there has been a preponderant focus on male athletes and very few studies have investigated the potential influence of sex in the expression and release of brain injury-related fluid markers following sports-related concussion. The very few studies that have included female and male athletes are summarized here.

In a recent study by Asken and colleagues, male athletes exhibited substantially higher baseline concentrations of UCH-L1 and S100B than females, who, on the other hand, had higher CNPase. The investigators concluded that a better understanding of sex-related variability in these fluid biomarkers is essential for research and appropriate clinical interpretation, and they further suggested that normative data stratified by sex might be necessary.[83] A peculiar phenotype characterized by higher circulating levels of t-tau and worse outcome following sports-concussion has also been identified in female athletes,[84] suggesting a sex-based increased brain vulnerability and predisposition to certain types of injury.

Taken together, these preliminary observations indicate that the identification of sex-related biomarker signatures and the elucidation of their biological and pathophysiological basis to inform tailored management and treatment will be an important avenue for future investigation.

Summary

The literature to date has not provided sufficiently conclusive evidence for a modulating effect of sex and gender on outcome following sports-related concussion. Nonetheless, despite a few studies that found no significant differences between males and females following concussion, the accumulation of evidence does indeed point to sex-related differences across a range of clinical and neurological outcomes. It should be noted, however, that most studies investigating sex-related differences in sports-related concussion predominantly used subjective assessment tools, such as symptom reports and brief computerized neurocognitive testing, e.g., ImPACT, as the only outcome measure. This was particularly true for the few studies that did not find sex-specific differences.

In those studies that report significant sex-related differences following concussion, there are several subtle patterns that emerge. For example, examining postconcussive symptoms, multiple studies report greater symptom burden in female athletes in conjunction with a longer recovery period, with some evidence of differences in symptom clusters (i.e., somatic vs. cognitive symptoms) in males and females. There are a number of factors that may contribute to these differences, including sociological factors that may make males less likely to report symptoms.[85,86] Regarding neurocognitive performance, the most consistent findings appear to be for poorer visual memory performance in female athletes than in male athletes. However, it is important to note that sex-related differences in certain cognitive functions may exist preinjury and need to be taken into account when interpreting sex-related differences following injury. Further, sex-related differences may be subtle and require sensitive neuropsychological assessment, which is currently lacking in most studies on sports-related concussion.

Finally, although yielding promising results, currently, there are only few studies using neuroimaging to investigate sex-related differences following sports-related concussion and these studies generally are with fairly small sample sizes, thereby limiting our ability to glean much from the results. What is clear is that imaging biomarkers will likely play an important role in complementing clinical and behavioral outcome measures with objective results. There are also new advances in imaging that may add to our understanding of brain injuries (e.g., free water imaging developed by Pasternak et al).[87] Such new measures, which are typically more biologically driven and more specific, can add to the precision of measuring and characterizing brain injury as they are based on radiological evidence and can thus be considered objective outcome measures. Future studies should also use multimodal imaging assessments to quantify sex-related differences following sports-related concussion. Furthermore, fluid biomarkers are an emerging field in the diagnosis and prognosis of TBI. Their applicability in the study of sex-related specific differences following sports-related concussion needs to be assessed in future studies.

Nonetheless, the distinct pathomechanisms and reasons behind sex-related differences in sports-related concussion are far from being understood. To date, two major components contributing to such differences are herein discussed. First, sex-related differences could be associated with differences in injury incidences and intensities. In this context, studies indicate that female athletes are at greater risk for concussions when compared to males,[9,88,89] which has been associated with smaller neck girth and weaker neck muscles in females.[90] Second, sex-related differences could be closely associated with biological, physiological, or hormonal differences between males and females, as suggested by investigations among patients suffering from TBI.[91–94] These two major components are primarily based on observations among subjects with different and more severe TBI or animal models, thus leaving open the question of whether they can hold true in sports-related concussions in humans. Moreover, there is initial evidence to suggest a sex/gender by age interaction in the context of recovery from sports-related concussion. Further research is needed to elucidate the processes of age-differential recovery from concussion in females and the role of hormonal profile with regard to pubertal development as well as menopause. Future evidence, ideally derived from studies integrating findings from clinical assessments, advanced neuroimaging, and fluid biomarkers, is critically needed to gain insights into the pathomechanisms of sex-specific differences following sports-related concussions. Finally, as mentioned above, the vast majority of studies on sports-related concussion published to date did not differentiate between biological sex differences and gender-related differences. Future studies need to include information on both biological sex and gender to enable evaluation of the independent effects and interaction between sex and gender on outcome after sports-related concussion. What is clear is that females remain an understudied population in the context of brain injury. Studies investigating sports-related concussion should strive to include an equal number of males and females to facilitate elucidation of the underlying mechanism of sex-related differences following concussion. Future studies, including objective and sensitive outcome measures, multimodal neuroimaging, and fluid biomarkers, will likely lead to a better understanding of sex-specific differences in concussion/postconcussion. Results from these studies will help to optimize diagnosis, as well as return-to-play decisions, improve the individual clinical management of concussed athletes, and, ultimately, guide effective, individually tailored treatment for those who are more likely to experience postconcussive symptoms.

Acknowledgments and Disclosures:

The authors of this study were supported by the NIH (R01 NS 100952: IKK and APL; U01 NS 093334: IKK and MES), the European Research Council (ERC Starting Grant NEUROPRECISE: IKK), the Veterans Affairs (VA Merit Award I01 RX00928: MES), and the Department of Defense Congressionally Directed Medical Research Programs (W81XWH-08-2-0159: MES). This research project was also partially supported by LMU Munich's Institutional Strategy LMUexcellent within the framework of the German Excellence Initiative (IKK, DK, and VS), as well as the German Academic Exchange Service (VS). None of the authors have any potential conflict of interest related to this manuscript.

References

1. Clay MB, Glover KL, Lowe DT. Epidemiology of concussion in sport: a literature review. J Chiropr Med 2013;12:230–51. [PubMed: 24396326]
2. Iverson GL, Gaetz M, Lovell MR, et al. Cumulative effects of concussion in amateur athletes. Brain Inj 2004;18:433–43. [PubMed: 15195792]
3. Moser RS, Schatz P. Enduring effects of concussion in youth athletes. Arch Clin Neuropsychol 2002;17:91–100. [PubMed: 14589756]
4. Steenerson K, Starling AJ. Pathophysiology of sports-related concussion. Neurol Clin 2017;35:403–8. [PubMed: 28673406]
5. Abrahams S, Fie SM, Patricios J, et al. Risk factors for sports concussion: an evidence-based systematic review. Br J Sports Med 2014;48:91–7. [PubMed: 24052371]
6. NCAA. NCAA student participation rates. Available at: https://www.ncaapublications.com/p-4445-2015-16-ncaa-sports-sponsorship-and-participation-rates-report.aspx. Last accessed April 6, 2020.
7. O'Reilly K, Wilson N, Peters K. Narrative literature review: health, activity and participation issues for women following traumatic brain injury. Disabil Rehabil 2018;40:2331–42. [PubMed: 28585486]
8. Black AM, Sergio LE, Macpherson AK. The epidemiology of concussions: number and nature of concussions and time to recovery among female and male Canadian varsity athletes 2008 to 2011. Clin J Sport Med 2017;27:52–6. [PubMed: 26862834]
9. Covassin T, Swanik CB, Sachs ML. Sex differences and the incidence of concussions among collegiate athletes. J Athl Train 2003;38:238–44. [PubMed: 14608434]
10. Gessel LM, Fields SK, Collins CL, et al. Concussions among United States high school and collegiate athletes. J Athl Train 2007;42:495–503. [PubMed: 18174937]
11. Colantonio A, Harris JE, Ratcliff G, et al. Gender differences in self reported long term outcomes following moderate to severe traumatic brain injury. BMC Neurol 2010;10:102. [PubMed: 21029463]
12. Baker JG, Leddy JJ, Darling SR, et al. Gender differences in recovery from sports-related concussion in adolescents. Clin Pediatr (Phila) 2016;55:771–5. [PubMed: 26378093]
13. Berz K, Divine J, Foss KB, et al. Sex-specific differences in the severity of symptoms and recovery rate following sports-related concussion in young athletes. Phys Sportsmed 2013;41:58–63.
14. Broshek DK, Kaushik T, Freeman JR, et al. Sex differences in outcome following sports-related concussion. J Neurosurg 2005;102:856–63. [PubMed: 15926710]
15. Colvin AC, Mullen J, Lovell MR, et al. The role of concussion history and gender in recovery from soccer-related concussion. Am J Sports Med 2009;37:1699–704. [PubMed: 19460813]
16. Covassin T, Elbin R, Kontos A, et al. Investigating baseline neurocognitive performance between male and female athletes with a history of multiple concussion. J Neurol Neurosurg Psychiatry 2010;81:597–601. [PubMed: 20522868]
17. Covassin T, Elbin RJ, Bleecker A, et al. Are there differences in neurocognitive function and symptoms between male and female soccer players after concussions? Am J Sports Med 2013;41:2890–5. [PubMed: 24197616]
18. Covassin T, Elbin RJ, Harris W, et al. The role of age and sex in symptoms, neurocognitive performance, and postural stability in athletes after concussion. Am J Sports Med 2012;40:1303–12. [PubMed: 22539534]

19. Covassin T, Moran R, Elbin RJ. Sex differences in reported concussion injury rates and time loss from participation: an update of the National Collegiate Athletic Association Injury Surveillance Program from 2004–2005 through 2008–2009. J Athl Train 2016;51:189–94. [PubMed: 26950073]
20. Covassin T, Schatz P, Swanik CB. Sex differences in neuropsychological function and post-concussion symptoms of concussed collegiate athletes. Neurosurgery 2007;61:345–50. [PubMed: 17762747]
21. Covassin T, Swanik CB, Sachs M, et al. Sex differences in baseline neuropsychological function and concussion symptoms of collegiate athletes. Br J Sports Med 2006;40:923–7. [PubMed: 16990442]
22. Frommer LJ, Gurka KK, Cross KM, et al. Sex differences in concussion symptoms of high school athletes. J Athl Train 2011;46:76–84. [PubMed: 21214354]
23. Helmer KG, Pasternak O, Fredman E, et al. Hockey concussion education project, part 1. Susceptibility-weighted imaging study in male and female ice hockey players over a single season. J Neurosurg 2014;120:864–72. [PubMed: 24490839]
24. Henry LC, Elbin RJ, Collins MW, et al. Examining recovery trajectories after sport-related concussion with a multimodal clinical assessment approach. Neurosurgery 2016;78:232–41. [PubMed: 26445375]
25. Merritt VC, Arnett PA. Premorbid predictors of postconcussion symptoms in collegiate athletes. J Clin Exp Neuropsychol 2014;36:1098–111. [PubMed: 25493542]
26. Mihalik JP, Register-Mihalik J, Kerr ZY, et al. Recovery of posttraumatic migraine characteristics in patients after mild traumatic brain injury. Am J Sports Med 2013;41:1490–6. [PubMed: 23696213]
27. Miller JH, Gill C, Kuhn EN, et al. Predictors of delayed recovery following pediatric sports-related concussion: a case-control study. J Neurosurg Pediatr 2016;17:491–6. [PubMed: 26684762]
28. Ono KE, Burns TG, Bearden DJ, et al. Sex-based differences as a predictor of recovery trajectories in young athletes after a sports-related concussion. Am J Sports Med 2016;44:748–52. [PubMed: 26672026]
29. Preiss-Farzanegan SJ, Chapman B, Wong TM, et al. The relationship between gender and postconcussion symptoms after sport-related mild traumatic brain injury. PM R 2009;1:245–53. [PubMed: 19627902]
30. Zuckerman SL, Apple RP, Odom MJ, et al. Effect of sex on symptoms and return to baseline in sport-related concussion. J Neurosurg Pediatr 2014;13:72–81. [PubMed: 24206343]
31. Brooks BL, Mrazik M, Barlow KM, et al. Absence of differences between male and female adolescents with prior sport concussion. J Head Trauma Rehabil 2014;29:257–64. [PubMed: 24413074]
32. Kontos AP, Covassin T, Elbin RJ, et al. Depression and neurocognitive performance after concussion among male and female high school and collegiate athletes. Arch Phys Med Rehabil 2012;93:1751–6. [PubMed: 22503738]
33. Piland SG, Ferrara MS, Macciocchi SN, et al. Investigation of baseline self-report concussion symptom scores. J Athl Train 2010;45:273–8. [PubMed: 20446841]
34. Register-Mihalik JK, Mihalik JP, Guskiewicz KM. Association between previous concussion history and symptom endorsement during preseason baseline testing in high school and collegiate athletes. Sports Health 2009;1:61–5. [PubMed: 23015855]
35. Zuckerman SL, Solomon GS, Forbes JA, et al. Response to acute concussive injury in soccer players: is gender a modifying factor? J Neurosurg Pediatr 2012;10:504–10. [PubMed: 23030348]
36. Howell DR, Stracciolini A, Geminiani E, et al. Dual-task gait differences in female and male adolescents following sport-related concussion. Gait Posture 2017;54:284–9. [PubMed: 28384609]
37. Farace E, Alves WM. Do women fare worse: a metaanalysis of gender differences in traumatic brain injury outcome. J Neurosurg 2000;93:539–45. [PubMed: 11014529]
38. Kontos AP, Elbin RJ, Schatz P, et al. A revised factor structure for the post-concussion symptom scale: baseline and postconcussion factors. Am J Sports Med 2012;40:2375–84. [PubMed: 22904209]

39. Ahman S, Saveman BI, Styrke J, et al. Long-term follow-up of patients with mild traumatic brain injury: a mixed-method study. J Rehabil Med 2013;45:758–64. [PubMed: 24002311]
40. Bazarian JJ, Blyth B, Mookerjee S, et al. Sex differences in outcome after mild traumatic brain injury. J Neurotrauma 2010;27:527–39. [PubMed: 19938945]
41. Dillard C, Ditchman N, Nersessova K, et al. Post-concussion symptoms in mild traumatic brain injury: findings from a paediatric outpatient clinic. Disabil Rehabil 2017;39:544–50. [PubMed: 26971917]
42. Hsu HL, Chen DY, Tseng YC, et al. Sex differences in working memory after mild traumatic brain injury: a functional MR imaging study. Radiology 2015;276:828–35. [PubMed: 25919663]
43. Meares S, Shores EA, Taylor AJ, et al. Mild traumatic brain injury does not predict acute postconcussion syndrome. J Neurol Neurosurg Psychiatry 2008;79:300–6. [PubMed: 17702772]
44. Styrke J, Sojka P, Bjornstig U, et al. Sex-differences in symptoms, disability, and life satisfaction three years after mild traumatic brain injury: a population-based cohort study. J Rehabil Med 2013;45:749–57. [PubMed: 24002310]
45. Tator CH, Davis HS, Dufort PA, et al. Postconcussion syndrome: demographics and predictors in 221 patients. J Neurosurg 2016;125:1206–16. [PubMed: 26918481]
46. KoerteI K, Lin AP, Willems A, et al. A review of neuroimaging findings in repetitive brain trauma. Brain Pathol 2015;25:318–49. [PubMed: 25904047]
47. Sharp DJ, Jenkins PO. Concussion is confusing us all. Pract Neurol 2015;15:172–86. [PubMed: 25977270]
48. Quarrie KL, Murphy IR. Towards an operational definition of sports concussion: identifying a limitation in the 2012 Zurich consensus statement and suggesting solutions. Br J Sports Med 2014;48:1589–91. [PubMed: 25257231]
49. McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med 2017;51:838–47. [PubMed: 28446457]
50. Song H, Cui J, Simonyi A, et al. Linking blast physics to biological outcomes in mild traumatic brain injury: narrative review and preliminary report of an open-field blast model. Behav Brain Res 2018;340:147–58. [PubMed: 27555538]
51. Bigler ED. Neuropsychological results and neuropathological findings at autopsy in a case of mild traumatic brain injury. J Int Neuropsychol Soc 2004;10:794–806. [PubMed: 15327725]
52. Guskiewicz KM, Marshall SW, Bailes J, et al. Recurrent concussion and risk of depression in retired professional football players. Med Sci Sports Exerc 2007;39:903–9. [PubMed: 17545878]
53. Kaufman MS, Concannon LG, Herring SA. Evaluation and treatment of the concussed athlete—update. Phys Med Rehabil Clin N Am 2014;25:707–22. [PubMed: 25442155]
54. Ponsford J, Cameron P, Fitzgerald M, et al. Long-term outcomes after uncomplicated mild traumatic brain injury: a comparison with trauma controls. J Neurotrauma 2011;28:937–46. [PubMed: 21410321]
55. Kurca E, Sivak S, Kucera P. Impaired cognitive functions in mild traumatic brain injury patients with normal and pathologic magnetic resonance imaging. Neuroradiology 2006;48: 661–9. [PubMed: 16786351]
56. Konrad C, Geburek AJ, Rist F, et al. Long-term cognitive and emotional consequences of mild traumatic brain injury. Psychol Med 2011;41:1197–211. [PubMed: 20860865]
57. Maruta J, Lee SW, Jacobs EF, et al. A unified science of concussion. Ann NY Acad Sci 2010;1208:58–66. [PubMed: 20955326]
58. Barlow KM. Postconcussion syndrome: a review. J Child Neurol 2016;31:57–67. [PubMed: 25330797]
59. King NS. A systematic review of age and gender factors in prolonged post-concussion symptoms after mild head injury. Brain Inj 2014;28:1639–45. [PubMed: 25265040]
60. Ruff RM, Camenzuli L, Mueller J. Miserable minority: emotional risk factors that influence the outcome of a mild traumatic brain injury. Brain Inj 1996;10:551–65. [PubMed: 8836512]
61. Madsen TE, Bourjeily G, Hasnain M, et al. Article commentary: sex- and gender-based medicine: the need for precise terminology. Gend Genome 2017;1:122–8.

62. Peters SAE, Norton R. Sex and gender reporting in global health: new editorial policies. BMJ Glob Health 2018;3:e001038.
63. Clayton JA, Tannenbaum C. Reporting sex, gender, or both in clinical research? JAMA 2016;316:1863–4. [PubMed: 27802482]
64. Brooks BL, Silverberg N, Maxwell B, et al. Investigating effects of sex differences and prior concussions on symptom reporting and cognition among adolescent soccer players. Am J Sports Med 2018;46:961–8. [PubMed: 29323926]
65. Broglio SP, Puetz TW. The effect of sport concussion on neurocognitive function, self-report symptoms and postural control: a metaanalysis. Sports Med 2008;38:53–67. [PubMed: 18081367]
66. Zuckerman SL, Yengo-Kahn AM, Buckley TA, et al. Predictors of postconcussion syndrome in collegiate student-athletes. Neurosurg Focus 2016;40:E13.
67. Smitherman TA, Burch R, Sheikh H, et al. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from National Surveillance Studies. Headache 2013;53:427–36. [PubMed: 23470015]
68. Wober-Bingol C Epidemiology of migraine and headache in children and adolescents. Curr Pain Headache Rep 2013;17:341. [PubMed: 23700075]
69. Sandel NK, Schatz P, Goldberg KB, et al. Sex-based differences in cognitive deficits and symptom reporting among acutely concussed adolescent lacrosse and soccer players. Am J Sports Med 2017;45:937–44. [PubMed: 27940807]
70. O'Connor KL, Dain Allred C, Cameron KL, et al. Descriptive analysis of a baseline concussion battery among U.S. Service Academy Members: results from the Concussion Assessment, Research, and Education (CARE) Consortium. Mil Med 2018;183:e580–90. [PubMed: 29608767]
71. Léveillé E, Guay S, Blais C, et al. Sex-related differences in emotion recognition in multi-concussed athletes. J Int Neuropsychol Soc 2017;23:65–77. [PubMed: 27974074]
72. Sicard V, Moore RD, Ellemberg D. Long-term cognitive outcomes in male and female athletes following sport-related concussions. Int J Psychophysiol 2018;132:3–8. [PubMed: 29572188]
73. Gallagher V, Kramer N, Abbott K, et al. The effects of sex differences and hormonal contraception on outcomes after collegiate sports-related concussion. J Neurotrauma 2018;35:1242–7. [PubMed: 29336208]
74. Chandran A, Elmi A, Young H, et al. Determinants of concussion diagnosis, symptomology, and resolution time in U.S. high school soccer players. Res Sports Med 2020;28:42–54. [PubMed: 30892095]
75. Sufrinko AM, Mucha A, Covassin T, et al. Sex differences in vestibular/ocular and neurocognitive outcomes after sport-related concussion. Clin J Sport Med 2017;27:133–8. [PubMed: 27379660]
76. Hutchison MG, Mainwaring L, Senthinathan A, et al. Psychological and physiological markers of stress in concussed athletes across recovery milestones. J Head Trauma Rehabil 2017;32:E38–48.
77. Chamard E, Theoret H, Skopelja EN, et al. A prospective study of physician-observed concussion during a varsity university hockey season: metabolic changes in ice hockey players. Part 4 of 4. Neurosurg Focus 2012;33:E4:1–7.
78. Fakhran S, Yaeger K, Collins M, et al. Sex differences in white matter abnormalities after mild traumatic brain injury: localization and correlation with outcome. Radiology 2014;272: 815–23. [PubMed: 24802388]
79. Chen CJ, Wu CH, Liao YP, et al. Working memory in patients with mild traumatic brain injury: functional MR imaging analysis. Radiology 2012;264:844–51. [PubMed: 22829681]
80. O'Connell B, Kelly AM, Mockler D, et al. Use of blood biomarkers in the assessment of sports-related concussion—a systematic review in the context of their biological significance. Clin J Sport Med 2018;28:561–71. [PubMed: 29035978]
81. Finnoff JT, Jelsing EJ, Smith J. Biomarkers, genetics, and risk factors for concussion. PM R 2011;3:S452–9. [PubMed: 22035689]
82. Zetterberg H, Winblad B, Bernick C, et al. Head trauma in sports—clinical characteristics, epidemiology and biomarkers. J Intern Med 2019;285:624–34. [PubMed: 30481401]
83. Asken BM, Bauer RM, DeKosky ST, et al. Concussion biomarkers assessed in collegiate student-athletes (basics) I: normative study. Neurology 2018;91:e2109–22. [PubMed: 30404785]

84. Gill J, Merchant-Borna K, Jeromin A, et al. Acute plasma tau relates to prolonged return to play after concussion. Neurology 2017;88:595–602. [PubMed: 28062722]

85. Kerr ZY, Register-Mihalik JK, Kroshus E, et al. Motivations associated with nondisclosure of self-reported concussions in former collegiate athletes. Am J Sports Med 2016;44:220–5. [PubMed: 26582799]

86. Torres DM, Galetta KM, Phillips HW, et al. Sports-related concussion: anonymous survey of a collegiate cohort. Neurol Clin Pract 2013;3:279–87. [PubMed: 24195017]

87. Pasternak O, Sochen N, Gur Y, et al. Free water elimination and mapping from diffusion MRI. Magn Reson Med 2009;62:717–30. [PubMed: 19623619]

88. Marar M, McIlvain NM, Fields SK, et al. Epidemiology of concussions among United States high school athletes in 20 sports. Am J Sports Med 2012;40:747–55. [PubMed: 22287642]

89. Forward KE, Seabrook JA, Lynch T, et al. A comparison of the epidemiology of ice hockey injuries between male and female youth in Canada. Paediatr Child Health 2014;19:418–22. [PubMed: 25382998]

90. Tierney RT, Sitler MR, Swanik CB, et al. Gender differences in head-neck segment dynamic stabilization during head acceleration. Med Sci Sports Exerc 2005;37:272–9. [PubMed: 15692324]

91. Roof RL, Hall ED. Gender differences in acute CNS trauma and stroke: neuroprotective effects of estrogen and progesterone. J Neurotrauma 2000;17:367–88. [PubMed: 10833057]

92. Kupina NC, Detloff MR, Bobrowski WF, et al. Cytoskeletal protein degradation and neurodegeneration evolves differently in males and females following experimental head injury. Exp Neurol 2003;180:55–73. [PubMed: 12668149]

93. Emerson CS, Headrick JP, Vink R. Estrogen improves biochemical and neurologic outcome following traumatic brain injury in male rats, but not in females. Brain Res 1993;608:95–100. [PubMed: 8495351]

94. Djebaili M, Guo Q, Pettus EH, et al. The neurosteroids progesterone and allopregnanolone reduce cell death, gliosis, and functional deficits after traumatic brain injury in rats. J Neurotrauma 2005;22:106–18. [PubMed: 15665606]

95. Desai N, Wiebe DJ, Corwin DJ, et al. Factors affecting recovery trajectories in pediatric female concussion. Clin J Sport Med 2019;29:361–7. [PubMed: 31460948]

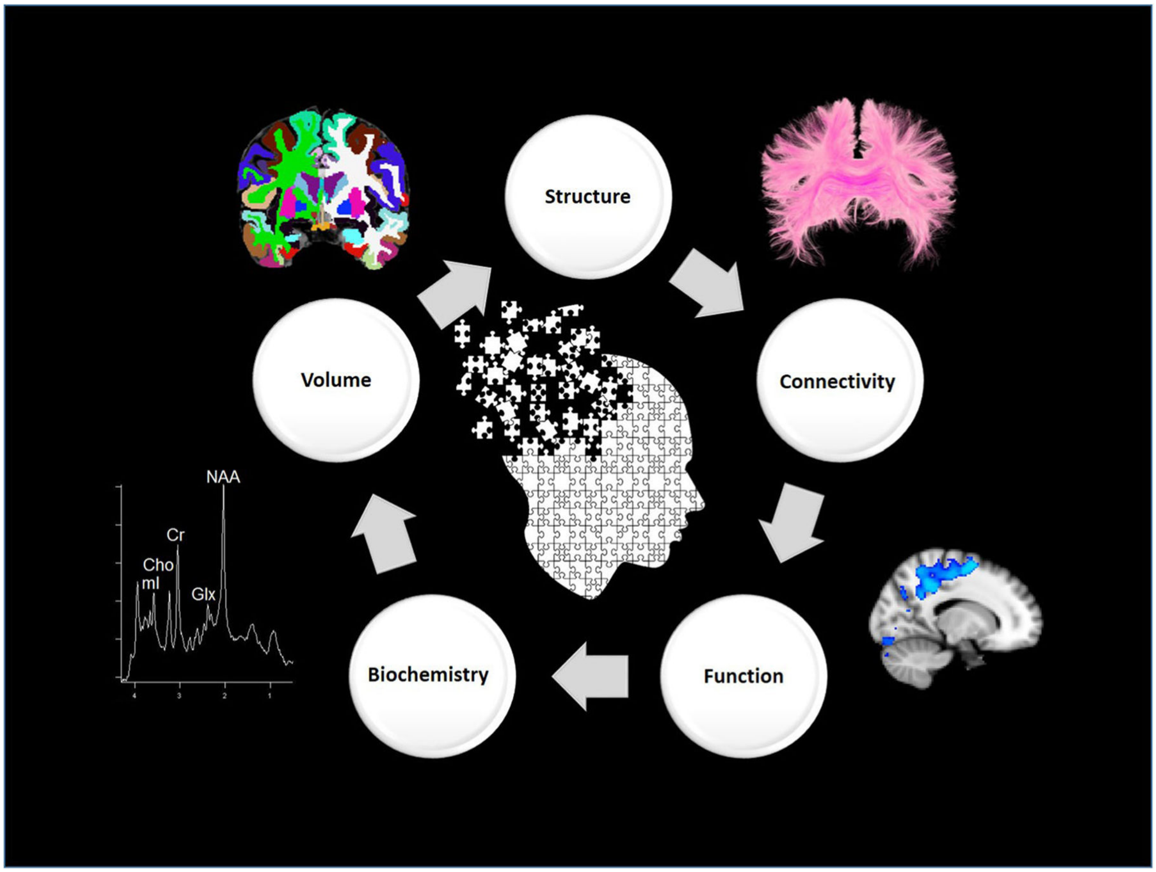

Fig 1.

Complementary advanced neuroimaging techniques that are used in studies on sex-related differences after concussion. Abbreviations: Cho, choline; Cr, creatine; Glx, glutamate-glutamine; mI, myo-Inositol; NAA, N-acetylaspartate.

Table 1.

Clinical Measures Used to Examine Sex-Related Differences Following Sports-Related Concussion

Measure	Description
Symptom inventories	
PCSS	Used within the SCAT, this symptom scale assesses 22 concussion symptoms rated by the patient on a 0–6 scale. It was developed specifically to track the recovery of concussion symptoms in athletes over time. Severity scores are calculated as the summed total of all reported symptoms.
RPQ	The RPQ is a 16-item symptom inventory that assesses somatic, emotional, and cognitive symptom domains. Patients rate the degree to which each item in the inventory has been more of a problem in the past 24 hours than it was preinjury. Items are rated on a 0–4 scale.
DHI	On this 25-item questionnaire, patients rate the extent that their dizziness affects physical, emotional, and functional domains (“no,” “sometime,” and “always”). Higher scores on this 0–100 scale indicate greater dizziness-related handicap.
BDI II	On this 21-symptom inventory, patients rate depression-related symptoms on a 0–3 scale. Severity scores are calculated as the summed total of all reported symptoms. A score of 0–13 represents minimal depression, 14–19 represents mild depression, 20–28 moderate depression, and 29–63 severe depression.
BAI	The BAI assesses the severity of anxiety-specific symptoms. Patients rate 21 different items related to anxiety on a 0–3 scale. Severity scores are calculated as the summed total of all reported symptoms.
POMS-SF	The POMS-SF is a self-report scale that consists of 36 items related to tension, depression, fatigue, vigor, confusion, anger, and esteem-related affect, used to assess overall mood disturbance/instability and psychological distress.
SSS	The SSS is a scale used to quantify subjective sleepiness throughout the day. Patients read seven statements describing different levels of alertness and sleepiness, and select which statement best describes how they feel at different times in the day.
PSS	On this 14-item questionnaire, patients report how often events occurring in the past month felt unpredictable or uncontrollable, using a 0–4 scale (ranging from never to very often). Frequency scores are calculated as the summed total of all reported symptoms.
Sideline tests	
SCAT, SCAT2, and SCAT3	A combination of tests designed to evaluate acute postconcussion deficits. Tests include the SAC, the Glasgow Coma Scale, the Maddocks Questionnaire, the modified BESS test, a tandem gait test, and the PCSS.
Functional/physiologic tests	
BCTT	An exercise capacity test aimed to increase heart rate until concussion symptoms increase. This test has been used to provide individual exercise recommendations after a concussion.
BESS	A component of the SCAT employed to measure postural steadiness following concussion.
Dual-task gait evaluation	A test paradigm used to evaluate gait and cognitive performance after a concussion; evaluates both simultaneously under a dual-task condition. Outcome measures include walking speed, stride length, and cadence (ie, step rate).
VOMS	A test consisting of five assessments evaluating oculomotor and vestibular functioning: smooth pursuits, horizontal/vertical saccades, near point of convergence, horizontal/vertical ocular reflex, and visual motion sensitivity. Patients report if each test provokes or intensifies headache, dizziness, nausea, and fogginess symptoms.
Heart rate variability	Measures variability in the R-R interval (the time between successive heart beats). An assessment of how cardiovascular and central nervous systems integrate, theorized to represent physiological and psychological stress.
Neurocognitive tests	
ImPACT	A computerized evaluation of neurocognitive functioning that assesses several domains, including verbal memory, visual memory, visual-motor processing speed, reaction time, and impulse control, using six testing modules.
CRI	A computerized evaluation that calculates three summary scores in the domains of simple reaction time, complex reaction time, and processing speed.

Measure	Description
ANAM	A computerized evaluation that includes the following tests: simple reaction time, code substitution, code substitution-delayed, continuous performance test, mathematical processing, matching to sample, spatial processing, Sternberg memory procedure, and procedural reaction time.
BVMT-R	A visual learning test that consists of three practice trials followed by a free-recall trial. Patients view a 2×3 matrix of abstract designs and are asked to learn and reproduce them.
HVLT-R	An evaluation of memory in which patients view a 12-word list and subsequently identify the presented words, both immediately and following a delay.
TMT	A measure of processing speed and executive functioning. Form A: Patients search an array of numbers, connecting the numbers in ascending order. Form B: Patients search an array of numbers and letters, connecting numbers and letters in alternating ascending order (e.g., 1, A, 2, B, etc).
SDMT	A written measure of visual working memory, learning, visual scanning, psychomotor speed, and attention, wherein nine numbers and corresponding number-specific symbols are presented. Over a 2-minute period, patients identify which symbol corresponds with which number.
RAVLT	An assessment of learning and immediate/delayed verbal memory. Patients hear a list of 15 nouns and are asked to recall as many nouns as possible, both immediately and after a 20-minute delay.
Stroop test	In this evaluation of inhibition and mental flexibility, patients are given a set of cues that are either congruent or incongruent in nature. For example, they see a set of color names that either correspond with the color (eg, the word red written in red ink) or that do not correspond with the color (eg, the word red written in blue ink).

Abbreviations: ANAM, Automated Neuropsychological Assessment Metric; BAI, Beck Anxiety Inventory; BCTT, Buffalo Concussion Treadmill Test; BDI II, Beck Depression Inventory II; BESS, Balance Error Scoring System; BVMT-R, Brief Visuospatial Memory Test–Revised; CRI, Concussion Resolution Index; DHI, Dizziness Handycap Inventory; HVLT-R, Hopkins Verbal Learning Test–Revised; ImPACT, Immediate Postconcussion Assessment and Cognitive Testing; PCSS, Post-Concussion Symptom Scale; POMS-SF, Profile of Mood States Short Form; PSS, Perceived Stress Scale; RAVLT, Rey Auditory Verbal Learning Test; RPQ, Rivermead Post Concussion Symptom Questionnaire; SAC, Standardized Assessment of Concussion; SCAT, Sport Concussion Assessment Test; SDMT, Symbol Digit Modalities Test; SSS, The Stanford Sleepiness Scale; TMT, Trail-Making Test; VOMS, Vestibular-Ocular Motor Screen.

Table 2.

Neuroimaging Modalities

Imaging Modality	Brain Feature Measured	Description
High-resolution structural MRI	Macrostructural anatomy	Allows for the accurate quantification of macrostructural anatomical features of the brain, including regional volume, surface area, cortical thickness, or shape. Brain regions of interest can be delineated manually or using automated parcellation software.
DTI	White matter microstructure	Used to examine properties of brain tissue microstructure through the quantification of local water diffusion. DTI provides four main measures of white matter microstructure that are derived from the three eigenvalues of the diffusion tensor, including FA (describes the degree of diffusion anisotropy, scaled from 0 to 1), MD (a direction-independent measure of average diffusivity), AD (quantifies diffusion along the main axis of diffusion, ie, the primary eigenvalue), and RD (quantifies diffusion perpendicular to the main axis of diffusion, ie, the mean of the secondary and tertiary eigenvalues). Differences in DTI measures can be examined using white matter tract-based or voxel-based approaches.
MRS	Neurochemicals	Measures the concentration of diverse chemicals and metabolites in the brain based on known proton resonance frequencies, including NAA (a marker of neuronal density and viability), Cho (a component of membrane phospholipids), mI (a marker of astrocytes), Cr (a metabolite involved in brain energetics), and Glu (an excitatory neurotransmitter).
SWI	Microhemorrhages	Enables the identification of hemosiderin (iron storage complex) foci that develop following both large and small hemorrhages, given the different magnetic susceptibilities of these foci as compared to the surrounding tissue. Using SWI, a hypointensity burden can be calculated, which provides a normalized estimate of the total volume of hypointensities belonging to nonblood vessel hypointense voxel clusters. The hypointensity burden is believed to reflect the burden of microhemorrhages in the brain.
fMRI	Brain region or network activation	Detects changes in local levels of paramagnetic deoxyhemoglobin via the BOLD contrast, thus providing insight into changes in localized blood flow, oxygen concentration, and neuronal activity. FMRI can provide information about brain activity when individuals are in a state of rest (allowing for the evaluation of stable “resting-state” brain networks) or performing a task.

Abbreviations: AD, axial diffusivity; BOLD, blood oxygen level-dependent; Cho, choline; Cr, creatine; DTI, diffusion tensor imaging; FA, fractional anisotropy; fMRI, functional MRI; Glu, glutamate; MD, mean diffusivity; mI, myo-Inositol; MRS, magnetic resonance spectroscopy; NAA, N-acetyl aspartate; RD, radial diffusivity; SWI, susceptibility weighted imaging.

Note: A description of the neuroimaging methods that have been employed to examine differences in brain structure, function, and neurochemistry following sports-related concussion.

Table 3.

A Summary of Studies that Report No Sex-Related Differences after Sports-Related Concussion

First Author	Year	Title	Journal	Predominant Sport		Subjects (n, sex, and age)	Outcome Measure	Analysis Technique	Main Findings
Black et al[8]	2016	The Epidemiology of Concussions: Number and Nature of Concussions and Time to Recovery Among Female and Male Canadian Varsity Athletes 2008 to 2011	J Neurosurg Pediatr	**1** **2** **3**	Women's rugby Women's ice hockey Men's basketball	33 males and 42 females (mean age 19.34 years), all concussed at least once. 5 athletes with multiple concussions, in total 81 concussions were reported.	Neurocognitive testing and symptom report	ImPACT testing at baseline. Following concussion, athletes were examined with SCAT (before 2008) or SCAT2 (after 2008). Athletes had a daily follow-up with SCAT/SCAT2. Once no more symptoms were reported on SCAT/SCAT2, ImPACT was taken again. Time to symptom resolution was reported as the number of days from concussion to the day of first ImPACT follow-up.	Significantly more female athletes sustained a concussion than male athletes. Differences in symptoms and neurocognitive recovery, however, were not significant between sexes.
Brooks et al[31]	2014	Absence of Differences Between Male and Female Adolescents with Prior Sport Concussion	J Head Trauma Rehabil	Hockey		615 elite hockey players, 517 male (84%) and 98 female (16%). Mean age 15.5 years (range 13.0–17.9 years).	Neurocognitive testing	Baseline testing for all athletes included ImPACT. Moreover, concussion history was collected using preseason questionnaire.	At baseline, no differences in cognitive measures or symptoms were found between males and females with prior concussion(s). When comparing males and females without prior concussion history, females reported significantly greater symptom severity than males.
Brooks et al[64]	2018	Investigating Effects of Sex Differences and Prior Concussions on Symptom Reporting and Cognition Among Adolescent Soccer Players	Am J Sports Med	Soccer		9,314 youth soccer players grouped by number of prior concussions: 0 (4,012 males and 3,963 females); 1 (527 males and 457 females), 2 (130 males and 97 females), > = 3 (73 males and 55 females); mean age 14.8 years.	Neurocognitive testing and symptom report	Baseline preseason assessment using the ImPACT battery for testing of four cognitive domains and administration of the postconcussion symptom scale. Participants were divided into four groups: no concussion history, one prior concussion, two prior concussions, and three plus prior concussions. Interactions between concussion history group and sex were examined for various ImPACT measures.	No sex by number of concussion interactions was identified when examining the following ImPACT outcome measures: verbal memory, visual memory, visual motor, reaction time, and total symptoms.
Kontos et al[32]	2012	Depression and Neurocognitive Performance after Concussion among Male and Female High School and Collegiate Athletes	Arch Phys Med Rehabil	No information		75 athletes, 54 high school (40 males, mean age 15.9 years, and 14 females, mean age 15.29 years) and 21 collegiate (11 males, mean age 19.75 years,	Neurocognitive and depression symptoms testing	1 baseline and 3 postconcussion (day 2, 5–7, and 10–14 post injury) assessments with BDI II and ImPACT.	The incidence of clinical depression did not significantly increase following concussion. However, concussed athletes had increased depression scores (compared to baseline) for

First Author	Year	Title	Journal	Predominant Sport	Subjects (n, sex, and age)	Outcome Measure	Analysis Technique	Main Findings
					10 females with a mean age 19.6 years).			up to 14 days following concussion. Higher depression scores were additionally associated with worse performance on tests of visual memory and reaction time, as well as with increased postconcussive symptoms. No sex differences were found in depression levels.
Zuckerman et al[35]	2012	Response to Acute Concussive Injury in Soccer Players: Is Gender a Modifying Factor?	J Neurosurg Pediatr	Soccer	80 high school athletes, 40 males (mean age 15.8 years) and 40 females (mean age 15.9 years).	Neurocognitive testing	Baseline and postconcussion testing using ImPACT. Males were tested an average of 2 days earlier than females after injury (5.4 days vs. 7.18 days postconcussion).	No sex differences were found on baseline neurocognitive tests. Moreover, no differences in postconcussive symptoms or neurocognitive outcome were identified between sexes.
Zuckerman et al[66]	2016	Predictors of Postconcussion Syndrome in Collegiate Student-Athletes	Neurosurg Focus	**1** Football **2** Ice hockey	1,057 student athletes who sustained a concussion: 112 who developed PCS. In the PCS group, there were 70 males and 42 females. In the no PCS group, there were 967 males and 428 females.	Duration of concussion symptoms	Data acquired from the National Collegiate Athletic Association; Injury Surveillance Program between 2009 and 2015. For any sport-related concussion, event report data were extracted, including the duration of concussion symptoms reported by athletic trainers in their daily clinical practice. PCS was defined as cases where an athlete experienced one or more concussion symptom for longer than 1 month postinjury.	Several variables were associated with increased odds of developing PCS, including recurrent concussion, retrograde amnesia, difficulty concentrating, light sensitivity, and insomnia. Sex, helmet status, contact level, and loss of consciousness were not related to the development of PCS.

Abbreviations: BDI, Beck Depression Inventory; ImPACT, Immediate Postconcussion Assessment and Cognitive Testing; *n*, number of subjects; PCS, postconcussion syndrome; SCAT, Sport Concussion Assessment Test.

Table 4.

Summary of Studies that Report Sex-Related Differences after Sports-Related Concussion

First Author	Year	Title	Journal	Predominant Sport	Subjects (*n*, sex, and age)	Outcome Measure	Analysis Technique	Main Findings
Baker et al[12]	2015	Gender Differences in Recovery From Sports-Related Concussion in Adolescents	Clin Pediatr (Phila)	Males: **1** Football **2** Hockey **3** Lacrosse Females: **1** Soccer **2** Softball **3** Lacrosse **4** Basketball	147 student athletes, 117 participated in a previous study, 30 were seen through 2014. 110 males and 37 females (mean age females: 15.5 years, mean age males: 15.4 years).	Neurocognitive and neurotesting	SCAT2 and computerized testing (ImPACT) or ANAM was assessed within days after injury (mean 9.9–16.5 days), assessment clinic changed during the study period from ANAM to ImPACT due to more widespread use of ImPACT at high schools. Confirmation of atheletes' self-report to be "asymptomatic" by BCTT	Gender differences were found in symptom reporting, symptom severity, and time to become asymptomatic. Females reported a greater number of symptoms overall, and additionally rated symptoms as more severe. Females also took almost twice as long to recover. After adjusting for gender differences in initial symptom scores, however, the difference in recovery time only approached significance, suggesting that differences in symptom reporting may underlie the difference found in recovery time.
Broshek et al[14]	2005	Sex Differences in Outcome Following Sports-Related Concussion	J Neurosurg	Males: **1** Football **2** Lacrosse **3** Wrestling **4** Other Females: **1** Soccer **2** Field hockey **3** Lacrosse **4** Basketball **5** Cheerleading	131 athletes, 94 males (mean age: 19.2 years) and 37 females (mean age: 17.5 years). Almost equal number of college and high school athletes (47.3% compared to 52.7%); however, females were overrepresented in the high school group with 64.9%.	Neurocognitive testing	CRI was administered at baseline and at each posttrauma evaluation. Immediately following head injury, questions concerning athlete's symptom presentation were answered by either the athletic trainer or the team physician who witnessed the injury. The presence and intensity of postconcussion symptoms were rated by the athlete at testing time within 1–2 days after injury.	Females reported significantly more postconcussive symptoms than males did. In addition, females showed significantly greater changes from baseline cognitive performance, despite being evaluated a mean of 24 hours later following concussion. Compared to males, females exhibited a 1.5X greater chance of being cognitively impaired following concussion. After adjusting for the wearing of protective head gear in male sports (e.g., football), females were more than twice as likely as males to be cognitively impaired following concussion.

First Author	Year	Title	Journal	Predominant Sport	Subjects (*n*, sex, and age)	Outcome Measure	Analysis Technique	Main Findings
Berz et al[13]	2013	Sex-Specific Differences in the Severity of Symptoms and Recovery Rate Following Sports-Related Concussion in Young Athletes	Phys Sportmed	No information	37 athletes: mean age of 15 years. No information is provided regarding the number of males and females included.	Symptom severity and initial presentation time (days postinjury)	Patients were divided by sex (male vs. female) and group (those presenting 7 days or less after injury vs. those presenting more than 7 days postinjury).	Males had lower scores on a 22-item postconcussion symptom score scale than females, but the recovery rate did not differ between sexes. No sex differences in degree of loss of consciousness, amnesia, confusion, or age were found.
Chandran et al[74]	2019	Determinants of Concussion Diagnosis, Symptomology, and Resolution Time in U.S. High School Soccer Players	Res in Sports Med	Soccer	Data were collected based on head/neck injury events, thus total number of high school athletes and ages are unknown. Events included 189 concussions (106 in females and 83 in males) and 189 other head/neck injuries (82 in females and 107 in males).	Occurrence of concussion following head/neck injury and symptom information	Information regarding head and neck injury events in high school soccer players was documented by athletic trainers. Injuries were characterized by concussion diagnosis (yes/no), concussion symptom presentation (yes/no for 17 symptoms), and symptom resolution time (7, 14, 28, or > 28 days).	The odds of sustaining a concussion following an injury to the head or the neck were 84% higher in females than in males; female sex was a significant predictor of a positive concussion diagnosis. Females had significantly higher odds of experiencing light sensitivity and drowsiness compared to males. Sex was not a significant predictor of time to symptom resolution.
Colvin et al[15]	2009	The Role of Concussion History and Gender in Recovery from Soccer-Related Concussion	Am J Sports Med	Soccer	234 athletes, 141 females (mean age: 16.5 years) and 93 males (mean age: 16.3 years).	Neurocognitive testing	ImPACT at an average time of 13.3 days (males), and 12.0 days (females) after injury. Concussion history was gathered by ImPACT concussion history questions and clinical interview.	Following concussion, females reported a significantly greater number of symptoms, and exhibited poorer performance on neurocognitive testing.
Covassin et al[17]	2013	Are There Differences in Neurocognitive Function and Symptoms between Male and Female Soccer Players after Concussions?	Am J Sports Med	Soccer	39 male and 56 female high school and collegiate athletes (mean age: 18 years).	Neurocognitive testing	ImPACT at baseline and in case of concussion at an average of 8 days after injury.	Females reported a higher number of postconcussive symptoms, and performed worse on visual memory tasks, 8 days after concussion.
Covassin et al[20]	2007	Sex Differences in Neuropsychological Function and Post-Concussion Symptoms of Concussed Collegiate Athletes	Neurosurgery	**1** Wrestling **2** Soccer **3** Football	41 male and 38 female collegiate athletes.	Neurocognitive testing	ImPACT at baseline and on average 2 and 8 days after injury.	Females exhibited poorer performance on visual memory tasks following a concussion, whereas males were significantly more likely to report

First Author	Year	Title	Journal	Predominant Sport	Subjects (*n*, sex, and age)	Outcome Measure	Analysis Technique	Main Findings
								vomiting and sadness postconcussion.
Covassin et al[18]	2012	The Role of Age and Sex in Symptoms, Neurocognitive Performance, and Postural Stability in Athletes after Concussion	Am J Sports Med	**1** Football **2** Soccer **3** Volleyball **4** Basketball **5** Wrestling **6** Ice hockey **7** Softball **8** Women's crew **9** Baseball **10** Cheerleading **11** Lacrosse	222, 157 males and 65 females, 150 high school and 72 college athletes (mean age males in high school: 15.6 years, in college: 19.52 years, mean age females in high school: 15.43 years, in college 18.94 years).	Neurocognitive and neurotesting	Administration of ImPACT at baseline and at 2, 7, and 14 days after concussion. Moreover, administration of BESS at baseline as well as 1, 2, and 3 days after concussion.	Females reported more symptoms following concussion than males, and they performed worse on visual memory tasks. The results of the study also suggest an interaction between gender and age on postural stability following concussion: high school male athletes performed worse on the BESS than college male athletes, while high school female athletes performed better on the BESS than college female athletes. Overall, males and females demonstrated similar reaction times.
Desai et al[95]	2019	Factors Affecting Recovery Trajectories in Pediatric Female Concussion	Clin J Sport Med	**1** Baseball **2** Basketball **3** Cheer **4** Field hockey **5** Football **6** Lacrosse **7** Soccer **8** Track **9** Volleyball **10** Other	192 athletes, 177 males (mean age years) and 75 females (mean age years).	Symptom severity and time to return to preinjury status, including time to return to school without accommodations, time to return to noncontact exercise, time to return to full sport, time to neurocognitive recovery, and time to clinical recovery of vision and vestibular deficits	Individuals presenting to a hospital-based sports medicine clinic for sport-related concussion completed the PCSS at initial presentation, and were furthermore followed over time to determine time to neurocognitive and symptom recovery and time to return to school and sport.	On average, females presented significantly later (15 days postinjury) to the speciality sports medicine clinic than males (9 days postinjury). Compared to males, females presented with higher average symptom scores and furthermore took longer to return to "preinjury" status for all five recovery metrics (school, noncontact sport, full sport, neurocognition, and vision/vestibular functioning). When examining only individuals who presented to the clinic within the first 7 days of injury, however, no differences in recovery metrics were found between males and females.

First Author	Year	Title	Journal	Predominant Sport	Subjects (*n*, sex, and age)	Outcome Measure	Analysis Technique	Main Findings
Frommer et al[22]	2011	Sex Differences in Concussion Symptoms of High School Athletes	J Athl Train	Males: **1** Football **2** Soccer **3** Basketball **4** Wrestling **5** Baseball Females: **1** Soccer **2** Basketball **3** Volleyball **4** Softball	From 100 high schools, a total of 812 concussions were reported (610 males and 202 females).	Data collection via high school RIO	Coaches reported via RIO athlete-exposures and injury data. During year 1, the coaches were asked to record the primary symptom experienced by the athletes. In year 2, the clinician reported the symptoms instead of the coach.	No sex differences were found in the number of postconcussive symptoms reported; however, reported symptom clusters differed. Males reported more cognitive symptoms (amnesia and disorientation/confusion), whereas females reported more somatic and neurobehavioral symptoms (drowsiness and sensitivity to noise).
Gallagher et al[73]	2018	The Effects of Sex Differences and Hormonal Contraception on Outcomes after Collegiate Sports-Related Concussion	J Neurotrauma		90 student athletes, 40 males (mean age: 19.8) and 50 females (mean age 19.6).	Symptom severity	SCAT completed every 24 hours following concussion until return to play.	Females had longer length of recovery despite similar peak symptom severity
Henry et al[24]	2016	Examining Recovery Trajectories After Sport-Related Concussion With a Multimodal Clinical Assessment Approach	Neurosurgery	**1** Football **2** Soccer **3** Hockey	66 subjects were enrolled, 42 males (mean age: 16.5 years) and 24 females (mean age: 16.4 years).	Neurocognitive and neurotesting	ImPACT, short interview, adapted from the DHI, and clinical examination to assess vestibular functioning and impairment. The tests began within 1 week of the concussion and subjects were followed up at subsequent 1-week postinjury intervals over 4 weeks.	Sex did not play a role in initial symptom recovery, but, beginning in week 2, males began to recover from symptoms more quickly than females. Females reported a higher number of symptoms in weeks 2–4, and greater postconcussive dizziness at all time points. Males were significantly more likely to be asymptomatic by week 4. Conversely, there were no differences in the rate of neurocognitive recovery across sexes.
Howell et al[36]	2017	Dual-Task Gait Differences in Female and Male Adolescents Following Sport-Related Concussion	Gait Posture	No information	86 athletes: 18 males with concussion (mean age = 15.4 years), 17 females with concussion (mean	Symptom inventory and dual-task walking protocol	Concussed athletes were tested within 13 days of a concussion. All subjects completed an instrumented dual-task walking protocol	Differences between males and females were found for the dual-task cost of cadence among concussed subjects, but not controls. Females

First Author	Year	Title	Journal	Predominant Sport		Subjects (n, sex, and age)	Outcome Measure	Analysis Technique	Main Findings
						age =14.6 years), 25 male controls (mean age = 14.2 years), 26 females controls (mean age =14.6 years).		and PCSS symptom inventory. Walking outcomes included average walking speed, stride length, and cadence. Dual-task costs were used to calculate the relative change between single-task and dual-task conditions.	with concussion walked with lower dual-task cadence than both concussed males and female controls. Stride lengths were shorter for all concussed participants than they were for controls.
Hutchison et al[76]	2016	Psychological and Physiological Markers of Stress in Concussed Athletes Across Recovery Milestones	J Head Trauma Rehabil	**1** **2** **3** **4** **5** **6** **7** **8**	Rugby Hockey Football Soccer Lacrosse Volleyball Basketball Baseball	52 university athletes: 16 males and 10 females with concussion, 16 male and 10 female controls (mean age: 21 years).	Physiological measures (heart rate variability and salivary cortisol) and psychological measures (RPQ, POMS-SF, PSS, and SSS)	Physiological and psychological measures at three times points during recovery from concussion: first, within first week after injury, second, after resolution of symptoms, and third, 1 week after medical clearance to return-to-play.	In the week following concussion, athletes showed significantly worse total mood disturbances and sleep quality, and increased depression, anger, confusion, and tension, compared to controls. These findings were reversed at return-to-play. Analyses of heart rate variability revealed reduced variability in all concussed athletes, extending into the post return-to-play phase. Female athletes had a more sensitive cardiac response to concussion than males, evinced by greater heart rate variability suppression.
Léveillé et al[71]	2016	Sex-Related Differences in Emotion Recognition in Multi-Concussed Athletes	J Int Neuropsycholog Soc	**1** **2** **3** **4** **5**	Basketball Football Ice hockey Soccer Noncontact sports	22 multiconcussed athletes (n = 10 males) and 28 control athletes (n = 15 males). Mean age = 21 years for males and 22 years for females.	The PCSS, an emotion recognition task, BAI, BDI-II, SDMT, RAVLT, and the Stroop test	Tests were completed during a single session lasting approximately 30 minutes. Males with a concussion history sustained their injury a mean of 24 months prior to testing. Females with a concussion history sustained their injury a mean of 38 months prior to testing.	Compared to male controls, males with a history of concussion demonstrated impairments in negative emotion recognition. Females with a history of concussion performed similarly to female controls.

First Author	Year	Title	Journal	Predominant Sport		Subjects (n, sex, and age)	Outcome Measure	Analysis Technique	Main Findings
Merritt and Arnett[25]	2014	Premorbid Predictors of Postconcussion Symptoms in Collegiate Athletes	J Clin Exp Neuropsychol	**1** **2** **3**	Football Lacrosse Basketball	55 collegiate athletes were included, 47 males and 8 females (mean age: 19.91 years).	Neurocognitive and neurobehavioral testing	Baseline testing and testing following concussion at an average of 61 hours post injury. Testing included: BVMT-R, HVLT-R, Digit Span Test, SDMT, CTMT, Penn State University Symbol Cancellation Task, Vigil/W Continuous Performance Test, SCWT, ImPACT (incl. PCSS), and WTAR	Females were more likely to become part of the "high total symptoms score group."
Mihalik et al[26]	2013	Recovery of Posttraumatic Migraine Characteristics in Patients after Mild Traumatic Brain Injury	Am J Sports Med	**1** **2** **3**	Football Soccer Lacrosse	296 student athletes, 241 males and 55 females (mean age: 16.7 years). Subjects were divided into three groups based on subject's symptom report on day 1 after concussion. Migraine group (n = 52), headache group (n = 176), and no headache group (n = 68).	Neurocognitive and neurotesting	Baseline testing including a standardized concussion history questionnaire as well as BESS, SAC, and GSC. Postconcussion testing completed by the clinician included a standard injury history, an on-field evaluation, BESS, SAC, and GSC at the time of injury, after the event (e.g., end of game), and on days 1, 2, 3, 5, 7, and 90.	Athletes suffering from migraine-like symptoms after concussion had greater symptom severity scores (immediately following the injury and 7 days post) than those with posttraumatic headache only and those without headache. Headache reporting at baseline (preconcussion) did not differ between males and females; however, female athletes were 2.13 times more likely to report posttraumatic migraine symptoms following concussion.
Miller et al[27]	2016	Predictors of Delayed Recovery Following Pediatric Sports-Related Concussion: A Case-Control Study	J Neurosurg Pediatr	**1** **2** **3**	Football Basketball Other	Total of 294 subjects: 105 subjects with postconcussive symptoms (longer than 28 days), control group of 189 subjects (symptom resolution within 28 days). Mean age of subjects with SCAT2 score was 13.7 years, without SCAT2 score was 12.6 years.	Symptom report and neurotesting	Patient demographic data, medical history, SCAT2 score, symptom severity score on presentation, injury characteristics, and balance assessment results were analyzed for each outcome group. All analyses were conducted separately for patients with and without SCAT2 scores.	Female sex, a history of previous concussion(s), a history of ADHD, playing a nonhelmet sport, and a SCAT2 score of < 80 were associated with a higher risk for prolonged recovery (>28 days). Loss of consciousness, balance difficulties, and amnesia were not associated with prolonged recovery.

First Author	Year	Title	Journal	Predominant Sport	Subjects (*n*, sex, and age)	Outcome Measure	Analysis Technique	Main Findings
O'Connor et al[70]	2018	Descriptive Analysis of a Baseline Concussion Battery Among U.S. Service Academy Members: Results from the Concussion Assessment, Research, and Education (CARE) Consortium	Mil Med	Full contact, limited contact, and noncontact sports at three levels of competition (varsity, club, and intramural)	2,140 males, 856 females of university age	Neurocognitive testing and symptom inventory	SCAT3, BSI-18, SAC, BESS, and ImPACT at baseline, ImPACT assesment	Females performed worse than males on the ImPACT visual memory task, although this difference was small. Males more likely to report zero symptoms on SCAT or BSI. There were no sex differences in BESS or SAC scores.
Ono et al[28]	2016	Sex-Based Differences as a Predictor of Recovery Trajectories in Young Athletes After a Sports-Related Concussion	Am J Sports Med	**1** Football **2** Soccer **3** Lacrosse	176 child, middle, and high school athletes, 135 males and 41 females (10–18 years old).	Neurocognitive testing	ImPACT at baseline and at least once postconcussion within 1 week after injury.	Female athletes had a higher number of symptoms at baseline and throughout the whole recovery process, especially for emotional and somatic symptoms. No sex differences in the rate of recovery were found.
Preiss-Farzanegan et al[29]	2009	The Relationship between Gender and Postconcussion Symptoms after Sport-Related Mild Traumatic Brain Injury	PM R	**1** Football **2** Soccer **3** Horseback riding **4** Snow sledding **5** Basketball	215 subjects, 78 adults: 47 males (mean age: 36.9 years), 31 females (mean age: 30.1 years), and 137 minors: 97 males (mean age: 13.1 years) and 40 females (mean age: 13.1 years)	RPQ symptom questionnaire	Initial data collection at the emergency department. The follow-up assessments were conducted at 3 months after the initial assessment. The postconcussive symptoms were obtained by subject self-report or proxy respondent using the RPQ.	Adult female athletes (18 years and over) had an approximately 2.9X higher risk of experiencing greater RPQ scores. More specifically, adult female athletes were at increased risk for headache, dizziness, fatigue, irritability, and concentration problems. No such sex differences were found in minors.
Sandel et al[69]	2017	Sex-Based Differences in Cognitive Deficits and Symptom Reporting Among Acutely Concussed Adolescent Lacrosse and Soccer Players	Am J Sports Med	**1** Soccer **2** Lacrosse	224 athletes, 112 lacrosse and 112 soccer players. Groups were matched for sport, sex, and age (mean age 15.43).	Neurocognitive testing	Medical records were extracted from ImPACT Applications Inc. database from athletes with baseline and postinjury testing. Baseline testing had to occur < = 2 years before postinjury testing. Postinjury testing had to occur within 3 days of sustaining a concussion.	Females reported greater symptom severity at baseline (preinjury). Following concussion, females demonstrated more symptoms and greater neurocognitive decline than males. A higher proportion of female athletes (30% compared to 13%) demonstrated neurocognitive scores suggestive of protracted recovery.

First Author	Year	Title	Journal	Predominant Sport	Subjects (n, sex, and age)	Outcome Measure	Analysis Technique	Main Findings
Sicard et al[72]	2018	Long-Term Cognitive Outcomes in Male and Female Athletes Following Sport-Related Concussions	Int J Psychophys	Football, soccer, rugby, hockey, volleyball, and cheerleeding	196 asymptomatic athletes: 98 male (mean age: 21.5), 98 female (mean age: 21.6)	Neurocognitive testing	Subjects completed the battery 6–60 months postinjury. Battery included Cogstate subscales and *N*-back tests	Females with a history of concussion had a slower response time on the *N*-back test. Accuracy did not differ by sex. Response time on a visual memory task was slower and performance poorer in female athletes, but there was no concussion history × sex interaction. No sex differences in processing speed or attention
Sufrinko et al[75]	2017	Sex Differences in Vestibular/Ocular and Neurocognitive Outcomes After Sport-Related Concussion	Clin J Sport Med	No information. (All patients sustained a concussion during school or other organized sports.)	64 total athletes: 36 males (mean age = 13.6 years) and 28 females (mean age = 14.3 years).	Symptom report, computerized neurocognitive test, balance test, and VOMS test	Subjects completed the VOMS, BESS, PCSS, and ImPACT within 21 days of a concussion. Males were tested a mean of 4.5 days postinjury and females a mean of 6.0 days postinjury.	Females reported significantly greater symptom severity, but no between-sex differences were found for ImPACT measures or BESS errors. Females demonstrated a significantly greater symptom provocation during the horizontal vestibular-ocular reflex test of the VOMS compared to males. No other VOMS components were significantly different between males and females.
Zuckerman et al[30]	2014	Effect of Sex on Symptoms and Return to Baseline in Sport-Related Concussion	J Neurosurg Pediatr	Males: **1** Football **2** Soccer **3** Basketball Females: **1** Soccer **2** Basketball **3** Volleyball	244 middle, high school, and collegiate athletes. 122 males and females, matched for age (mean age in both groups 16.1 years), prior concussions, and days to first postconcussion test.	Neurocognitive testing	ImPACT at baseline and several tests postconcussion within 30 days after injury.	Females reported greater overall symptom severity at baseline and postconcussion. Females took an average of 2.1 days longer to return to their baseline symptom profile.

Abbreviations: ADHD, attention deficit hyperactivity disorder; ANAM, Automated Neuropsychological Assessment Metric; BAI, Beck Anxiety Inventory; BCTT, Buffalo Concussion Treadmill Test; BDI, Beck Depression Inventory; BESS, Balance Error Scoring System; BSI, Brief Symptom Inventory; BVMT-R, Brief Visuospatial Memory Test-Revised; CTMT, Comprehensive Trail Making Test; CRI, Concussion Resolution Index; DHI, Dizziness Handicap Inventory; GSC, graded symptom checklist; HVLT-R, Hopkins Verbal Learning Test – Revised; ImPACT, Immediate Postconcussion Assessment and Cognitive Testing; *n*, number of subjects; PCSS, Post-Concussion Symptom Scale; POMS-SF, Profile of Mood States–Short Form; PSS, Perceived Stress Scale; RAVLT, Rey Auditory Verbal Learning

Test; RIO, Reporting Information Online; RPQ, Rivermead Post Concussion Symptom Questionnaire; SAC, Standardized Assessment of Concussion; SCAT, Sport Concussion Assessment Test; SCWT, Stroop Color and Word Test; SDMT, Symbol Digit Modalities Test; SSS, Stanford Sleepiness Scale; VOMS, Vestibular-Ocular Motor Screen; WTAR, Wechsler Test of Adult Reading.

Table 5.

Summary of Imaging Studies on Sex Differences after Concussion

First Author	Year	Title	Journal	Predominant Sport	Subjects (*n*, sex, and age)	Outcome Measure	Analysis Technique	Main Findings
Chamard et al[77]	2012	A Prospective Study of Physician-Observed Concussion During a Varsity University Hockey Season: Metabolic Changes in Ice Hockey Players. Part 4 of 4	Neurosurg Focus	Ice hockey	45 subjects, 25 males (mean age: 22.24 years) and 20 females (mean age 20.21 years). Among males, there were five confirmed concussions, among females, there were six confirmed concussions.	3T MRI and MRS	All athletes received baseline MRI evaluation. Follow-up imaging in case of concussion was conducted 72 hours, 2 weeks, and 2 months after concussion. Voxels were applied for the corpus callosum and spectroscopic examination was done using a PRESS sequence. The linear combination model was used for metabolite quantification: glutamate/Cr, myoinositol/Cr, and NAA/Cr.	No longitudinal differences in metabolic ratios were found between individuals with and without a history of concussion. However, concussed athletes did show a pattern of initial impairment, followed by a gradual return to metabolic ratios that were near-to, but still lower than, baseline ratios. Female athletes who did not sustain a concussion showed a significant decrease in their NAA/Cr ratios over time, suggestive of an effect of subconcussive impacts. All metabolite ratios remained stable in nonconcussed male athletes.
Fakhran et al[78]	2014	Sex Differences in White Matter Abnormalities after Mild Traumatic Brain Injury: Localization and Correlation with Outcome	Radiology	No information	90 subjects, 47 males and 22 females with concussion (mean age males: 18.0 years, females: 16.7 years), 10 male and 11 female control subjects (mean age males: 20.3 years, females: 17.0 years). Major mechanism of trauma was a sports-related injury (32 of 47 male subjects, 10 of 22 female subjects).	1,5 T MRI and DTI	Within concussion-group, ImPACT testing was performed at patients' presentation. The DTI scan was collected within 3 days after initial clinical evaluation and assessed using a voxelwise TBSS analysis. ROI analysis was based on the TBSS mean FA skeleton overlaid with FA differences between males and females with concussion.	No sex differences were found for ImPACT symptom scores. Concussed males took a significantly longer time to reach symptom resolution. Concussed males additionally showed bilateral FA reductions in the uncinate fasciculus compared to concussed females and all controls. Sex and FA values of the uncinate fasciculus were predictors of having a time to symptom resolution greater than 3 months; initial symptom severity was not a predictor.
Helmer et al[23]	2014	Hockey Concussion Education Project, Part 1. Susceptibility-Weighted Imaging Study in Male and Female Ice Hockey Players over a Single Season	J Neurosurg	Hockey	45 subjects, 25 males (mean age: 23 years) and 20 females (mean age: 21 years). Among males, there were five confirmed concussions, among females, there were six confirmed concussions.	3T MRI and SWI	Scans were obtained pre and postseason. Moreover, the concussed athletes underwent imaging at 72 hours, 2 weeks, and 2 months after injury.	A significant increase in overall HIB was found in male subjects 2 weeks postconcussion, compared to baseline HIB. A small (nonsignificant) increase in the HIB was also observed in female subjects.
Hsu et al[42]	2015	Sex Differences in Working Memory after Mild Traumatic Brain Injury: A Functional MR Imaging Study	Radiology	Injury mechanisms: 1. fall, 2. car accident and 3. sports 4. Assault	60 subjects, 15 males (mean age: 35.00 years) and 15 females (mean age: 35.18 years) with concussion as well as a 15 male (mean age: 33.65) and 15 female controls (mean age: 34.24 years).	3T fMRI	Working memory fMRI scans were obtained twice: 1. within 1 month after concussion, 2. scan 6 weeks after the first scan. For each subject, digit span and continuous performance testing were performed before fMRI.	Lower digit span scores were found in concussed females, compared to female controls. Scans taken within a month of concussion revealed hyperactivation of working memory regions in concussed males and hypoactivation of these regions in concussed females, compared with respective controls. In the follow up scan, concussed females still evinced activation abnormalities, whereas the hyperactivation previously exhibited by males had

First Author	Year	Title	Journal	Predominant Sport	Subjects (*n*, sex, and age)	Outcome Measure	Analysis Technique	Main Findings
								resolved. In the first scan, concussed males had a higher ß value than their male control group; no significant differences were found at the follow up scan. Among the females, the ß value was lower among concussed individuals in both the initial and the follow up scan compared to controls, but the differences were not statistically significant.

Abbreviations: Cr, creatine-phosphocreatine; DTI, diffusion tensor imaging; FA, fractional anisotropy; fMRI, functional MRI; HIB, hypointensity burden; ImPACT, Immediate Postconcussion Assessment and Cognitive Testing; MRS, magnetic resonance spectroscopy; *n*, number of subjects; NAA, N-acetylaspartate; NAA/Cr, N-acetylaspartate to creatine ratio; PRESS, point-resolved spectroscopy; ROI, region of interest; SWI, susceptibility weighted imaging; TBSS, tract-based spatial statistics.