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A brief descriptive outline of the rules of mixed martial arts and concussion in mixed martial arts

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Mixed martial arts (MMA), a combat sport consisting of wrestling, boxing, and martial arts, is a popular activity associated with danger and violence. Of concern are the repetitive head impacts, both subconcussive and concussive, sustained by MMA athletes. The rules of MMA encourage head strikes, but there was no formal concussion protocol in the Ultimate Fighting Championship (UFC) until 2021. Because the UFC was established less than 30 years, the long-term consequences of these repetitive concussive head blows are lacking. In this review, we focus on current literature sought to summarize the current knowledge of repetitive head impacts and concussions in MMA. The objectives

were to outline (a) the rules of MMA; (b) the postconcussion protocol for UFC athletes; (c) current behavioral and biochemical diagnostic measures; (d) epidemiology and prevalence of concussion in MMA; (e) long-term effects of subconcussive repetitive head impacts; (f) biomechanics of head impacts; and (g) considerations and research topics that warrant future research.

Keywords: Mixed martial arts, Concussion, Mild traumatic brain injury, Chronic traumatic encephalopathy, Repetitive subconcussive head impacts

INTRODUCTION

Mixed martial arts (MMA) can be traced back to 648 B.C.E. in ancient Greece where it was called pankration, a combat sport consisting of wrestling, boxing, and street fighting. After pankration was banned in 393 C.E., this sport did not resurface until the 20th century in Brazil where it was called "vale tudo" or "anything goes" (https://www.britannica.com/sports/mixed-martial-arts). MMA made its mark in 1993 during a competition called the Ultimate Fighting Championship (UFC) in the United States (U.S.). MMA then became known as a no-holds-barred combat sport, meaning that anything other than biting or eye-gouging was fair game. As the top promoter for MMA, the UFC has turned MMA into the fastest-growing sport in the world. Since its inception, the UFC has grown exponentially with an estimated net worth of approximately \$10 billion. Because of the popularity and growth of the UFC and MMA, it is more crucial than ever to better understand the effects of repetitive head impacts (RHIs) and

concussions sustained by the athletes.

In the U.S., the UFC and MMA came under fire in the early years for being so dangerous. Because of this, the Unified Rules of MMA were established in 2001. Even though rules are in place, one of the main objectives of MMA is to give the opponent a concussion via knockout. Head injuries are encouraged in MMA, but the UFC did not release its first concussion protocol until 2021. This raises the question of whether the true prevalence of concussions is known within MMA. Many studies have attempted to determine the prevalence of concussions in MMA, with variable ranges of 8.3% to 62.3% (Curran-Sills and Abedin, 2018; Fares et al., 2021; Ji, 2016; Karpman et al., 2016). Regardless of the large variation, concussion rates are still much higher than those cited in the National Football League (NFL). The average concussion rate among NFL players over a 5-year period from 2015 to 2019 was 7.4% (Mack et al., 2021).

There has yet to be written a comprehensive review of the literature, to our best knowledge, relating to RHIs and concussions in

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Table 1. Sport-related concussion (SRC)

According to McCrory et al. (2017), a sport-related concussion is a mild traumatic brain injury that can be characterized by the following features:

- · Caused by biomechanical forces transferred to the head following a blow to the body, which may or may not result in loss of consciousness.
- · Signs and symptoms typically occur quickly or may develop minutes to hours following SRC.
- · Signs and symptoms vary and typically resolve progressively, but they may be prolonged.
- · May result in neurological dysfunction that shows up as normal on structural neuroimaging.

MMA athletes. Therefore, the objectives of this literature review were to outline (a) the rules of MMA; (b) the postconcussion protocol for UFC athletes; (c) diagnostic measures; (d) epidemiology and prevalence of concussion in MMA; (e) long-term effects of subconcussive RHIs; (f) biomechanics of head impacts; and (g) future considerations and research topics needed moving forward. Although mild traumatic brain injury (mTBI) and concussion are often used interchangeably, operational definitions vary across the literature (Greenwald et al., 2012; McCrory et al., 2017). For the sake of consistency, we will be using the term 'concussion' throughout this paper. The definition of 'sport-related concussion' is summarized in Table 1.

SUMMARY

Rules of MMA

After a public outcry over the danger of the sport, the UFC adopted new rules for the safety of the athletes in 2001. The Association of Boxing Commissions and Combative Sports created the Unified Rules of Mixed Martial Arts in 2001. Since then, the rules have been amended several times, most recently in 2019 (https:// www.abcboxing.com/wp-content/uploads/2020/02/unified-rulesmma-2019.pdf). The Unified Rules of MMA state that a fight must consist of 5-minute rounds and a 1-minute rest between rounds with no more than five rounds total. All athletes are required to wear a mouthguard during the game, thus the referee will call 'time' if the mouthguard becomes dislodged and needs to be replaced. Originally, MMA only prohibited biting and eyegouging; however, the Association of Boxing Commissions and Combative Sports added additional fouls to the Unified Rules of MMA, which are delineated in Table 2.

Despite the rules in place, one of the main objectives of a fight is to knock the opponent unconscious. This is demonstrated by the types of decisions that determine the outcome of a fight, as described in the Unified Rules of MMA. The scenarios in which an athlete wins a fight include the following: technical submission (when a submission results in unconsciousness), technical knockout (TKO) by referee stoppage (when an athlete is not intelligently defending themselves, e.g., physical exhaustion), TKO by medical stoppage (includes when an athlete loses control of bodily function), and knockout (KO; when the referee stops a game because an athlete cannot intelligently defend themselves because they are unconscious). These decisions encourage strikes to the head, which can result in repetitive, subconcussive, or concussive head impacts, and eventually cause chronic traumatic encephalopathy (CTE).

A brief overview of the postconcussion protocol can be found in Table 3, and the full concussion protocol can be found in the UFC Performance Institute's 2021 volume of research (https://ufc-pi. webflow.io/). Following a fight, MMA athletes with suspected concussions should be assessed by a medical professional (McCrory et al., 2017). Concussion evaluation should include a detailed concussion history, presence of clinical symptoms and physical signs, and neurocognitive testing such as the Sport Concussion Assessment Tool-5 (SCAT5) (McCrory et al., 2017). The UFC concussion protocol states that athletes should be managed by a healthcare provider to ensure proper completion of each progression stage, and if at any point in the protocol athletes experience symptoms, they must rest and be symptom-free for at least 24 hr before returning to the stage prior to when symptoms arose.

As described above, the postconcussion protocol is fairly comprehensive, sequential, and detailed; however, it is only the first official concussion protocol of the UFC, and there is room for improvement. During stage one, the protocol requires athletes to go to the hospital if they experience 'red-flag' symptoms, but the redflag symptoms are not listed on the protocol itself. It is recommended that the red-flag symptoms are detailed, so athletes can accurately identify them.

Current status of diagnostic measures of concussions

Elucidating the underlying mechanisms of head impacts that occur during MMA fights may be helpful to diagnose concussions (Karton and Hoshizaki, 2018). Concussions are difficult to diagnose because diagnoses are subjective in nature and rely on information obtained regarding signs and symptom severity, concussion history, and neurocognitive and behavioral testing (Jackson and Starling, 2019; McCrory et al., 2017); however, researchers are exploring new ways to potentially diagnose concussions. The objective of this section is to evaluate current neurocognitive and



Table 2. Fouls as outlined in the unified rules of mixed martial arts

Fouls	Description		
Head-butting	The head may not be used to strike the opponent.		
Eye-gouging	Eye-gouging using fingers, chin, or elbow is illegal. Legal strikes or punches to the eye socket are not considered eye-gouging.		
Biting or spitting at an opponent	Biting or spitting in any form is illegal.		
Fish-hooking	An athlete may not use their fingers to stretch the skin of their opponent's mouth, nose, or ears. Fish-hooking usually involves an athlete placing their fingers into the mouth of the opponent and pulling their hands in opposite directions.		
Hair-pulling	Hair-pulling in any fashion is illegal. An athlete may not grab a hold of their opponent's hair. If an athlete has long hair, they may not use their hair as a tool for holding or choking their opponent.		
Spiking the opponent to the floor onto the head or neck (pile-driving)	A pile-driver occurs when an athlete holds the opponent with their feet in the air and head straight down and then forcibly drive the opponent's head into the floor.		
Strikes to the spine or back of the head	The back of the head starts at the crown of the head with a one-inch variance to either side, running down the back of the head to the occipital junction. This area stretches out at the occipital junction (nape of the neck) to cover the entire width of the neck. It then travels down the spine with a one-inch variance from the spine's centerline, including the tailbone.		
Throat strikes of any kind and/or grabbing the trachea	No directed throat strikes are allowed, including an athlete pulling his opponent's head in a way to open the neck area for a striking attack. An athlete may not gouge their fingers or thumb into their opponent's neck or trachea in an attempt to submit their opponent.		
Fingers outstretched toward an opponent's face/eyes	An athlete may not move their arm(s) toward their opponent with an open hand, fingers pointing at the opponent's face/eyes.		
Downward pointing elbow strike (12 to 6)	The use of a linear 'straight up, straight down' elbow strike is prohibited.		
Groin attacks of any kind	Any attack to the groin area including striking, grabbing, pinching, or twisting is illegal for both men and women.		
Kneeling and/or kicking the head of a grounded opponent	A grounded athlete is defined as any part of the body, other than a single hand and soles of the feet, touching the floor. At time, kicks or knees to the head will not be allowed.		
Stomping of a grounded opponent	Stomping is when the athlete lifts their leg by bending at the knee and initiates a striking action with the bottom of their foot or heel.		
Small joint manipulation	Fingers and toes are considered small joints. Grabbing the majority of fingers or toes at once is allowed.		
Throwing an opponent out of the ring or cage area	An athlete shall not throw their opponent out of the ring or cage.		
Intentionally placing a finger into any orifice or laceration of your opponent	An athlete may not place their fingers into an open laceration in an attempt to enlarge the cut. An athlete may not place their fingers into an opponent's nose, ears, mouth, or body cavity.		
Clawing, pinching, and twisting the flesh	Any attack that targets the athlete's skin by clawing at the skin or attempting to pull or twist the skin to apply pain is illegal.		
Unsportsmanlike conduct that causes an injury to the opponent	Any athlete that disrespects the rules of the sport or attempts to inflict unnecessary harm on an opponent who has been eit taken out of the competition by the referee or has tapped out of the competition shall be viewed as being unsportsmanlik		
Attacking an opponent after the bell has sounded	The end of a round is signified by the sound of the bell and the call of time by the referee. Once the referee has made the call of time, any offensive actions initiated by the athlete shall be considered after the bell and illegal.		
Attacking an opponent during the break	An athlete shall not engage their opponent in any fashion during a time-out or break of action in competition.		
Attacking an opponent who is under the care of the referee	Once the referee has called for a stop of the action to protect an athlete who has been incapacitated or is unable to continue to compete in the fight, an athlete must cease all offensive actions against their opponent.		

behavioral assessments that assist in concussion diagnosis, as well as explore novel diagnostic techniques such as imaging and biomarker analysis.

Neurocognitive and behavioral testing

Following a head impact, athletes with a suspected concussion must be properly assessed using neurocognitive and behavioral testing (McCrory et al., 2017). The SCAT5 is a commonly used standardized assessment tool, which can help with concussion recognition; however, it should not be solely used to diagnose or rule out a concussion (McCrory et al., 2017; Putukian and Schepart, 2018; Sport concussion assessment tool, 2017). The SCAT5 consists of

multiple components, including the background of the athlete, symptom checklist, the Standardized Assessment of Concussion (SAC), neurological screen, and delayed recall (McCrory et al., 2017; Putukian and Schepart, 2018; Sport concussion assessment tool, 2017).

The symptom checklist is useful in tracking symptoms over time, especially with recovery, as symptom resolution is necessary for athletes when completing the UFC concussion protocol and prior to returning to play (McCrory et al., 2017; Putukian and Schepart, 2018). The SAC is useful in testing orientation, immediate memory, concentration, and delayed memory in order to assess neurocognitive function following injury (Putukian and Schep-



Table 3. Postconcussion protocol for Ultimate Fighting Championship athletes

Stage 1: Initial recovery

- 24 to 48 hr of physical and mental rest
- Monitor symptoms
- Allowed to sleep and take Acetaminophen

For each following stage:

- · Check symptom score daily with concussion assessment tool
- Physical therapy (if needed)
- Post-exercise symptom check and progress to next stage if symptom-free

Stage 2: No contact I

Stage 2.1: Low intensity aerobic training

Stage 2.2: Moderate intensity aerobic training

Stage 2.3: Low intensity technical training

Stage 3: No contact II

Stage 3.1: Low intensity strength training

Stage 3.2: Moderate intensity strength training

Stage 3.3: Low to moderate intensity technical training

Stage 4: Moderate contact

Stage 4.1: Moderate to high intensity interval training

Stage 4.2: High intensity strength training

Stage 5: Return to Full Contact

- Medical clearance from physician needed before being cleared to return to contact
- · Strength and conditioning program to resume as normal

Stage 5.1: Moderate intensity technical training and low intensity live work

Stage 5.2: High intensity technical training and moderate intensity live work

Stage 5.3: Return to sparring

art, 2018; Sport concussion assessment tool, 2017). The neurological screen assesses an athlete's ability to read and follow instructions, passively move their cervical spine without pain, look up-anddown and side-to-side without double vision, touch their finger to their nose, walk with a tandem gait, and perform the modified Balance Error Scoring System (BESS) test (Putukian and Schepart, 2018; Sport concussion assessment tool, 2017).

The King-Devick test is another neurocognitive test useful in concussion diagnosis, and it assesses eye movement, attention, and language (Putukian and Schepart, 2018). Boxers and MMA athletes were assessed using the King-Devick test pre- and postfight (Galetta et al., 2011). Statistical analyses were performed to compare participants who sustained head trauma during the fight to those who did not sustain head trauma on differences in postfight scores and to compare changes in scores from pre- to postfight (Galetta et al., 2011). Results showed that athletes who suffered head trauma during the fight performed significantly worse on the postfight King-Devick test compared to those without head trauma (Galetta et al., 2011). Athletes who suffered from head

trauma during the fight saw a significantly worse change in score from pre- to postfight (Galetta et al., 2011). Among those who suffered from head trauma, athletes who lost consciousness had higher postfight scores than those who did not lose consciousness (Galetta et al., 2011). Athletes who did not sustain head trauma during their fight showed high test-retest reliability between the pre- and postfight scores, with an intraclass correlation coefficient of 0.95 (95% confidence interval [CI], 0.87-1.0) (Galetta et al., 2011). These results suggest that the King-Devick test is an accurate and reliable measure of head trauma and concussions among MMA athletes and boxers (Galetta et al., 2011).

Neuroimaging

Concussions are functional impairments of the brain, not structural injuries, meaning that brains suffering from these conditions show up normally on neuroimaging (McCrory et al., 2017; Suri and Lipton, 2018). However, there have been great strides to utilize advanced imaging techniques to view the microstructural and functional impairments of the brain following mTBI (McCrory et al., 2017; Suri and Lipton, 2018). Computed tomography (CT) and magnetic resonance imaging (MRI) are conventional imaging techniques that can be used to rule out moderate to severe TBI, which may be characterized by intracranial bleeding, contusion, edema, and fracture (Suri and Lipton, 2018).

Barring the presence of any characteristics of moderate to severe TBI, neuroimaging results will be normal for those suffering from a concussion (McCrory et al., 2017; Suri and Lipton, 2018). This may prompt the use of advanced imaging to determine the presence of concussion. One such technique is diffusion tensor imaging (DTI), a specific type of MRI (Suri and Lipton, 2018). DTI has been found to distinguish between individuals with concussion from healthy controls, making this a viable imaging technique in the diagnosis of concussion (Hulkower et al., 2013; Suri and Lipton, 2018). A study found that the number of knockouts in MMA athletes correlated with decreased fractional anisotropy in the posterior corpus callosum and increased transversal diffusivity in the posterior cingulate using DTI, both of which have been found in individuals with concussion compared to healthy controls (Shin et al., 2014).

Resting-state functional MRI (rs-fMRI) has also shown promise as an imaging technique that can be used to diagnose concussions (Suri and Lipton, 2018; Zhu et al., 2015). Because conventional imaging techniques do not find structural damage to the brain following concussion, the rs-fMRI can be used to detect the disruption of functional connectivity of the default-mode network



(DMN), which is a potential sign of concussion (Zhu et al., 2015). Concussed collegiate football players were sign and symptom-free 6.0 ± 2.4 days following injury; however, within 24 hr of injury, rs-fMRI showed high functional connectivity of the DMN, but was significantly impaired 7 days postinjury and was not fully recovered 30 days later (Suri and Lipton, 2018; Zhu et al., 2015). Compared to the healthy control subjects, functional connectivity of the DMN in the concussed athletes was 14.5% higher on day 1, 41.4% lower on day 7, and 15% lower on day 30. Because of the comparison to healthy control subjects who showed no significant difference across the 3 time points, this study showed evidence that rs-fMRI has utility as a diagnostic imaging technique (Zhu et al., 2015). Additional imaging techniques that show promise in the diagnosis of concussions include magnetic resonance spectroscopy (MRS), arterial spin labeling, magnetoencephalography, single-photon emission CT, and positron emission tomography (PET) (Suri and Lipton, 2018).

Biomarkers

Candidate biomarkers for use as diagnostic tools to assess concussion have emerged in recent years. Although many potential biomarkers have been investigated, the main proteins that are currently identifiable in the peripheral circulation and have remained highly regarded as top candidates include amyloid beta 42 peptide (A β 42) (Asken et al., 2018), neuron-specific enolase (Thelin et al., 2019), neurogranin (Çevik et al., 2019), and phosphorylated tau at threonine 181 (Sjögren et al., 2001). Although well studied, S100 calcium-binding protein B (Thelin et al., 2019) is influenced by exercise and consequently has become less desirable as a potential biomarker for concussion.

Other candidate biomarkers include inflammatory cytokines (Peltz et al., 2020) such as interleukin 6 or interleukin 10, and damage-associated molecular patterns (Corps et al., 2015). With advancements in scientific technology, tau, glial fibrillary acidic protein (GFAP), ubiquitin carboxyl hydrolase L1 (UCH-L1), neurofilament light chain peptides (NfL), and other brain-specific markers can be quantified in the blood through single-molecule array technologies, which have also been termed digital enzymelinked immunosorbent assay (ELISA) due to the greater sensitivity and automation compared to traditional ELISA methods.

Many studies investigating the effect of concussion on candidate biomarkers have included contact sport athletes, rather than professional athletes. Early biomarker research investigated tau and NfL as potential biomarkers for axonal injury or disease using the cerebrospinal fluid (CSF) collected from boxers following a

fight (Neselius et al., 2012). NfL is the most abundant neurofilament and key structural component of axons, while tau is a microtubule stabilizing protein. Both are believed to increase in the CSF and blood following concussion (Zetterberg et al., 2006). Previous findings suggest plasma NfL concentrations significantly increase from baseline to 24–48 hr postinjury among contact sport athletes diagnosed with concussion (Asken et al., 2020). Among athletes with more severe concussions, as determined by loss of consciousness (LOC) or postinjury amnesia, plasma NfL concentrations followed an upward trajectory and remained elevated even after medical clearance to return-to-play compared to athletes with less severe concussions (without LOC or postinjury amnesia) and athlete controls (McCrea et al., 2020).

Recently, NfL and tau were detected in the blood of professional and retired athletes (Bernick et al., 2018). Professional, active athletes included boxers and MMA athletes, while retired athletes included only boxers. Among all MMA athletes and control group, MMA athletes experienced a significant increase in plasma tau concentrations between measurements approximately 1 to 2 years apart, which was not observed with the active boxers. Baseline concentrations of NfL among athletes were elevated in active boxers compared to MMA athletes and retired boxers. This evidence is the first to compare blood-based biomarkers between different style athletes and the effect of repetitive impacts on plasma concentrations over time. These findings suggest that MMA athletes experience a different physiological response, as shown by differing tau and NfL longitudinal changes in plasma concentrations, from boxers. Additionally, MMA athletes may experience differences in baseline concentrations of tau compared to contact sport athletes. The largest study to date, with over 200 athletes diagnosed with concussion, found plasma tau concentration rapidly decreases and is significantly lower than healthy athletes 24-48 hr after injury, despite an initial increase within the first 4–16 hr following concussion (McCrea et al., 2020).

As recently as 2018, two known brain-specific proteins were approved by the U.S. Food and Drug Administration for use in Emergency Department (ED) settings to determine if patients admitted to the ED needed a CT scan to examine cerebral lesions or not (Gill et al., 2018; Welch et al., 2016). GFAP and UCH-L1 were shown to discriminate patients with normal and abnormal CT scans postconcussion. Although approved in this context, evidence regarding the use of GFAP and UCH-L1 for diagnostic tools in the identification of athletes suffering from concussion has been equivocal. GFAP is a cytoskeletal protein found predominantly in glial cells, most notably astrocytes. Concentrations of



GFAP detected in the blood have been significantly elevated hours and days after concussion among contact sport athletes. Additionally, circulating levels of GFAP were significantly high among athletes with an acute concussion than at baseline (Asken et al., 2020; McCrea et al., 2020).

First investigated in patients with severe TBI, UCH-L1 significantly increases in the CSF and serum within the first 24 hr of injury, followed by a rapid decline over the following 7 days. UCH-L1 is predominantly expressed in the neuronal soma and has been shown to be released into the CSF after TBI (Mondello et al., 2012). More recent studies have found that UCH-L1 is significantly higher within the first 24 hr of injury among athletes with concussion and returns to near baseline levels after 24-48 hr (Asken et al., 2020; McCrea et al., 2020). As promising as these biomarkers may be, GFAP and UCH-L1 have not yet been studied in MMA athletes.

LITERATURE REVIEW

Epidemiology/prevalence of sport-related concussion in **MMA**

Many studies have examined the incidence of head strikes and concussion relationships in MMA; however, the literature reports significantly varying rates of concussions (Table 4). One study

Table 4. Prevalence of injuries and concussions in mixed martial arts athletes

Study	Subjects	Methods	Outcomes
Ngai et al. (2008)	635 MMA matches in Nevada with no data on sex of athletes.	Retrospective cohort study analyzing data from MMA fights between 2002 and 2007.	1,270 Fight exposures occurred across all matches. 23.6% (n = 300) of fight exposures resulted in injury. Out of 635 matches, 3.3% ended by KO, resulting in a severe concussion.
Rainey (2009)	55 MMA athletes (n=3 women) in Missouri, Kansas, and Illinois.	Data was collected retrospectively from questionnaires.	38.2% of injuries occurred in the head, face, and neck region; however, concussions accounted for only 1.8% of injuries.
Hutchison et al. (2014)	844 MMA matches involving 508 athletes (n = 0 women).	Descriptive epidemiology study. Competition data and video records of UFC MMA matches between 2006 and 2012 were analyzed.	12.8% (n = 108) of matches ended by a KO, with an incidence rate of 6.4 per 100 AEs. 21.2% (n = 179) of matches ended by TKO, with 89.9% ending after repetitive strikes to the head. The incidence rate of TKOs due to repetitive head strikes was 9.5 per 100 AEs.
Ji (2016)	455 MMA athletes in South Korea (n = 17 women).	Convenience sampling method used. Data was collected via questionnaires between June 3, 2015, and November 6, 2015.	14.2% (118/831) injuries were to the head. 20.8% (179/860) of diagnosed injuries were concussions.
Karpman et al. (2016)	1,181 MMA athletes (n = 12 women) and 550 boxers (n = 57 women) in Canada.	Data collected from postfight medical examinations between 2000 and 2013.	8.3% (n=98) of MMA athletes were diagnosed with a concussion. Only $4.2%$ (n=50) lost consciousness.
Curran-Sills and Abedin (2018)	343 Bouts with 686 MMA athletes (n = 24 women) in Calgary, Canada.	Retrospective cohort study analyzing official records of MMA matches between 2010 and 2015.	The total injury rate per 100 AE was 23.6, and the concussion injury rate per 100 AE was 14.7. Concussions were the most common injury, representing 62.3% (n=101) of all injuries.
Fares et al. (2019)	285 UFC MMA matches with 36 female athletes.	Descriptive epidemiological study analyzing match scorecards and medical records in Nevada between 2016 and 2018.	291 Injuries occurred across all matches. Head injuries (including concussions, fractures, and lacerations) consisted of 66% (193) of injuries, with a head injury rate of 34 per 100 AE. Concussions represented 32.3% (94/291) of all injuries.
Fares et al. (2021)	816 MMA athletes (n = 106 women) in the U.S.	Descriptive epidemiological study of 408 matches. Data was collected via medical records from fights starting in 2016 and ending in December 2019.	Head injury rate was 35 injuries per 100 AE, with 65% of injuries (288/445 injuries) occurring to the head. 45% (130/288) of head injuries were concussions, resulting in 29.2% (130/445) of injuries being concussions.
Bernick et al. (2021)	60 MMA athletes (n = 0 women) and 60 boxers (n = 0 women) in the U.S.	Retrospective video analysis by four physicians and four nonphysicians. 30 MMA fights in the UFC and 30 boxing fights in the Premier Boxing Champions.	The mean number of concussions per minute of fight time for MMA was 0.085, with the winner sustaining a mean number of concussions of 0.011/minute and the loser sustaining 0.159 concussions/minute.
Ross et al. (2021)	503 MMA matches in Arizona and Wisconsin with no data on sex of athletes.	Descriptive epidemiology study analyzing postfight injury reports from MMA matches between 2018 and 2019.	38% (n=189) of matches ended in TKO or KO. 15.7% of injuries among amateur athletes were concussions, while 8.6% of injuries among professional athletes were concussions. 1.5% of winners sustained a concussion compared to 17.4% of losers.

MMA, mixed martial arts; AEs, athletic exposures; KO, knockou; TKO, technical knockout; UFC, Ultimate Fighting Championship.



found the prevalence of concussions in MMA to be as low as 1.8% of injuries (Rainey, 2009), while another found it to be as high as 62.3% of injuries (Curran-Sills and Abedin, 2018). The study by Rainey (2009) should be interpreted carefully because injuries were self-reported and only 20.1% of MMA athletes received medical attention, thus injury rates may be underestimated. Likewise, Curran-Sills and Abedin (2018) may overestimate the rate of concussions in MMA by counting all TKOs as concussions even though a TKO does not necessarily occur due to head trauma (e.g., physical exhaustion). It was also reported that 8.3% of injuries sustained by MMA athletes were concussions, but only 4.2% of athletes lost consciousness (Karpman et al., 2016); this reinforced the knowledge that not all concussions result in LOC, so a postfight medical examination is of the utmost importance.

Not surprisingly, when analyzing concussion rates based on the winner and loser of a match, it was observed that the loser of both boxing and MMA matches sustains more suspected concussions compared to the winner, and the loser sustains the first concussion 98% of the time (Bernick et al., 2021). Another study reported differing results with only 83% of MMA athletes sustaining head injuries eventually losing the match; however, this takes into consideration all types of head injuries, not just concussions (Fares et al., 2021). Similarly, Curran-Sills and Abedin (2018) observed that 86.1% of injured MMA athletes lost their match. Additionally, it was found that 17.4% of losers sustained a concussion compared to 1.5% of winners in MMA (Ross et al., 2021).

On average, MMA athletes with a head injury sustained 32 significant head impacts during a single match (Fares et al., 2021). It was reported that the average time to stop a match following a KO was 3.5 ± 2.8 sec, and during this time, knocked out athletes sustained an additional average of 2.6 ± 3.0 strikes to the head (Hutchison et al., 2014). It is just as concerning that athletes who lost by TKO sustained 18.5 ± 8.8 strikes in the 30 sec before match stoppage, and 92.3% of those strikes were to the head (Hutchison et al., 2014). Additionally, physicians analyzing videos of MMA matches reported that 43% should have been stopped an average of 44.5 sec sooner than they were (Bernick et al., 2021). Letting a match go longer than necessary can lead to additional head impacts and concussive injuries, with a potential for brain damage (Bernick et al., 2021).

When considering sex, Fares et al. (2021) discovered that males in MMA suffer from concussions at a rate of 17 injuries per 100 athletic exposures (AEs), while women suffer from concussions at a rate of 11 injuries per 100 AEs. In another Fares et al. (2019) study, males and females in MMA sustained similar head injury

rates of 28 and 29 injuries per 100 AEs, respectively. Note that these head injuries included fractures, lacerations, and choking, not just concussions. In the same Fares et al. (2019) study, it was found that 36% and 14% of matches ended with TKO/KO for males and females, respectively, while 33% of matches overall ended with TKO/KO.

Long-term effects of subconcussive RHIs

Research on the long-term effects of RHIs on MMA athletes is sparse, with most of the existing research focusing on boxers. The objective of this section is to evaluate CTE and examine long-term effects of RHIs, including changes in brain volume, brain structure, and cognition.

CTE is described as a progressive tauopathy of the brain found in individuals who have suffered repetitive subconcussive and/or concussive head impacts (McKee et al., 2013). CTE was first discovered in boxers who were described as "punch drunk" (Martland, 1928). Since then, the neuropathology, signs and symptoms, risk factors, and diagnostic criteria of CTE have been explored, but are not well-defined (D'Ascanio et al., 2018; McKee et al., 2018; McKee et al., 2013). CTE is characterized by hyperphosphorylated tau (p-tau) accumulation within neurons and astroglia at the depths of the cortical sulci (D'Ascanio et al., 2018). There are four stages of CTE, each with their own neuropathology (tauopathy) and signs and symptoms (D'Ascanio et al., 2018; McKee et al., 2013).

Stage I CTE is characterized by focal epicenters of p-tau at the depths of the cortical sulci. Subjects with stage I CTE suffer from varying symptoms including headaches, issues with attention and concentration, short-term memory loss, aggression, depression, executive dysfunction, and explosivity. In stage II CTE, p-tau spreads to adjacent superficial cortical layers. In addition to the symptoms seen in stage I CTE, those with stage II CTE experience mood swings, symptoms of motor neuron disease, impulsivity, suicidality, and language difficulties. Stage III CTE is characterized by p-tau widespread throughout the cortices. Symptoms of stage III CTE, in addition to those previously listed, include memory loss, visuospatial difficulties, apathy, and cognitive impairment. Finally, stage IV CTE is distinguished by widespread p-tau in the cerebrum, diencephalon, basal ganglia, brainstem, and spinal cord, as well as neuronal loss. Symptoms of stage IV CTE are more severe and include extreme memory loss in the form of dementia, executive dysfunction, paranoia, gait difficulties, dysarthria, Parkinson disease, and suicidality (D'Ascanio et al., 2018; McKee et al., 2018; McKee et al., 2013).



Unfortunately, risk factors for CTE are not well known; however, there are potential factors that have been explored. The most likely risk factor for CTE is RHIs, but not all individuals who experience RHIs are affected by CTE (D'Ascanio et al., 2018). This suggests that additional risk factors must be present for an individual to develop CTE. Advanced age may also play a role in CTE development, as seen in the study by McKee et al. (2013), where those exposed to RHIs but negative for CTE were on average 32.6 ± 22.4 years old, while those exposed to RHIs and positive for CTE were on average 59.5 ± 20.4 years old. Additional risk factors may include genetics, medical history, lifestyle, and other head impact variables like age of first exposure (AFE) to head impacts, frequency of impacts, and severity of impacts. These risk factors all warrant further research to best determine those that are modifiable in order to decrease the risk of CTE in individuals.

In addition to CTE, RHIs have been shown to affect brain volume, brain structure, and cognition. Much of the research on the long-term effects of RHIs in MMA athletes has been conducted through the Professional Athletes Brain Health Study (PFBHS), an observational and longitudinal study of the brain health of active and retired MMA athletes and boxers (Bernick et al., 2013). MMA athletes did not have a significant difference in brain structure volumes compared to healthy controls in the PFBHS; however, boxers had significantly lower left and right thalamus, caudate, putamen, hippocampus, and amygdala volumes compared to MMA athletes (Bernick et al., 2015). When combined, both MMA athletes and boxers had an estimated 0.3% decrease in caudate volume per professional fight (Bernick et al., 2015). MMA athletes had an estimated 0.2% and 0.3% decrease in thalamus volume for both the left and right sides, respectively, per professional fight (Bernick et al., 2015). Seemingly in opposition to those findings, when looking at a larger cohort from the PFBHS, AFE did not correlate with changes in the volume of the thalamus or caudate (Bryant et al., 2020). However, the same study found that AFE for active and retired athletes correlated with smaller left hippocampal, right hippocampal, and posterior corpus callosum volumes (Bryant et al., 2020). Interestingly, active athletes had smaller left amygdala volume in correlation with AFE, while retired athletes had smaller right amygdala volume (Bryant et al., 2020). Lee et al. (2020) found that boxers and MMA athletes have smaller thalamus (-650 mm³ mean difference) and corpus callosum (-402 mm³ mean difference) volumes when compared to healthy controls.

Two additional alterations in the brain, cavum septum pellucidum and cavum vergae, have been seen in MMA athletes (Lee et al., 2017; Lee et al., 2020). Cavum septum pellucidum and cavum vergae are two types of anterior midline intracranial cysts, which can be congenital and benign or form due to head trauma (Tubbs et al., 2011). The PFBHS found that boxers and MMA athletes had a higher prevalence of cavum septum pellucidum and cavum vergae compared to healthy controls. The presence of cavum vergae was associated with smaller brain volumes in the supratentorium, thalamus, corpus callosum, caudate, putamen, hippocampus, and amygdala compared to athletes without cavum vergae (Lee et al., 2020).

Compared to healthy controls, boxers and MMA athletes scored lower on processing speed and psychomotor speed (Lee et al., 2020). Lower processing speed scores were associated with increased number of professional fights, increased fight exposure scores, earlier AFE, and smaller volumes of the thalamus, amygdala, and left hippocampus for both MMA athletes and boxers combined (Bernick et al., 2015; Bryant et al., 2020). Interestingly, sex was found to moderate the effects of number of professional fights on brain structure volumes and cognition, with male athletes having significantly smaller brain regions than female athletes when associated with number of professional fights (Bennett et al., 2020). Additionally, as number of professional fights increased, male athletes had lower verbal memory scores, while female athletes had better verbal memory scores (Bennett et al., 2020). In retired boxers, earlier AFE was correlated with higher BESS test scores, meaning that earlier AFE is correlated with worse balance (Bryant et al., 2020). When measuring neuropsychiatric symptoms, there was a correlation between earlier AFE and depression, impulsivity, attention issues, and motor impairments in retired boxers (Bryant et al., 2020).

Biomechanical insights on head impacts

The biomechanics of head impacts have been studied more extensively compared to the epidemiology and long-term effects of concussions within MMA. Through different mechanisms of head impacts, linear and rotational accelerations/decelerations contribute to head injuries (Karton and Hoshizaki, 2018). Within MMA specifically, head impact biomechanics are not as well known. However, strain and shear stress in the brain have been documented in MMA athletes, with variation between weight classes, as well as within specific regions of the brain (Khatib et al., 2021; Tiernan et al., 2021).

The study of head impact biomechanics has largely focused on contact sports such as American football, ice hockey, soccer, and boxing. Head impacts in sports are each unique and depend on a



set of characteristics, including magnitude, frequency, interval, and duration of head impact(s) (Karton and Hoshizaki, 2018). When these characteristics were compared between light weight (LW) and heavy weight (HW) MMA athletes, it was found that the frequency and interval of head impacts were similar between the weight classes; however, the magnitude of maximum principal strain (MPS) differed between the weight classes with the LW athletes sustaining a greater frequency of very low and high magnitude MPS head impacts (Khatib et al., 2021). Interestingly, LW athletes sustained high magnitude MPS impacts from punches to the head, while HW athletes sustained high magnitude MPS impacts from elbows to the head, implying that fighting-style differs between weight classes (Khatib et al., 2021). As seen in the study by Khatib et al. (2021), the magnitude, frequency, interval, and duration of head impact(s) are influenced by the type of head impact observed in sports, which include but are not limited to, collisions between athletes, falls, projectile impacts, and punches (Karton and Hoshizaki, 2018).

Linear and rotational accelerations contribute to the resulting head injury through different mechanisms (Karton and Hoshizaki, 2018). High linear acceleration/deceleration results in pressure changes in the head, which leads to brain injury (Gurdjian et al., 1958). Ommaya and Gennarelli (1974) argued that rotational acceleration causes shear stress between the skull and brain, thus resulting in brain injury, including concussions. Similar results were found in MMA athletes where knockouts resulting in transient LOC were overwhelmingly due to rotation of the head (Fogarty et al., 2019). Tiernan et al. (2021) found that the best strain indicator for concussion is the corpus callosum where concussed MMA athletes had 87.9% higher strain values than uninjured athletes. Furthermore, it was discovered that shear stress measured in the corpus callosum is the best predictor for concussion. This was evidenced by a 111.4% higher shear stress in the corpus callosum among concussed MMA athletes compared to uninjured athletes (Tiernan et al., 2021).

Future considerations and research topics

While there have been efforts to better define mTBI and concussion, consensus is required on the definitions of these conditions such that they can be used consistently across the literature. Currently, mTBI and concussion are used interchangeably (Greenwald et al., 2012; McCrory et al., 2017), while the literature defines them differently depending on the focus of the research, making it difficult to truly know the prevalence of concussions across all sports and within MMA.

The rules of MMA encourage head strikes, particularly ones that will knock out an opponent and result in a concussion. The best way to reduce head trauma sustained by MMA athletes is to change the rules. One method is to discourage head strikes by deducting points any time the head is hit. However, rules are unlikely to change this drastically. To mitigate the effects of head strikes, MMA athletes should always wear a mouthguard and headgear, but there is conflicting evidence on whether protective gear can reduce concussion risk. The UFC took a step in the right direction by implementing its first concussion protocol in 2021; however, one of the biggest issues with the concussion protocol is that athletes return home following a fight, so it is up to the athlete and the coach to turn to a healthcare provider for guidance in following the return-to-play protocol. Enforcing the concussion protocol will not be easy, so the UFC must better educate athletes and coaches on the symptoms and dangers of concussion.

Diagnosis of CTE is another area that merits further research because CTE can only be diagnosed postmortem (D'Ascanio et al., 2018; Lin et al., 2018; Zetterberg and Blennow, 2018). Through a literature review on CTE, McKee et al. (2013) defined neuropathologic diagnosis of CTE as the presence of the following: "(a) perivascular foci of p-tau immunoreactive astrocytic tangles and neurofibrillary tangles; (b) irregular cortical distribution of p-tau immunoreactive neurofibrillary tangles and astrocytic tangles with a predilection for the depth of cerebral sulci; (c) clusters of subpial and periventricular astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia and brainstem; and (d) neurofibrillary tangles in the cerebral cortex located preferentially in the superficial layers." However, this diagnostic criterion can only be used when examining a brain postmortem. Clinical diagnosis is not currently possible, but researchers have proposed clinical diagnostic criteria that have not yet been accepted. There is a need for neuroimaging biomarkers or fluid biomarkers that can be used to diagnose CTE antemortem (Lin et al., 2018; Zetterberg and Blennow, 2018). Neuroimaging technology that may potentially be adapted in the future to diagnose CTE includes PET, MRS, MRI, DTI, and fMRI (Lin et al., 2018). Fluid biomarkers found in CSF, blood, saliva, urine, and tears still need to be explored, especially because p-tau is associated with other tauopathies, like Alzheimer disease, and may not be distinguishable from p-tau associated with CTE (Zetterberg and Blennow, 2018).

It is also important to accurately determine the prevalence of concussions in MMA because studies show conflicting results. To aid in this, concussions must be defined consistently across the literature. One study counted all TKOs as concussions (Curran-



Sills and Abedin, 2018), but this is not necessarily true. Another study only counted KOs as concussions (Ngai et al., 2008), but not all concussions result in LOC. Finally, an additional study relied on self-reported injury, with only 20.1% of athletes receiving medical attention, likely underestimating the concussion rate (Rainey, 2009). All MMA athletes must be examined by a medical professional after a fight, and notes from the examination should be documented properly.

To aid in the diagnosis of concussions, the biomechanics of head impacts sustained by MMA athletes must be observed and analyzed. Few studies have reported on the head impact biomechanics of MMA athletes (Bartsch et al., 2012; Fogarty et al., 2019; Khatib et al., 2021; Tiernan et al., 2021), but knowing the mechanism of injury could provide additional information to assist in diagnosing concussions. Of the utmost importance is developing novel, reliable diagnostic measures that can objectively determine the presence or absence of a concussion. Imaging and fluid biomarkers show the most promise, and future studies should focus on finding novel biomarkers to be used moving forward. This also applies to the diagnosis of CTE, which is currently only possible postmortem. Focusing on the prevention of head injuries and mitigation of risk factors will hopefully decrease the prevalence of concussions and reduce the long-term effects of RHIs.

CONCLUSION

To the knowledge of the authors, this is the first overview of the literature on RHIs and concussions sustained by MMA athletes to outline (a) the rules of MMA; (b) the postconcussion protocol for UFC athletes; (c) diagnostic measures; (d) epidemiology and prevalence of concussion in MMA; (e) long-term effects of subconcussive RHIs; (f) biomechanics of head impacts; and (g) future considerations and research topics needed moving forward (for summary, refer to Fig. 1). There are significant knowledge gaps in the

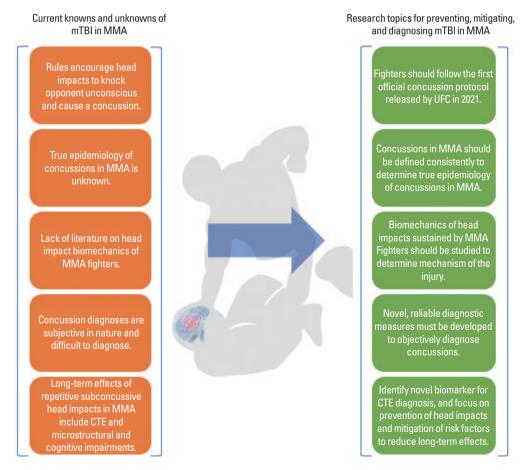


Fig. 1. Current knowledge of head impacts sustained by MMA fighters and suggestions for future prevention, mitigation, diagnosis, and care of head impacts. MMA, mixed martial arts; mTBI, mild traumatic brain injury; CTE, chronic traumatic encephalopathy; UFC, Ultimate Fighting Championship.



literature related to RHIs and head trauma sustained by MMA athletes that need to be addressed in order to prevent future head trauma, mitigate the risk of head trauma and long-term effects, and diagnose head trauma properly.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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