

## RESEARCH REVIEW ON MULTIPLE CONCUSSIONS AND REPETITIVE SUBCONCUSSIVE HEAD IMPACTS

### PURPOSE

The purpose of this research review is to summarize recent peer-reviewed scientific literature on multiple concussions, including the epidemiology, risk factors, pathophysiology, affected populations, evaluation, and treatment of this condition.

### BACKGROUND

Traumatic brain injuries trigger dynamic and potentially chronic pathological processes that are thought to make the brain more vulnerable to impairment upon subsequent head impacts<sup>1-3</sup>; thus, much research has been done to develop a better understanding of the incidence, outcomes, treatment, and prevention of multiple TBIs. Multiple TBIs occur when an individual with a prior history of TBI sustains one or more additional TBIs of any severity. The Department of Defense defines TBI as “a traumatically induced structural injury or physiological disruption of brain function as a result of an external force”<sup>4</sup>; therefore, TBIs can be sustained through several different mechanisms, including a direct head impact, exposure to explosive blasts, or rapid rotational acceleration of the head, such as during a vehicle collision. Most TBIs are categorized as mild (mTBI),<sup>5</sup> which the DOD also refers to as concussion; thus, the terms mTBI and concussion are often used interchangeably. A concussion is clinically defined by a Glasgow Coma Scale score of 13-15, alteration of mental state (e.g., confusion, disorientation, slowed thinking), loss of consciousness for up to 30 minutes, or memory loss lasting less than 24 hours with normal structural imaging results and excluding penetrating TBI.<sup>6</sup>

Most cases of multiple TBIs involve individuals with a prior history of concussion, and multiple concussions are most common in populations most at risk for exposure to repetitive head impacts through their daily activities, including athletes and military service members. The cumulative effects of repetitive subconcussive head impacts, or head impacts that do not result in symptoms consistent with a diagnosis of concussion but that may nevertheless cause microstructural damage,<sup>7</sup> have also been receiving more widespread investigation. Overall, recent evidence suggests that multiple concussions and repetitive subconcussive head impacts cause a wide range of structural pathology and functional deficits, promote the progression of neuropsychological, cognitive, and physical symptoms, and impact a nonnegligible proportion of military and civilian populations. Therefore, the development of effective tools for the evaluation, management, and treatment of these conditions is an area of extensive research. This research review will focus primarily on repetitive head injury related to participation in military service and sports.

## **PATHOPHYSIOLOGY OF MULTIPLE CONCUSSIONS**

### **Preclinical Data on the Pathology of Multiple Concussions**

Concussions initiate a dynamic cascade of neuropathological processes, including sudden neuronal depolarization, alterations in glucose metabolism, glutamate release, and disrupted cerebral blood flow and axonal function, which occur during different time periods after the initial injury.<sup>8,9</sup> The disruptions in neuronal ion balance triggered by concussion promote blood-brain barrier dysfunction while preventing the clearance of cellular debris and inflammatory signals and slowing regenerative processes.<sup>9,10</sup> Recent preclinical studies have provided new insights into these pathological processes by utilizing repetitive blast,<sup>11</sup> rotational acceleration,<sup>12</sup> and various nonpenetrating head impact models.<sup>13-16</sup> In some studies, multiple concussions have been found to alter cortical lipid profiles,<sup>13</sup> axonal metabolism,<sup>16</sup> and neuronal firing dynamics,<sup>15,17,18</sup> which may contribute to any associated cognitive deficits. Recent studies also suggest a potential role of the gut microbiome, and repeat head injury was found in one study to induce a transient increase in the levels of beneficial gut microbes.<sup>19</sup> Specifically, the abundance of *Faecalibaculum* increased, and this microbe produces butyrate, a key anti-inflammatory and immunomodulatory short-chain fatty acid, leading investigators to speculate that this increase may occur to protect against damage from the injury cascades induced by TBI. In another study investigating glymphatic function, repetitive concussions were found to alter glymphatic clearance in specific brain regions, including the limbic system and olfactory bulb.<sup>20</sup> Although this work is in an early stage, these findings suggest promising new avenues for continued research into the pathology of multiple concussions that should be assessed in humans in future studies.

### **Clinical Findings on the Pathology of Multiple Concussions**

The evidence that is currently available from human studies indicates that multiple concussions and repetitive subconcussive impacts can result in detectable axonal and parenchymal damage. Diffusion tensor imaging has revealed that alterations in white matter microstructure can be observed in individuals who have sustained multiple concussions<sup>21-23</sup> and repetitive subconcussive head impacts,<sup>24-28</sup> which may underlie the later development of neurological deficits.<sup>29</sup> Multiple concussions and repetitive subconcussive head impacts have also been shown to cause disrupted blood-brain barrier integrity<sup>30</sup> and functional impairments, including altered functional connectivity<sup>31,32</sup> and ophthalmologic dysfunction.<sup>33</sup> Other studies have observed that decreased gray-matter volume,<sup>34</sup> impaired cerebral blood flow,<sup>34-37</sup> and changes in cerebral oxygenation and oxygen consumption<sup>34,38-40</sup> are associated with a high frequency of repetitive head impacts, suggesting that sustaining multiple concussions increases cerebral metabolic demand.

Additionally, in rare cases, second impact syndrome (SIS) can occur when a second TBI is sustained before the full recovery from a previous TBI, which can result in catastrophic and rapid clinical deterioration, coma, and even death. The first TBI is typically a concussion, and headache is a key symptom of the initial TBI that often persists at the time of the second

impact.<sup>41</sup> The onset of SIS typically occurs within seconds or minutes of the second impact and is typically associated with cerebral swelling accompanied by a subdural hematoma and ischemic lesions.<sup>42,43</sup> Reported cases of SIS have almost exclusively involved male athletes younger than 20 and have mainly been reported among American football players.<sup>41,42</sup> Estimates of the number of SIS cases are difficult to obtain; however, one study reported that of 1.8 million high school and collegiate athletes, there was one case of possible SIS for a team of 50 players every 4,100 seasons.<sup>44</sup> Due to the rare nature of this condition and the wide variability in reported symptoms and pathologies, controversy remains over the exact criteria that should be used to define SIS.<sup>42,45</sup> Nevertheless, understanding of the pathophysiology of multiple concussions has rapidly expanded in recent years, and the connections between these processes and clinical symptoms are beginning to be revealed.

## **MULTIPLE CONCUSSIONS IN THE MILITARY**

### **Incidence and Risk Factors**

In the military population, TBI has been described as a “signature injury” of the post-9/11 combat operations in Iraq and Afghanistan, most commonly occurring through blast exposure, direct head impacts from flying debris, falls, vehicle collisions, and injuries from other service-related activities.<sup>46</sup> An estimated 479,953 service members sustained a TBI from 2000 through the first quarter of 2023; of these cases, 82.2% were classified as mild.<sup>47</sup> However, due to the difficulty of distinguishing initial incidents of TBI from routine follow-up medical care visits for TBI in the Military Health System, the official reporting of TBI follows a once-per-lifetime incidence rule.<sup>48</sup> Therefore, the reported number of TBI cases has likely been underestimated as it does not explicitly account for multiple TBIs sustained by a single service member. To better evaluate the incidence of multiple concussions in the military, the Traumatic Brain Injury Center of Excellence (TBICoE) surveillance team conducted a study of the electronic health records of service members who sustained their first active duty TBI from 2015 to 2017.<sup>48</sup> The results revealed that between 1.93% and 2.32% of service members sustained multiple concussions annually, which established a baseline for future assessments of the incidence rate of multiple concussions in the military.

The specific risk factors associated with the incidence of multiple concussions in the military population are unknown; however, some studies have investigated the relationship between age-related factors and history of multiple concussions, which may be particularly relevant to veterans. One recent study revealed that 12% of elderly individuals (aged 65 years or older) who experienced one TBI sustained a second TBI within five years; factors that were associated with an increased risk of multiple TBIs in this sample included epilepsy, Alzheimer’s disease and other dementias, and depression.<sup>49</sup> Individuals who exhibit risk factors for falls, including frailty and impaired mobility and balance (e.g., in elderly individuals), those with cognitive impairment, and those who use alcohol and certain medications, may also be more likely to sustain multiple TBIs.<sup>49-52</sup> While knowledge regarding the prevalence of multiple concussions among military service members has begun to emerge, further research is needed to identify other potential risk factors of sustaining multiple concussions in this population.

## Symptoms

The outcomes associated with a single concussion, such as posttraumatic stress disorder (PTSD), impaired cognitive function, and post-concussion symptoms, in the military population have been well characterized.<sup>53-55</sup> Early research on the cumulative effect of multiple concussions on these outcomes has revealed that multiple concussions among military personnel are also associated with severe post-concussive symptoms,<sup>56</sup> such as sleep disturbance,<sup>57</sup> headache,<sup>58</sup> depression and PTSD,<sup>59,60</sup> and anxiety.<sup>60</sup> One study demonstrated that 21.7% of the deployed service members assessed who sustained multiple concussions reported experiencing suicidal thoughts or behaviors during their lifetime compared to 6.9% of soldiers who had a single concussion and 0% of soldiers with no history of concussion.<sup>59</sup> However, the group without prior history of concussion was considerably smaller than the groups with a history of one concussion and multiple concussions in this study, which may have led to an underestimation of the occurrence of suicidal ideation in those with no concussion history.

More recent research continues to corroborate these previous findings. A study of veterans revealed that a remote history of multiple concussions was associated with greater impairment in prospective and retrospective memory and a higher severity of posttraumatic amnesia and PTSD symptoms than a history of a single concussion. In this study, mTBIs were sustained at least 7-12 weeks prior to the study, demonstrating the potentially chronic nature of post-concussive symptoms.<sup>61</sup> Another study of veterans who underwent comprehensive evaluations for mild-to-moderate TBI from 2011 to 2021 showed that more severe headache and migraine-like features were associated with a history of multiple TBIs.<sup>62</sup> A study of men aged 50-79 years also found that those with a history of three or more concussions reported a higher incidence of memory problems, in addition to more frequent fatigue and migraines.<sup>63</sup> In a study in which most of the investigated service members had sustained multiple concussions, neurovascular coupling, which represents the cerebrovascular system's ability to respond to neurological stimuli, was found to be related to subtle vision impairments.<sup>64</sup> Importantly, the authors suggest that since neurovascular coupling is not associated with more commonly tested visual and sensory outcomes, the evaluation of neurovascular coupling may provide distinct information that allows clinicians to detect physiological damage that would otherwise be missed.

Notably, research suggests that the severity of the outcomes associated with multiple TBIs may depend on the number and severity of TBIs sustained. One study reported that deficits in measures of cognitive function, including processing speed and working memory, were not observed in individuals who sustained a concussion despite the fact that more than half of this concussion group included individuals who sustained multiple head injuries.<sup>65</sup> Other investigators found that only individuals with a prior history of moderate-to-severe TBI showed impaired cognitive and motor function during the five-year follow-up after sustaining a second TBI; a history of prior concussion did not significantly impact longitudinal outcomes.<sup>66</sup> While this research provides important new insights into the consequences of multiple TBIs, additional studies confirming the relationship between multiple TBIs and other outcomes that have been less studied in recent years, such as suicide risk, sleep disorders, substance abuse, and other factors affecting patient quality of life, should be conducted.

## **MULTIPLE CONCUSSIONS IN SPORTS**

### **Incidence and Risk Factors**

In civilians, recreational activities and competitive sports are common causes of multiple TBIs. The recent surge in public attention to the long-term effects of concussions sustained by football players in particular has led to increased interest in accurately determining the incidence of TBI, including multiple TBIs, among athletes. As with TBIs in the military population, most sports-related TBIs are classified as mild or concussive.<sup>67</sup> Evidence suggests that nearly 30% of all TBIs may be sports related,<sup>67</sup> with those occurring in children and adolescents accounting for a large proportion.<sup>68</sup> However, the incidence of sports-related TBI may be underestimated as head injuries associated with sports frequently are underreported. Nevertheless, currently available evidence does indicate that the incidence and severity of sports related TBI depends on the duration of participation in the sport,<sup>69</sup> position played,<sup>70-72</sup> and other factors, including race and sex.<sup>73,74</sup> Contact sports, such as football, boxing, hockey, soccer, and rugby, are associated with the highest rates of TBI.<sup>75-80</sup>

Findings from the National Collegiate Athletic Association (NCAA) Injury Surveillance Program from 2009-2010 to 2013-2014 academic years indicate an average concussion recurrence rate across 17 sports of 13.9% and 10.3% for men's and women's sports, respectively.<sup>75</sup> Men's ice hockey exhibited the highest rate of multiple concussions at 20.1%, while men's baseball had a recurrence rate of 0.0%.<sup>75</sup> Among women's sports, soccer (12.5%) and volleyball (5.4%) had the highest and lowest rates of recurrent concussions, respectively.<sup>75</sup> In National Football League (NFL) players from 2015 to 2019, the risk of sustaining a subsequent concussion within one year of an initial concussion was found to be between 5.3% to 8.3%,<sup>76</sup> which is similar to the rate of 6.7% reported for same-year repeat concussions in adolescent athletes.<sup>81</sup> However, more recent estimates of concussion recurrence in specific sports have been limited.

### **Symptoms**

In athletes, a history of two or more concussions is associated with a greater number of symptoms, greater severity of symptoms, and slower recovery from symptoms than a history of no or one concussion.<sup>82-86</sup> Headache and fatigue symptoms are particularly more severe in individuals who sustain multiple concussions.<sup>70,82,86-88</sup> A history of both a single concussion and multiple concussions also increases the odds of sustaining a lower extremity injury in NFL players and collegiate athletes,<sup>89,90</sup> supporting the idea that TBIs may render individuals more vulnerable to subsequent injury. Other studies have reported acute neurocognitive deficits, including impaired memory, processing speed, and impairment of new learning, in athletes who sustained multiple concussions.<sup>88,91-94</sup> Researchers have also begun investigating the connection between neurodevelopmental disorders and multiple concussions, revealing that a diagnosis of attention deficit hyperactive disorder (ADHD) may be associated with an increased risk for multiple concussions in males and exacerbated cognitive deficits.<sup>95,96</sup>

However, other studies have shown conflicting findings regarding certain outcomes from multiple TBIs. Some have found no evidence of cognitive differences in athletes with a remote history of multiple concussions compared to those with no history of concussion.<sup>97-99</sup> Findings regarding the impairments in balance and vestibular changes associated with multiple TBIs have similarly been limited and inconsistent.<sup>100-107</sup> The relationship between concussion history and neuropsychological disorders, such as depression, is also uncertain. For example, while one study demonstrated that concussion history was a predictor of poor sleep quality and was related to the severity of depressive symptoms,<sup>108</sup> another found no association between concussion history and depression.<sup>109</sup>

The differences among study findings could be due to several factors, including differences in study design. For example, one study showing changes in postural control due to subconcussive head impacts evaluated sway velocity while the players assumed various stances on different surfaces<sup>102</sup>; in contrast, two studies that found no changes following repetitive subconcussive head impacts evaluated quiet stance metrics from eyes-open and eyes-closed tasks.<sup>100,107</sup> However, a systematic review of studies on this relationship showed that the majority of both intervention studies investigating the effects of controlled soccer heading and cohort studies investigating pre-to-post-season changes found no significant changes in postural control metrics.<sup>104</sup> Similarly, studies on the relationship between concussion history and depression used different tests to evaluate depression symptom severity; one study that reported an association used the Beck Depression Inventory-II,<sup>108</sup> while another that reported no association used the more comprehensive Depression, Anxiety, and Stress Scale.<sup>109</sup> An increased understanding of the relationship between multiple concussions and these outcomes will likely emerge from the efforts of the NCAA Concussion Assessment, Research and Education Consortium, a large study that initiated in 2014 and includes participants from 30 campuses across the country.<sup>110</sup>

## **EVALUATION AND MANAGEMENT**

### **Military Evaluation and Management**

Prior to 2006, evaluations for TBI were only regularly performed in service members who suffered severe injuries and were medically evacuated, but concerns over the number of undocumented head injuries and increased awareness of the consequences of TBI led to more frequent assessments of TBI.<sup>111</sup> In 2012, the DOD Instruction 6490.11, *DOD Policy Guidance for Management of Mild Traumatic Brain Injury/Concussion in the Deployed Setting* was first established to provide guidance on the management of concussion and to standardize terminology, procedures, and leadership actions for this effort.<sup>112</sup> Recently, the Defense Health Agency established the Acute Concussion Care (ACC) Pathway as part of the FY21 Quadruple Aim Performance Process to standardize acute concussion assessment and care across the Military Health System.<sup>113</sup> The ACC mandates:

- Using the Military Acute Concussion Evaluation 2 (MACE 2), a tool designed to screen service members following potentially concussive events, for acute assessment as close to the time of injury as possible
- Following up within 72 hours after diagnosis of concussion

- Completing the Progressive Return to Activity (PRA) protocol prior to return to full duty

To support these efforts, the DOD Instruction 6490.11 now includes recently developed clinical tools needed to ensure patients achieve optimal recovery.<sup>112</sup> This instruction mandates that all service members diagnosed with a concussion have, at a minimum, 24 hours of rest unless the results of subsequent clinical evaluation indicate a longer period is needed. Before return to full duty, the DODI 6490.13 mandates that service members undergo neurocognitive assessment with the Automated Neuropsychological Assessment Metrics (ANAM) tool.<sup>114</sup>

When a service member experiences a potentially concussive event, the MACE 2 is used to document the incident, record concussion history, and assess the patient's symptoms and cognitive and neurologic function.<sup>115</sup> The MACE 2 was updated in 2021 to include vestibular/ocular-motor screening to assess and document vestibular function. When a diagnosis of concussion is confirmed, the TBICoE PRA Clinical Recommendation titled *Progressive Return to Activity Following Acute Concussion/Mild Traumatic Brain Injury: Guidance for the Primary Care Manager in Deployed and Non-Deployed Settings*, which was updated in 2023, is used to guide progressive return to duty.<sup>116</sup> This tool uses a stepwise approach to progress from Stage 1 ("Relative Rest") to Stage 6 ("Return to Duty") and provides an algorithm for the appropriate progression through the stages based on symptomatology. Those who have sustained one or two concussions in the past 12 months are instructed to progress through the return-to-duty protocol and undergo follow-up every three days to ensure symptom resolution. If the individual has sustained three or more concussions in the past 12 months, the Recurrent Concussion Evaluation is performed.<sup>117</sup> This tool directs the individual to undergo a comprehensive evaluation by a neurologist, neuroimaging as necessary, neuropsychological testing, functional assessments, and ultimately clearance by a neurologist for return to duty. The recovery period for service members experiencing recurrent concussions depends on the number of incidents, and recovery care includes uninterrupted sleep and symptom management. All activities with a risk of concussion are prohibited until the service member is cleared by a licensed independent practitioner. Additionally, a recurrent concussion evaluation may be performed any time it is clinically indicated (i.e., if symptoms are persistent).

### **Evaluation and Management of Sports Related TBI**

Similar to TBI evaluation in the military, before the 1990s, protocols for injury management after sports related concussion were rarely followed, and athletes often returned to play on the day of or the day after a concussion.<sup>118,119</sup> However, the first large prospective study to investigate the time course of recovery from concussion revealed that adequate recovery from concussion required 7-10 days, and athletes were found to be at the greatest risk of a repeat concussion during this period.<sup>3</sup> Subsequently, efforts to improve the evaluation and management of sports related concussion resulted in more rigorous policies for return to play (RTP). The Lystedt Law was enacted in Washington State in 2009 to prevent complications from concussions sustained by adolescents involved in sports.<sup>120</sup> Concussion laws in all 50 United States and the District of Columbia now include removal from play at the time of the concussion, no same-day RTP, evaluation and clearance by a trained health care provider prior to RTP, and required education for coaches, parents, and athletes on concussion and appropriate

management.<sup>121-123</sup> To date, surveillance data suggest that these laws have reduced the incidence of repeat concussions among athletes.<sup>124,125</sup>

At the time of a potentially concussive event, the Sport Concussion Assessment Tool – 6<sup>th</sup> Edition (SCAT6) and Child SCAT6 are used to evaluate and diagnose concussion in adults and minors (12 years and younger), respectively.<sup>126</sup> Similar to the MACE 2, the SCAT6 is used to document the incident, assess concussion history, and record information on the individuals' symptoms and cognitive and neurologic function.<sup>127</sup> This tool also includes the Balance Error Scoring System (BESS) to evaluate coordination, but unlike the MACE 2, it does not directly assess vestibular function. Similar to PRA guidelines used in the military, athletes diagnosed with a concussion via the SCAT6 undergo a progressive return to sport protocol involving six stages that begins with Stage 1, "symptom-limited activity."<sup>128</sup> The Immediate Post-Concussion Assessment and Cognitive Test (ImPACT), similar to the ANAM used in the military, is a computerized cognitive test often used to aid RTP decision making.<sup>129</sup> For individuals who sustain multiple concussions, particularly those who have had two or three within a year or during one season, more conservative management is warranted and may involve removal from play for the season or year.<sup>130</sup> However, standardized guidelines for managing individuals who experience persisting or new symptoms after multiple sports related concussions are lacking.

## **PREVENTION AND TREATMENT**

Recommended treatment for individuals who have sustained multiple TBIs currently includes relative rest and symptom management, and no specific pharmacologic agents or nutritional substances have been approved to accelerate recovery. However, efforts to mitigate the risk of multiple TBIs among military personnel, athletes, and other individuals at high risk for head trauma, such as construction workers, have achieved more success. Specifically, advancements in knowledge regarding head impact velocities during sport and combat have enabled improvements in the design of protective head gear.<sup>131-133</sup> Helmets are currently designed with a variety of shock-absorbing technologies that utilize different mechanisms for attenuating forces directed toward the head,<sup>134</sup> and protocols have been developed to evaluate their ability to reduce high and low velocity impacts.<sup>135,136</sup> Although research has shown that these efforts have helped reduce the incidence of more severe forms of head injury,<sup>137</sup> research on improving helmet design is still ongoing due to concerns regarding the ability of current helmets to protect against concussive and subconcussive head impacts.<sup>131,138-141</sup>

Various computational models have been developed to assess helmet performance and identify promising helmet designs that protect military service members from blast-related concussion. A study of one model showed that helmets with more padding and smaller gaps between padding elements effectively mitigated the effects of repetitive blast exposures.<sup>142,143</sup> The addition of a face shield has also been found to reduce the transmission of blast overpressures to the head.<sup>144</sup> In the context of sports-related concussion, an early study conducted by the Virginia Tech Helmet Lab showed that one helmet with 40% thicker foam than a previous model was associated with a 56% lower risk of concussion,<sup>145</sup> likely because the additional foam better reduced the acceleration of the head after impact. A recent innovation in helmet design is padded covers placed over the helmet's exterior; while these covers are now commercially available and



have even become mandated under certain conditions in elite football, evidence from human studies has not consistently shown their ability to reduce impact severity or brain injury risk metrics.<sup>146</sup>

The investigation of potential neuroprotective agents for preventing cumulative neurotrauma from multiple TBIs and alleviating post-concussive symptoms is also a key research area. A meta-analysis of nutritional interventions for repetitive concussive and subconcussive head injury revealed that fatty acids and melatonin supplementation were the most studied in recent years, and fatty acids showed the strongest evidence of a beneficial effect on preventing neurotrauma.<sup>147</sup> However, clinical trials on supplementation with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the most commonly studied fatty acids, produced mixed findings. This supplementation has been shown to reduce the levels of a biomarker of axonal injury in some studies<sup>148,149</sup> but not in others<sup>150</sup> and to have no effects on white matter integrity.<sup>151</sup> One study reported faster recovery and RTP with DHA and EPA supplementation,<sup>152</sup> but additional studies are needed to confirm this effect in a larger sample size. Similarly, some studies have observed benefits of melatonin supplementation on sleep parameters in pediatric patients with persistent post-concussive symptoms,<sup>153-155</sup> while others found no effects on sleep,<sup>156</sup> indicating that additional studies are necessary before melatonin supplementation can be recommended for the treatment of sleep symptoms after TBI. Collectively, the findings supporting the use of these treatments are preliminary, and the investigation of additional therapeutic candidates has mainly been limited to preclinical studies. Large multicenter randomized controlled trials are needed to confirm the efficacy of treatments for multiple concussions.

## **CONCLUSION**

For many decades, TBI research primarily concentrated on improving the outcomes of patients experiencing the most severe and devastating forms of this condition. This benefited only a small proportion of the TBI patient population, and the effects of prior TBI history were rarely investigated. Imaging studies have since demonstrated the structural and functional damage associated with repetitive concussions, and other studies have shown the persistence of cognitive, physical, and psychological symptoms in some patients. Heightened awareness of the long-term effects of sustaining multiple concussions and subconcussive impacts has thus led to an era of intensified research interest in characterizing and preventing post-concussive symptoms in these individuals. The knowledge gained from these efforts has led to more robust policies for documenting, evaluating, managing, and preventing multiple concussions.

While understanding of the effects of multiple concussions has progressed, several aspects of this condition are unknown, and challenges in studying and treating multiple concussions remain. Although preclinical research has provided new findings regarding the pathology of multiple concussions that could eventually expand the range of therapeutic targets, the actual roles of these processes, such as alterations in the gut microbiome and glymphatic function, in human TBI must first be confirmed. Many studies reporting structural damage or functional deficits in humans following multiple TBIs have been conducted during the acute or subacute period after

injury or have used samples with high variability in the time elapsed since injury, and information on the specific timing of and dynamic changes in TBI pathology and symptoms is limited. Some longitudinal findings with common data elements from DOD-funded studies, including the Long-Term Impact of Military-Relevant Brain Injury Consortium Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC) and other data repositories, may help address this gap. Studies of multiple concussions have overwhelmingly focused on sports-related TBI, which may limit our ability to generalize findings regarding recovery and treatment to other populations. Efforts to address these remaining questions and challenges will further advance the long-term treatment and management of multiple concussions.

## **KEY POINTS & RECOMMENDATIONS**

- A history of multiple concussions or repetitive subconcussive impacts is associated with a wide range of pathologies and symptoms that can considerably affect patient quality of life.
- Identifying aspects of the pathophysiology of multiple concussions that could be readily targeted to prevent or delay symptom progression should be prioritized in preclinical and clinical studies.
- The overall incidence and outcomes of multiple TBIs, particularly in the military population, should be investigated more routinely to provide up-to-date information on the impact of this condition.
- Service members who sustain TBIs should undergo timely evaluation to determine prior TBI history and should be managed conservatively to reduce the risk of a subsequent TBIs and allow for recovery from post-concussive symptoms before returning to full duty.
- Health care professionals treating individuals who have sustained multiple TBIs should prioritize clear TBI documentation and reporting to enable more accurate estimates of TBI recurrence.

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## **DISCLAIMER**

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