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Long-Term Cognitive and Neuropsychiatric Consequences of Repetitive Concussion and Head-Impact Exposure

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Initially, interest in sport-related concussion arose from the premise that the study of athletes engaged in sports associated with high rates of concussion could provide insight into the mechanisms, phenomenology, and recovery from mild traumatic brain injury. Over the last decade, concerns have focused on the possibility that, for some athletes, repetitive concussions may raise the long-term risk for cognitive decline, neurobehavioral changes, and neurodegenerative disease. First conceptualized as a discrete event with variable recovery trajectories, concussion is now viewed by some as a trigger of neurobiological events that may influence neurobehavioral function over the course of the life span. Furthermore, advances in technology now permit us to gain a detailed understanding of the frequency and intensity of repetitive head impacts associated with contact sports (eg, football, ice hockey). Helmet-based sensors can be used to characterize the kinematic features of concussive impacts, as well as the profiles of typical head-impact exposures experienced by athletes in routine sport participation. Many large-magnitude impacts are not associated with diagnosed concussions, whereas many diagnosed concussions are associated with more modest impacts. Therefore, a full understanding of this topic requires attention to not only the effects of repetitive concussions but also overall exposure to repetitive head impacts. This article is a review of the current state of the science on the long-term neurocognitive and neurobehavioral effects of repetitive concussion and head-impact exposure in contact sports.

Key Words: traumatic brain injuries, symptom reporting, recovery, neurodegeneration

Over the past 2 decades, we have witnessed a rapid transformation in how the scientific community, sporting organizations, athletes themselves, legislative bodies, and the general public view sport-related concussion (SRC). Researchers have delivered major breakthroughs in the basic and clinical science of concussion, clarifying the acute effects of injury on brain structure and function that underlie the common signs and symptoms of injury.[1] Sporting organizations have leveraged those key scientific advances to implement standardized protocols for injury assessment, management, and return to play after concussion. All 50 states in the United States have passed legislation dictating minimum standards for determining an athlete's fitness to return to play after concussion. At the same time, athletes, parents, and other key stakeholders have shown a heightened level of interest in understanding the short- and long-term effects of concussion. In the United States and worldwide, the combined result has been the recognition of SRC as a major public health problem that requires further advances in research, clinical care, and public policy.[2]

In the past 10 years, 3 major shifts have occurred in the "narrative" around concussion. First, attention has turned to risks associated with repetitive concussion (*how many are too many?*), above and beyond the transient effects of a single injury. Second, the focus has expanded from the incidence of multiple concussive injuries (*how many?*) to potential risks associated with cumulative head-impact exposure (*how much*?) through routine participation in contact sports, even in the absence of formally diagnosed concussion. Third, the view of concussion has broadened into attempts to understand the effects of injury across the lifespan (*what happens down the road?*), not simply the acute injury and recovery period (*when can he or she return to play?*).

These concerns are particularly relevant in the setting of contact sports, given the known incidence of concussion[3,4] and the reported volume of exposure to repetitive head impacts as part of routine participation.[5–8] Unfortunately, data on the epidemiology of repetitive concussion and head-impact exposure in contact-sport athletes are limited, due in part to the large-scale efforts necessary to determine the population-based frequency of repeat concussion and technological resources required to reliably quantify head-impact exposure across sports and athlete subpopulations. Other papers in this special issue provide an overview of the known epidemiology of SRC and recent advances in the measurement of head-impact exposure in sports.

We will briefly review the current state of the science on potential long-term risks associated with repetitive concussion and head-impact exposure in sports. Given their relevance in the context of existing literature on the effects of traumatic brain injury (TBI), we will discuss the evidence related to cognitive, neuropsychiatric, and neuro-

degenerative disorders. Gaps in the literature will be described, along with recommendations for future research directions to fundamentally determine the true, population-based risk of neurologic health problems associated with repetitive concussion and head-impact exposure in sports.

CURRENT STATE OF THE SCIENCE

Repetitive Concussion in Sports

Although we have gained a clearer understanding of the overall epidemiology of concussion across sports at various levels of athletic competition, less is known about the incidence of recurrent concussion and associated risks. Authors of prior studies[9–11] with relatively small sample sizes have reported on the symptoms, cognitive changes, and recovery time during the acute and subacute periods after recurrent concussion, but the population-based risks of recurrent concussion and resulting effect on recovery and outcome remain unclear. The literature on this topic is also limited by a lack of truly prospective studies, which affects the scope and quality of data available for review and interpretation.

A recent, large-scale epidemiologic study[12] indicated that recurrent concussion is far less common than first concussion. In 2012, Castile et al[12] reported that the rate of recurrent concussion in high school athletes was 3.1 per 100 000 athlete-exposures (AEs), compared with a rate of 22.2 per 100 000 AEs for new concussions. In that same study, however, recurrent concussion was associated with a higher incidence of unconsciousness caused by injury, longer symptom recovery time, delayed return to play, and greater likelihood of an athlete being disqualified for the season compared with a first concussion. These findings suggest that recurrent concussion is relatively uncommon among high school athletes, but they add to speculation about the potential negative effects associated with repetitive head injury in sports, at least over the short term. The extent to which injury-management strategies (as opposed to actual recovery time) may have influenced the results in the Castile et al study is unclear. Further, the Castile et al study was an epidemiologic survey; a prospective study design would be a more reliable and effective way of quantifying the risks associated with repeat concussion.

Repetitive Head-Impact Exposure in Sports

As noted earlier, concerns have been raised about the potential for neurobehavioral effects of repetitive head impacts, particularly those associated with contact sports, such as American football, ice hockey, and combat sports.[13] Although some have used the term *subconcussive impacts* to describe hits to the head not associated with a diagnosed concussion, this term is considered an imperfect characterization, as it implies that all concussions are diagnosed accurately (yet one cannot know if an impact is subconcussive unless one is sure that it was not concussive); it suggests that we know the lower boundary threshold for concussion, and it seems to indicate an as yet unproven conclusion that such impacts produce brain injury (albeit a milder form than concussion).

Evidence for the concern that repetitive head impacts might cause harm follows from the observation that, in some animal models, mild head impacts not typically associated with cellular injury can nonetheless cause damage when repeated several times within a short time period.[14,15] Emerging data from studies in American football and ice hockey using helmet-based accelerometers have quantified the frequency and magnitude of head impacts associated with playing a contact sport and the resulting effects on brain structure and function.[16,17]

A variety of researchers have looked at both impact frequency and magnitude in high school and collegiate athletes in helmeted contact sports. Schnebel et al[18] studied 16 high school players over a single season and reported that they sustained an average of 520 impacts. Broglio et al[6] demonstrated an average of 652 impacts per player over a single season in a larger sample of 35 high school athletes, observed a significant range of impact frequencies across athletes in the same sport (maximum = 2235 impacts), and noted that impact frequency varied by position. Similarly, Crisco et al,[7] in a large study of 3 collegiate teams, showed that impact exposure varied across teams (median impacts ranged from 257 to 438 per season), type of activity (game versus practice), and position (more frequent in linemen). In that study, frequency of impacts also varied by sport and sex. In an investigation of collegiate ice hockey players, Wilcox et al[19] found that men experienced an average of 287 head impacts per season compared with 170 for women.

Magnitude of impact also varies across these factors.[20] Crisco et al[7] in their cohort of 314 collegiate football players at 3 institutions, encompassing 286 636 impacts, found 50th and 95th percentile peak linear accelerations of 20.5*g* and 62.7*g* and peak rotational accelerations of 1400 and 4378 rad/s^2, respectively.

Studies are now being conducted in an effort to more broadly characterize the frequency and magnitude of head impacts that contact-sport high school and collegiate athletes commonly sustain, as well as to inform the biomechanics and kinematics of head impacts causing concussive injury (see www.careconsortium.net). These same studies also include detailed clinical, neuroimaging, and neurobiological measures to investigate the effects of repetitive head-impact exposures and concussive impacts on brain structure and function.

Short-Range Effects of Repetitive Concussions and Head-Impact Exposures

Numerous prospective studies[21–23] over the past 2 decades have demonstrated that the overwhelming majority of athletes achieve a complete recovery in self-reported symptoms and performance-based measures of recovery (ie, cognitive, balance) by 1 to 2 weeks after SRC. However, recent reports on the frequency and magnitude of head impacts encountered by contact-sport athletes have led to concern that repetitive, high-impact blows might be injurious to their brains. To date, the data are somewhat conflicting.

Broglio et al[24] studied helmet impacts to 95 high school football players over 4 seasons using a head-impact telemetry system. Both cognitive and symptom-reporting measures were completed preseason and again within 24 hours of injury in those who sustained concussions. The concussed athletes demonstrated acute declines in cognitive

performance and increases in symptom reporting. Yet there were no significant relationships between changes in performance on cognitive tests and any of a number of impact-exposure variables (including number of impacts, peak or cumulative linear acceleration, peak or cumulative rotational acceleration, impact severity or cumulative profile, time from session start until injury, or time from the previous impact), nor was there a relationship between self-reported symptom severity and these impact-exposure variables.

Gysland et al[25] assessed cognitive, sensory, balance, and symptom self-report measures in 46 collegiate football players both before and after a single season during which a head-impact telemetry system was used. Changes in performance were mostly independent of concussion history, as well as the total number, magnitude, and location of sustained impacts over 1 season. Specifically, head-impact variables (including the total number of impacts, the total number of impacts greater than 90*g*, the total cumulative magnitude of impacts, and the total number of impacts to the top of the head) did not predict neurocognitive performance, balance, or symptom severity over time. This study did not address the potential effects of the lifetime impact dose, though the authors did note that the amount of collegiate football exposure (based on number of years played) was associated with poorer balance and increased symptom reporting. Miller et al[26] similarly assessed 76 collegiate football players at preseason, midseason, and postseason on neurocognitive measures and found no significant declines throughout the season on the Standardized Assessment of Concussion (SAC) or Immediate Post-Concussion Assessment and Cognitive Test (ImPACT), despite likely repeated head impacts. These researchers did not measure head impacts, so the relationship between magnitude and number of blows was not directly assessed.

McAllister et al[16] followed 214 nonconcussed collegiate football and hockey players from preseason to postseason and compared them with 45 noncontact-sport athletes assessed at the same intervals on a more extensive battery including ImPACT and 7 other neuropsychological measures. They observed few significant between-athletes group differences either at preseason baseline or at the postseason assessment on a variety of cognitive measures, even though the contact athletes sustained a seasonal average of 469 head impacts with an average acceleration of 32*g*. They concluded that the number of head impacts did not have a widespread short-term detrimental effect. However, a significantly higher percentage of athletes in the contact-sport group (24% versus 3.6%) performed below their predicted level on a single measure of verbal memory (the learning trials of the California Verbal Learning Test), raising the possibility that a subgroup of athletes might be vulnerable to the effects of repetitive head impacts.

Neuroimaging studies to date are limited by a number of factors (eg, extremely small sample sizes relative to large sets of dependent variables, lack of hypothesis-driven analyses, absence of control groups, failure to report false-positive and false-negative rates). Reports have raised the question of potential structural and functional sequelae associated with repetitive head impacts, at least in a subset of individuals. Talavage et al[27] conducted a small prospective study of 21 high school football players. Four of the 8 nonconcussed players with subconcussive blows who were reassessed in-season had significant reductions in verbal or visual (or both) memory scores on the ImPACT battery and decreased functional magnetic resonance imaging activation levels in the dorsolateral prefrontal cortex and cerebellum during working memory tasks.

Diffusion tensor imaging has also been used to investigate repetitive head impacts. In a prospective cohort of 9 high school football or ice hockey athletes and 6 controls, Bazarian et al[28] demonstrated changes in fractional anisotropy (FA) and mean diffusivity (MD) within 24 hours of injury that correlated with the proportion of white-matter voxels showing significant change. However, the changes in FA and MD were in both directions (increased and decreased), making interpretation difficult.

McAllister et al[17] used diffusion tensor imaging to study the effects of exposure to repetitive head impacts over a single season in 80 nonconcussed collegiate football or ice hockey players who wore instrumented helmets and in 79 noncontact-sport athletes. Differences were evident between athlete groups for MD in the corpus callosum ($P = .011$) and for postseason FA in the amygdala ($P = .001$). Measures of head-impact exposure correlated with white-matter–diffusion measures in several brain regions, including the corpus callosum, amygdala, cerebellar white matter, hippocampus, and thalamus. The magnitude of change in corpus callosum MD during the postseason was associated with poorer performance on a measure of verbal learning and memory. The authors interpreted their findings as consistent with a relationship among head-impact exposure, white-matter–diffusion measures, and cognitive changes over the course of a single season, even in the absence of diagnosed concussion.

Neuropsychiatric Effects of Repetitive Concussion and Head-Impact Exposure

A variety of neuropsychiatric sequelae are associated with SRC. These sequelae take 2 broad forms: neuropsychiatric distress immediately or shortly after the injury that can be considered part of the natural course of any form of injury, including mild TBI (mTBI), and an increased vulnerability to psychiatric disorders beyond the acute recovery period. Although a fair amount is known about the links between mTBI and neurobehavioral sequelae in general, less is known about SRC specifically and even less about potential neurobehavioral sequelae of repetitive head-impact exposure in the absence of diagnosed concussion.

Immediately after concussion, injured athletes, when asked, often report a variety of symptoms consistent with neuropsychiatric distress. Accordingly, standard checklists for assessing postconcussive symptoms include these domains. For example, the Sport Concussion Assessment Tool 3 (SCAT3) is a frequently used concussion-assessment tool recommended by the guidelines from the 4th International Consensus Meeting on Concussion in Sport.[2] The SCAT3 includes a 22-item symptom checklist of common postconcussive symptoms, several of which could be viewed as psychological health questions (eg, nervous or anxious, sadness, irritability, more emotional, trouble falling asleep). Within the typical window of recovery

after a concussion, indices of depression and anxiety are usually elevated.

It is important to stress, however, that transient elevations in these symptoms do not necessarily mean that an individual is suffering from a major depressive or anxiety disorder. For such a diagnosis, more sustained (of several weeks duration) symptom distress of sufficient severity to interfere with social or occupational function (or in the case of a student, educational efforts) is required. For example, Kontos et al[29] noted elevated depressive symptoms on a scale within 2 weeks of a concussion in high school and collegiate athletes, but the mean score was well below the threshold generally considered consistent with clinically significant depression. Vargas et al[30] recently reported similar results in a cohort of concussed collegiate athletes: predictors of postinjury depressive symptoms included greater baseline depressive symptoms and lower estimated premorbid intelligence. Roiger et al[31] also reported short-term elevations of depressive symptoms in concussed collegiate athletes, which were similar to those observed in athletes with orthopaedic or other nonhead injuries. This dual finding highlights the importance of including other injured control participants (with nonhead injuries), akin to the trauma control participants commonly included in studies of civilian mTBI, to better understand the nonspecific effects of injury on psychological health.

In addition to the immediate postinjury effects on emotion and behavior described earlier, TBI, including mTBI, increases the risk for developing a variety of psychiatric disorders.[32–34] This is generally considered to be related to the vulnerability to the effects of trauma on the brain regions critical to the modulation of mood, affect, and executive function,[33] as well as a complex relationship with preinjury psychiatric illness or altered psychological health.[33,34]

Postinjury psychiatric conditions can accentuate or increase the degree of distress associated with lingering symptoms.[33] Much of our knowledge on this topic comes from what we know of the neuropsychiatric aspects of TBI in general.

Relatively little is known about the long-range neuropsychiatric sequelae of SRC specifically, although a small body of literature is emerging. Most work to date has focused on the relationship between concussion and alterations in mood, particularly depression. For example, Chrisman and Richardson[35] reported a 3.3-fold increase in depression risk associated with a history of concussion in a sample drawn from the National Survey of Children's Health 2007–2008. Corwin et al[36] showed that depression and anxiety were drivers of prolonged recovery in a cohort of 247 concussed children and adolescents referred to a pediatric sports medicine clinic; successful treatment of comorbid conditions resulted in a significant reduction of postconcussive symptoms. Kerr et al[37] described a relationship between the number of reported concussions and diagnosis of depression in a cohort of retired professional football players. Both Hart et al[38] and Strain et al[39] found correlations between white-matter–diffusion metrics (FA) and a depression diagnosis and symptoms in retired football players.

More recently, there has been increasing interest in characterizing the neuropsychiatric component of neurodegenerative disorders linked to repetitive concussion and head-impact exposure in former athletes, including the features of chronic traumatic encephalopathy (CTE).[40,41] This work has focused primarily on changes in mood, personality, and behavior in cases of CTE.[42] Some have argued that these symptoms are a prominent part of the clinical picture of CTE and may even be key components of the early stages of this disorder.[40–42] However, it is important to note that, similar to symptoms of concussion, changes in mood, suicidal ideation, anxiety, and personality are nonspecific and can be associated with a variety of neuropsychiatric disorders or even transient responses to significant life events. Thus, confidently attributing such nonspecific symptoms to a putative neurodegenerative condition can be problematic.

A history of repetitive neurotrauma has also been speculated to be a risk factor for suicidality among former athletes, although this theory has been refuted in several publications.[43,44] Still, increased rates of suicide in individuals with a history of mTBI from various causes (not SRC specifically) have been shown. For example, Fralick et al[45] recently published a study of suicide rates in individuals in Ontario, Canada, with an International Classification of Diseases, Ninth Revision, primary diagnosis of concussion who received hospital-based care over a 20-year period. The concussed individuals had a 3- to 4-fold increase in suicide rates compared with the general population that was independent of various demographic and past psychiatric conditions. The researchers did not compare suicide rates in the concussion patients with those in individuals treated in hospitals for other nonhead injuries, again underscoring the importance of trauma control patients in studies of this nature. Further, Fralick et al[45] found an effect for concussions that occurred on weekends versus weekdays, raising the possibility that the association with suicide may be an epiphenomenon in the form of a link between behaviors that lead to concussion on a weekend (as opposed to concussion itself) and the risk of suicide. Existing data are neither substantive nor mature enough to allow us to draw firm conclusions, which emphasizes the need for further research on the causal link between concussion and neuropsychiatric disorders.

Cognitive Effects of Repetitive Concussion and Head-Impact Exposure

Few authors have prospectively investigated the association between repetitive concussion or head-impact exposure and neurocognitive function.[46] Investigators have primarily focused on cognitive test performance in current high school or collegiate athletes, stratified by their reported number of concussions (eg, 0, 1, 2, 3, or more).[9,10,47–50] These studies have not only been limited to short-term follow-up of young, currently active athletes, but they also varied widely in the methods employed, cohorts studied, and main findings.

An earlier meta-analysis[51] of 8 studies revealed no overall effect of multiple mTBIs on neuropsychological performance. A subsequent study[49] confirmed no association between a history of 1 or 2 concussions and any effects on neuropsychological performance. Additional researchers identified no association between concussion exposure and cognitive functioning in athletes with more extensive exposure histories (3 or 4 concussions).[52] Although select

investigators[47,50,53] have reported poorer neuropsychological performance in athletes with a history of multiple concussions, major differences in the methods and patterns of findings make it difficult to draw any singular or uniform conclusion about their association with prior injury exposure.

Long-Range Cognitive Change and Neurodegenerative Disease

In addition to potentially causing neurocognitive and neuropsychiatric changes, exposure to multiple concussions or repetitive head-impact exposure in sports may increase an athlete's risk for neurodegenerative disorders later in life. Epidemiologic research supports the idea that TBI is a risk factor for Alzheimer disease (AD), indicating that individuals with a history of severe TBI are at significantly elevated risk.[54] It remains unclear, however, if this association is also evident in milder forms of brain injury, particularly in the setting of SRC. From a larger-scale epidemiologic perspective, it would seem highly unlikely that a single incident of mTBI or SRC predisposes one to a long-term risk of neurodegenerative disease, given what we know about the incidence of concussion in the general population.[55]

The aforementioned studies provided data on the effects of repetitive concussion on cognitive function over a relatively short timeframe during young athletes' playing careers, but they did not include longitudinal follow-up to clarify any longer-range effects. To date, no prospective, longitudinal studies of well-defined cohorts over longer periods (eg, years, decades) have been conducted to determine how exposure to multiple concussions early in life may affect one's risk for late-life cognitive problems or neurodegenerative disease.

Several years ago, surveys of former professional football players suggested a possible link between a history of multiple concussions and late-life cognitive and psychological health problems. Although these survey results often depended on retrospective reports of concussion histories from participants and self-reports of chronic symptoms (ie, without formal evaluation or medical documentation), they nonetheless prompted speculation about long-term risks associated with repetitive concussions and set in motion a new line of research to examine the effects of concussion across the lifespan.

In 2005, Guskiewicz et al[56] reported on 2552 retired professional football players who completed a general health survey. The survey cohort averaged 54 years of age and 6.6 years of professional football experience. A second questionnaire focusing on memory and issues related to mild cognitive impairment (MCI) was subsequently completed by a subset of 758 players aged 50 years or older. A significant association existed between a reported history of recurrent concussion and the late-life presence of clinically diagnosed MCI and self-reported memory impairments. In particular, retired players with 3 or more reported concussions had a 5-fold greater prevalence of MCI diagnosis and a 3-fold greater prevalence of reported memory problems compared with retirees who did not have a history of concussion. No association was evident between a history of recurrent concussions and the occurrence of AD in the sample, but the researchers described an earlier onset of AD in the retirees than in the general American male population. The authors acknowledged the inherent limitations of their survey-based work and called for prospective, longitudinal studies to more deeply evaluate the association between repetitive concussion and late-life cognitive decline.

Over the past 10 years, CTE has been introduced as a unique pathologic syndrome identified on postmortem studies of former athletes who reportedly had a history of repetitive neurotrauma.[40,41] Traumatic encephalopathy, or "punch-drunk syndrome," was identified in boxers many decades ago, yet only in recent years have autopsies identified similar pathologic changes in athletes with a history of repetitive neurotrauma in football, hockey, soccer, and other contact sports.

Chronic traumatic encephalopathy is considered a neurodegenerative disease characterized by the accumulation of hyperphosphorylated τ protein in neurons and astrocytes.[40,41] The character and distribution of τ in CTE are thought to be different from those of other tauopathies, including AD and frontotemporal dementia (FTD). Researchers[42] recently proposed criteria for traumatic encephalopathy syndrome, a disorder caused by repetitive neurotrauma, with 4 principal subtypes: predominant behavioral or mood symptoms, cognitive symptoms, a mixed variant, or dementia that is considered to be distinguishable from AD, FTD, or another form of neurodegenerative disease.

In view of the nonspecificity of these clinical symptoms, a definitive diagnosis of CTE can only be made at autopsy. A recent National Institutes of Health-sponsored conference proposed required and supportive criteria for a pathologic diagnosis of CTE, the hallmark of which is a pattern of perivascular accumulation of abnormal amounts of τ in neurons, astrocytes, and cell processes in the depths of the cortical sulci.[57] However, the role of phosphorylated τ in the genesis of the clinical syndrome is not yet clear. Bieniek et al[58] reported findings of a neuropathologic investigation of the brains of 66 individuals exposed to contact sports, such as football, drawn from a brain bank for neurodegenerative disorders. Twenty-one individuals met the pathologic criteria for CTE, compared with 0 individuals from the group of 198 individuals without contact-sport exposure. The clinical significance of the findings was not clear, given that those with and those without CTE did not differ with respect to age at symptom onset, symptom duration, age at death, education, history of alcohol abuse, or military service. Ling et al[59] noted that 12% of 268 brains from the Queen Square Brain Bank met the neuropathologic criteria for CTE. The cohort included individuals with a variety of neurodegenerative conditions as the primary clinical and pathologic diagnosis, as well as 47 controls older than age 60. Although more than 90% of the CTE patients had a history of TBI, only a third had engaged in high-risk sports. The rate in elderly controls (12%) was not different from that of the group at large. Both studies were limited by the retrospective nature of brain-injury–exposure classification, but they raise the question of whether the excessive τ associated with the neuropathologic diagnosis of CTE is a marker for the clinical syndrome currently of concern in athletes (the "smoking gun") or a less specific marker of brain-injury exposure that may or may not be associated with a

progressive, deteriorating neurodegenerative disorder with prominent neuropsychiatric symptoms. In other words, the findings that define the neuropathologic picture of CTE may be a useful indicator of brain-injury exposure (necessary) but less helpful (not sufficient) in identifying those suffering from the clinical syndrome of progressive neuropsychiatric and neurocognitive deficits labeled as presumed CTE.

Authors of recent reviews[60–64] have attempted to critically evaluate the existing scientific evidence for the association between repetitive concussion, head-impact exposure, and long-term risk for CTE and other clinical phenomena known to cause cognitive impairment, including accelerated cognitive decline associated with normal aging, MCI, AD, FTD, and other neurodegenerative disorders. The literature in this area is largely limited to case studies or small case series. Interpreting existing case studies is problematic in that they often rely on the subjective and retrospective reports of family members regarding observed cognitive changes in the deceased person, lack any objective measurement of cognitive functioning, and do not allow detailed characterization of the nature of cognitive impairment essential to differential diagnoses. Retrospective studies make it difficult to tease apart factors principally contributing to reported cognitive decline and draw any formal conclusions about a causal association between a history of repetitive neurotrauma and cognitive decline.

In a critical review of the literature, Iverson et al concluded that

> . . .at present, the science underlying the neuropathology, clinical features, and causal relationship between the neuropathology and clinical features in CTE is very limited, leading some authors to question whether it has been clearly established as a disease.[61(p287)]

Other critics[63,65,66] argued that the pathologic findings in cases of apparent CTE are consistent with those often observed in preclinical AD, FTD, Lewy body disease, cerebrovascular disease, and other neurologic conditions known to cause neurodegeneration, raising speculation that CTE may not, in fact, represent a unique pathologic syndrome. In turn, this raises questions as to whether exposure to repetitive concussion or head impacts is the principal risk factor for so-called CTE.

With respect to the risk for long-term cognitive effects, it remains unclear whether repetitive concussion or head-impact exposure directly or indirectly leads to cognitive decline. Based on their detailed critical review of the literature, Iverson et al stated that

> . . .the current state of the science does not allow us to determine the extent to which repetitive neurotrauma uniquely causes, or partially contributes to, specific clinical symptoms such as depression, personality changes, or cognitive impairment.[61(p287)]

The authors described the need to further understand the role of comorbid health problems (eg, diabetes, cardiovascular disease), psychiatric disorders (eg, depression, anxiety, substance abuse), and other factors that contribute to one's risk for late-life cognitive decline, independent of a history of repetitive neurotrauma.

Data on the association between repetitive head-impact exposure (with or without concussive injury) and long-term cognitive problems are also lacking. Belanger et al[13] published a formative review on clinical outcomes associated with repetitive head-impact exposure, citing the lack of data from human studies to formally address the topic. Based on their review of the literature, the authors determined that

> . . .findings to date suggest that any effect of subconcussive blows is likely to be small and perhaps only evident in a subset of individuals on select measures. Even in this subset, it is unclear if differences are clinically meaningful and/or enduring.[13(p6)]

They advised the scientific community and general public to exercise caution in drawing conclusions about the occurrence of brain injury resulting from repetitive head-impact exposure in sports, particularly given the potential societal effect of overstating the current evidence. Similar to other experts, the authors called for prospective, controlled epidemiologic studies to further clarify the incidence of repetitive head impacts and their short- and long-term effects.

SUMMARY AND FUTURE RESEACH DIRECTIONS

The short-term cognitive and neurobehavioral effects of concussion during the acute and subacute recovery period have been well characterized in several prospective studies of high school and collegiate athletes.[22] Further, a growing body of literature based on advanced neuroimaging, electrophysiologic testing, and other technologies illustrates the acute effects of concussion on brain structure and function.

To date, however, little is known about even the short-term effects of multiple concussions or repetitive head-impact exposure in athletes. Recent epidemiologic studies indicated that recurrent concussion is a relatively uncommon occurrence but may negatively affect recovery and return to play over the short term compared with a first concussion. Studies of exposure have generated frequency statistics for football players, but less is understood about exposure among athletes in nonhelmeted sports.

More relevant to our review, no prospective, longitudinal studies have shown the long-term risks of cognitive decline, neuropsychiatric disorder, or neurodegenerative disease associated with repetitive SRC in contact sports. Furthermore, evidence from human studies of the neurologic and neuropsychological effects of repetitive impacts not associated with diagnosed concussion is currently quite limited. Although concerns about CTE have been raised based on recent postmortem case studies, critical reviews have cited the methodologic limitations of that approach and the clear lack of prospective data from unbiased samples. Critics have raised questions about the true population-based incidence of CTE, the extent to which there is a causal link between history of repetitive concussion or head-impact exposure and CTE, and even whether CTE represents a unique pathologic syndrome. Accordingly, experts have recommended caution in public

messaging that overstates the existing evidence for long-term risks to athletes in contact sports.

Our synthesis of the state of the science in this area strongly suggests that further research is required to answer a set of fundamental questions that are not only critical to our scientific understanding of the effects of repetitive neurotrauma but also central to the national narrative among the sporting community, including clinicians, researchers, athletes, parents, administrative bodies, and policy makers. Specifically, further investigation to address the following key questions is a pressing need:

- What are the true, population-based risks? A growing number of case series focus on individuals with varying but typically long-term exposure to repetitive concussions. These reports expand on the earlier boxing literature indicating that some individuals with a history of repetitive concussion and head-impact exposure may be at heightened risk of long-term neurologic problems and neurodegenerative disease. The overall incidence and relative risk of these problems across the population, however, remain unknown. Large-scale, population-based research efforts are necessary to gain a more precise understanding of the incidence of long-term neurologic problems in athletes.
- Who is at risk and why? Following from the first question, we do not know if equal exposure results in equal risk. Most successful models of illness and injury outcomes include both host and vector or environmental factors and their interaction. At this time, our sample size of athletes with CTE is small, and absent prospective characterization of the sample, it is difficult to identify risk factors other than rather crude measures of exposure (eg, years playing the sport), and remote retrospective recall of concussion history. Prospective, longitudinal studies are required to determine the association between exposure and risk. More broadly, improved sensor technologies are needed to measure exposure in sports beyond football (ice hockey, lacrosse, soccer, etc).
- Which factors predict an athlete's risk? A corollary of the second question is that, if host factors exist, what might they be? Certainly, the list of usual suspects is worth considering, including candidate alleles that modulate the response to neurotrauma, baseline cognitive reserve, and comorbid medical and psychiatric conditions, among others. Epidemiologic studies that combine careful baseline characterization across such domains with meticulous exposure metrics, proper control groups, and follow-up over time will be critical to address these questions.
- How can risks be modified to improve the safety of athletes at all levels? To address this question, progress will need to be made in answering the first 3 questions. Although it is tempting to suggest that reducing exposure to head impacts by such mechanisms as hit counts is the answer, until we have a clearer sense of a proper metric of exposure, the precise association between exposure and risk, and the host factors that modulate the response to exposure, such policies run the risk of being arbitrary and ineffective.

It is difficult to escape the conclusion that, to make significant progress in addressing these questions, we will need truly prospective, longitudinal studies that incorporate careful, multidimensional baseline characterization of a large cohort of contact-sport athletes with concussion, a cohort of contact-sport athletes without concussion (to address the subject of repetitive head impacts), and a cohort of relatively unexposed athletes (control group without a history of concussion or head-impact exposure) followed at intervals over time. Such efforts will require large-scale, long-term efforts and sizeable funding, yet the public health implications are of major proportions, given the masses of youth and young adults engaged in these activities with attendant risks. The overall health and welfare of our youth are also at stake here. That is, without the necessary evidence to guide us, misguided policies could have unanticipated and unjustified consequences that encourage youth to refrain from the sport participation that we know can result in improved health, fitness, and the related psychosocial benefits. As we reach these crossroads as a society, it will be imperative to move beyond the current narrative that lacks evidence and turn to science for the answers to these critical questions.

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