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Reassuring News About Football and Cognitive Decline?:

Not So Fast

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It is increasingly recognized that moderate to severe traumatic brain injury (TBI) (typically defined as loss of consciousness for >30 minutes¹) increases the risk for dementia in older adulthood,² a conclusion based primarily on epidemiologic research. Whether mild TBI, also called *concussion*, is associated with increased risk of dementia is less clear, especially because fewer prospective studies have focused on mild TBI.³ This is an important gap in the field, especially because concussion is relatively common, among both the general population and certain groups such as athletes and military service members.⁴ In recent years, concerns about potential for long-term negative consequences from concussion and even from subconcussive injuries have greatly intensified with the discovery of a distinct neuropathologic finding at autopsy among former US football players, other athletes, and military veterans exposed to repeated mild head injuries.⁵ This postmortem neuropathologic finding, which includes discovery of hyperphosphorylated τ in a characteristic cortical distribution, is now known as *chronic traumatic encephalopathy* (CTE).⁵ Although the clinical symptoms associated with CTE remain unclear, reports of deaths, including suicides of high-profile professional athletes later found to have CTE, have raised alarm about this condition and heightened fears about the potential risks of playing football and other contact sports.

Much remains to be understood about the association between concussion and CTE, in particular, and between mild TBI and risk of dementia, more broadly. Although CTE appears to be one possible neurodegenerative outcome following head injury, several other mechanisms may link TBI and the risk of dementia. For example, it has been suggested that TBI may increase the risk of developing Alzheimer disease⁶ and Parkinson disease,⁷ or that

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TBI may act by lowering one's reserve to increase susceptibility to cognitive decline more generally.⁸ In addition, there are limitations in the field of CTE research to date, primarily because most research has been based on retrospective studies, convenience samples, or case reports. Although these methods can be informative, especially for generating hypotheses, they have inherent biases. More important, the current state of the field does not tell us how common or rare CTE may be, including how likely it is for certain groups such as athletes to develop CTE. For this reason, population-based prospective studies are needed to investigate the prevalence and incidence of CTE and to identify risk factors associated with CTE.

Given that football players can experience concussions (often repeated) and that CTE has been identified among former football players, it seems logical that football players, as a group, may be at increased risk for neurodegenerative disease. The study by Deshpande et al⁹ in this issue of *JAMA Neurology* examines this hypothesis by investigating whether playing high school football is associated with cognition and mental health outcomes in older adulthood. Unlike prior emphasis on convenience samples and case reports, this study uses data from a large, population-based cohort study, the Wisconsin Longitudinal Study, which studies individuals who graduated from high school in Wisconsin in 1957 and who have been followed up in the study for decades after graduation. In a cohort of 3904 men, Deshpande et al⁹ compared men who played high school football with other men in the Wisconsin Longitudinal Study on measures of cognition, mood, and other emotional symptoms in older adulthood, with primary end points assessed at 65 years of age (2692 men had primary outcome data). Results revealed no deleterious effects of playing high school football, including the fact that former football players were no different from controls on a cognitive composite measure and even had lower depressive symptoms at 65 years of age than did controls.

Without question, findings of CTE among football players and other groups in neuropathologic studies, convenience samples, and case reports raise serious concern about the potential long-term effects of sports-related concussion. However, the results of the study by Deshpande et al⁹ offer some reassurance against CTE being a widespread epidemic among former football players, at least when considering high school football players as a group and examining long-term outcomes among this group on average.

Additional strengths of the study by Deshpande et al⁹ include their careful consideration of some potential confounding factors, comparison of football players with different control groups, and analysis examining potential attrition bias. Future longitudinal, population-based studies should continue to use such thoughtfulness in data analysis. However, the study by Deshpande et al⁹ has some limitations, which make their results far from conclusive in understanding the potential long-term risks of playing football. Most importantly, although the Wisconsin Longitudinal Study provides a rich data set, there is no information on concussion history per se. The study evaluates the overall effect on long-term outcomes of playing football vs not playing football, but it does not directly evaluate the association of football-related exposure to concussion or subconcussive injury with outcomes in older adulthood. In other words, their results suggest that, on average, high school football players are not at heightened risk of problems in older adulthood. However, there remains the important possibility that there may be a subset of football players who

have greater exposure to concussions and who, in turn, do experience long-term negative outcomes in aging. Indeed, quantification of concussive and subconcussive injuries experienced while playing football is needed to truly understand associations between playing football, football-related concussion, and risk of neurodegenerative disease. Accurate assessment of injury burden is indeed a challenge for the field. Recent work among former football players raises the possibility that likely exposure to football-related concussion could be estimated from other information, using an index shown to be associated with cognitive impairment, mood, and behavioral symptoms years after playing football.¹⁰

An additional limitation of the study by Deshpande et al⁹ is that their results may not generalize to understanding the risk of playing college-level or professional football, particularly as the risk may be greater for individuals who play football for a longer time or at higher levels of competition. Furthermore, an ideal study to investigate the potential for long-term risks associated with football and concussion would evaluate longitudinal trajectories in cognition and emotional well-being across the life span from youth through older adulthood. The study by Deshpande et al⁹ had some repeated measures of cognition and mood measured in later life, although the analysis strategy was focused primarily on outcomes measured at single time points. If future studies do find group differences, a trajectory-based approach would be more informative in differentiating the possibility of chronic, stable differences from a downward trajectory suggestive of neurodegenerative disease. In specifically investigating for CTE, a life-span approach may be especially important to evaluate how early in life symptoms begin to appear, given that neuropathologic findings of CTE are seen even in fairly young individuals.

The study by Deshpande et al⁹ provides an important first step in meeting the need for prospective, population-based studies. Future studies of this type should include comprehensive measurements of outcomes, including thorough neuropsychological, neuropsychiatric, and neurologic assessments to investigate the potential clinical phenotype of concussive-related neurodegeneration and its symptom course over time. For example, while the study by Deshpande et al⁹ focused on a cognitive composite measure as their primary outcome, future studies should be designed to include a more comprehensive neuropsychological battery to enable identification of whether there is a specific profile of cognitive decline. As the field continues to advance in biomarkers and neuroimaging methods to detect neuropathologic conditions while individuals are still alive, incorporation of these tools into population-based studies will be invaluable in helping to evaluate the specificity of findings to a particular neuropathologic process. Certainly, the public health significance of a potential link between concussion and neurodegenerative disease, and the many gaps that remain in our understanding of this link, necessitate additional population-based prospective studies to further investigate this issue.

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